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Electrochemical Installation of CFH_2–, CF_2H–, CF_3–, and Perfluoroalkyl Groups into Small Organic Molecules

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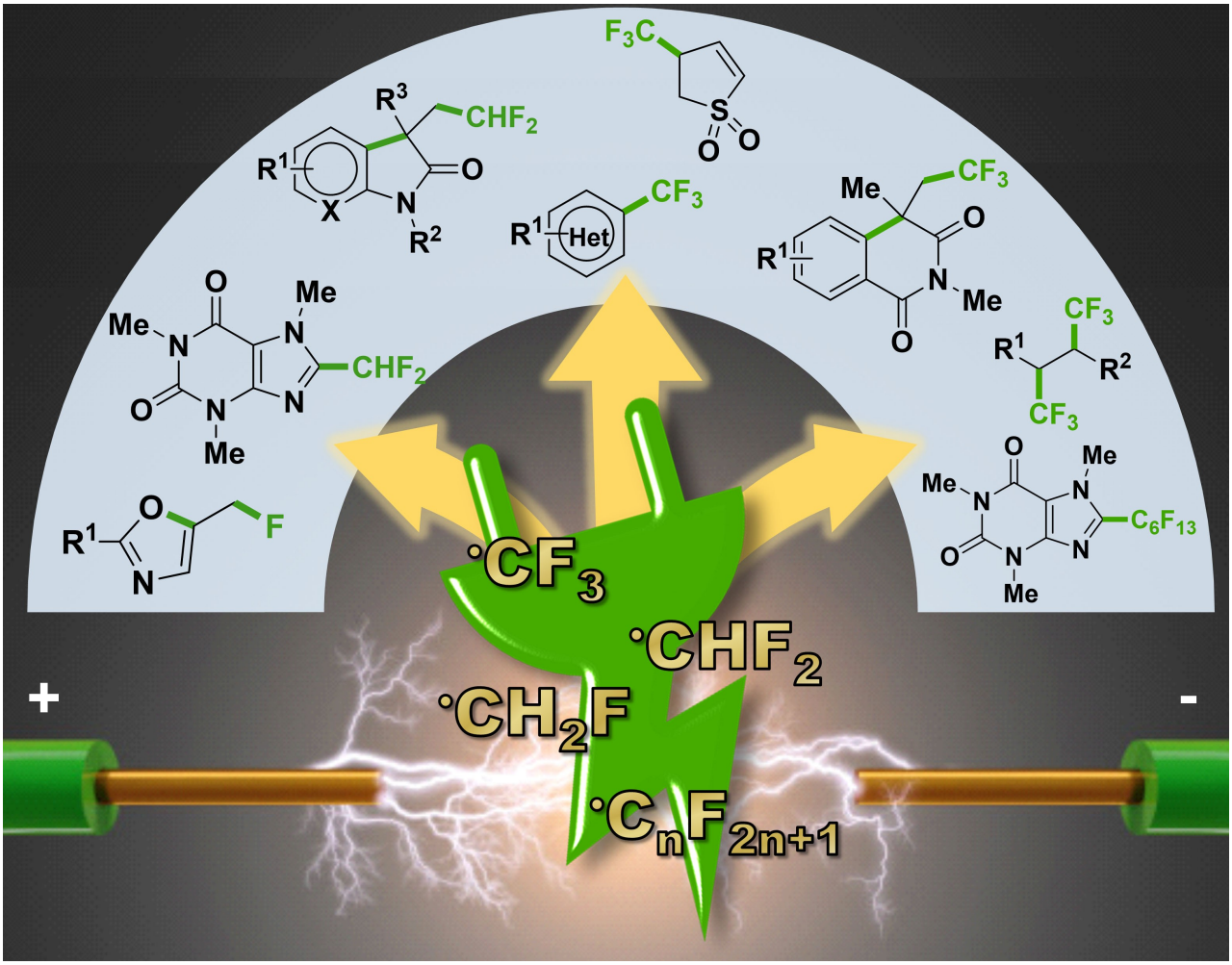

Abstract: Electrosynthesis can be considered a powerful and sustainable methodology for the synthesis of small organic molecules. Due to its intrinsic ability to generate highly reactive species under mild conditions by anodic oxidation or cathodic reduction, electrosynthesis is particularly interesting for otherwise challenging transformations. One such challenge is the installation of fluorinated alkyl groups, which has gained significant attention in medicinal chemistry and material science due to their unique physicochemical features. Unsurprisingly, several electrochemical fluoroalkylation methods have been established. In this review, we survey recent developments and established methods in the field of electrochemical mono-, di-, and trifluoromethylation, and perfluoroalkylation of small organic molecules.

Keywords: electrosynthesis, fluoromethylation, difluoromethylation, trifluoromethylation, perfluoroalkylation

1. Introduction

The installation of fluorine-containing moieties into small molecules has emerged as an important transformation in organic synthesis.[1] Due to the challenging nature of this manipulation, it has been in the focus of intensive research and development for almost a century. The reason for this ongoing interest are the unique physicochemical properties of the fluorine atom and thus of fluoroalkyl moieties.[1–5] Albeit fluoroalkyl groups do almost not appear in natural compounds, their incorporation in biologically active molecules allows for a rigorous change of the pharmacologic profile of lead structures due to enhanced lipophilicity or metabolic stability.[3,6–8] For example, molecules bearing a trifluoromethyl group are highly prone for technological innovations, e.g., in pharmaceuticals,[3–4,9] pesticides,[4] and materials.[5] The impact of fluoroalkyl groups on drug development is reflected by the continuously increasing number of fluoroalkyl-containing drugs already approved and drug candidates entering clinical trials (Figure 1).[3,9–10] To meet the demand for fluoroalkyl-containing small molecules, numerous conventional methods for their synthesis have been developed and extensively reviewed.[1,4,7–9,11] Two mechanistic pathways can be distinguished: nucleophilic or electrophilic/radical fluoroalkylation in the presence of an oxidant. With the recent rise of organic electrosynthesis, i.e., the synthesis of organic molecules using electricity as driving force,[12,13] a new approach for the generation of highly reactive intermediates such as trifluoromethyl radicals has opened up. Consequently, many researchers have used this promising technology to introduce fluoroalkyl groups in small molecules. In view of the fast-growing area of electrochemical fluoroalkylation, we provide here a critical survey of recent developments in this field. Some older seminal results were included to put the current examples into a historical context. The required fundamentals of electrosynthesis will be introduced to the reader in the following section.

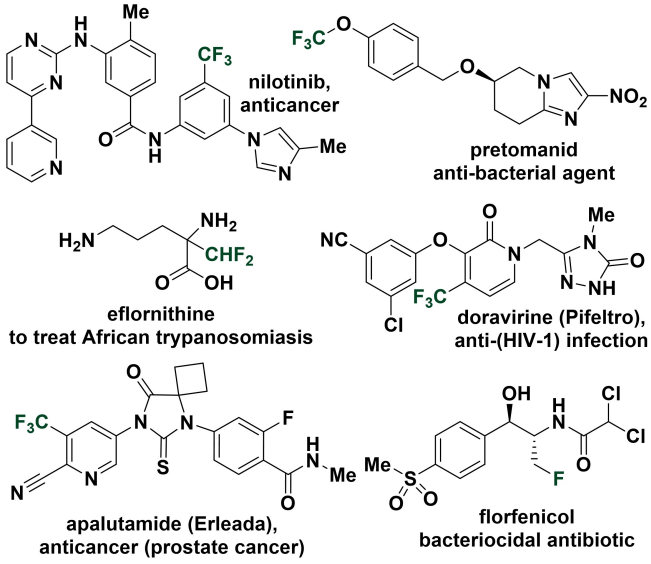

Figure 1. Selection of FDA-approved drugs containing fluoromethyl moieties.

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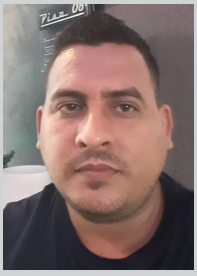

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Siegfried R. Waldvogel studied Chemistry in Konstanz and received his PhD in 1996 from the University of Bochum/Max-Planck-Institute for Coal Research with Prof. Dr. M. T. Reetz as supervisor. After Postdoctoral research at the Scripps Research Institute in La Jolla, California (Prof. Dr. J. Rebek, jr.), he started his own research career in 1998 with a habilitation at the University of Münster. In 2004, he moved to the University of Bonn as professor for organic chemistry. In 2010, he became full professor at the Johannes Gutenberg University Mainz. His major research interest is currently organic electrosynthesis ranging from screening techniques, novel transformations to scale-up. In 2018 he co-founded the start-up ESy-Labs GmbH which is also dealing with custom electrosynthesis.

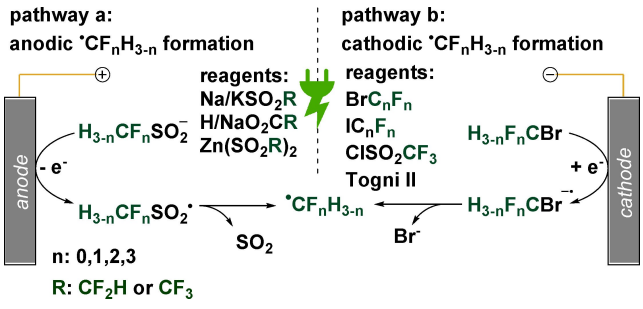
2. Fundamentals of Electrochemical Fluoroalkylation

Electrosynthesis has become an indispensable technology and vital field of research in the past two decades.[14] The fundamental idea is the use of electric current as a reagent. It can substitute conventional oxidizing or reducing agents,[15] and thereby reduce or avoid the generation of waste and the use of hazardous reagents. Electrical energy, the most versatile form of primary energy, is inexpensive, abundant, and can be obtained from renewable sources. Thus, with regard to efficiency and ecology, electrosynthesis can be considered a "green" methodology.[12b,16] Its application in the synthesis of small organic molecules has been reviewed.[12,17] From a synthetic point of view, electrosynthesis opens up a completely new parameter space, which renders hitherto unreachable reaction pathways accessible.[18] In general, electrosynthetic reactions can produce, often under ambient conditions, reactive intermediates, that are hardly obtainable with chemical reagents. The additional parameters in an electrochemical experiment are the current density (mA/cm^2) or electrode potential (V relative to a reference electrode), the applied charge (*F*, electron equivalents), the electrode material, the supporting electrolyte, and the cell design.[17d,f] To facilitate the comparison between different methods, the current densities in this review are uniformly given as current per geometrical electrode surface area, and the applied charge is calculated in relation to the limiting reactant to allow for an estimate of the faradaic efficiency. An important tool for the design of electrochemical reactions is cyclic voltammetry, which can provide useful information on the feasibility of redox processes.[19]

The electric current is fed to the electrolyte via electrodes. Commonly used electrode materials are platinum, nickel, lead, graphite, glassy carbon, boron-doped diamond, or stainless steel. Thus, an electrochemical experiment involves a heterogeneous electron transfer between the substrate and at least one of the electrodes (direct electrolysis). If a direct electron transfer between the substrate and the electrode is hampered by a large over- potential, a redox mediator can be used to facilitate the electron transfer (indirect electrolysis).[20] A combination of the advantages of direct and indirect electrolysis is the use of active electrodes, which are covered by an insoluble layer of a redox mediator.[21] Oxidation occurs always at the anode and reduction at the cathode. The electrolyte consists of the substrate, the reagent(s), an appropriate solvent, and often a supporting electrolyte: a salt, base, or acid to ensure ionic conductivity. The most commonly applied setup involves two electrodes that are operated under constant current control in an undivided cell. Experiments under constant potential control require an additional reference electrode. Control of the electrode potential can enhance the selectivity of an electron transfer, but prolongs reactions time, and requires a more sophisticated electrical power source. To avoid side-reactions or follow-up reactions at the respective counter-electrode, a divided cell can be employed, in which the anodic and cathodic compartment are separated by a porous glass frit or an ion-permeable membrane. Due to the additional barrier, higher terminal voltages need to be applied to a divided cell to reach the same current density as in an undivided cell. Nowadays, various types of electrolysis cells for laboratory scale experiments are commercially available.

The reactive species in electrochemical fluoroalkylation is in most cases a (per)fluoroalkyl radical ($^{\bullet}CH_2F$, $^{\bullet}CHF_2$, $^{\bullet}CF_3$, $^{\bullet}C_nF_{2n+1}$). The proposed mechanisms for fluoroalkylation methods are conceptually very similar and based on the formation of a radical by a single electron transfer between an electrode and an appropriate precursor (Scheme 1). Only few different precursors are reported so far: difluoroacetic acid (HCF_2CO_2H), sodium difluoromethanesulfinate (HCF_2SO_2Na), zinc difluoromethanesulfinate (DFMS, $(HCF_2SO_2)_2Zn$, difluoromethylsulfonyl hydrazide ($HCF_2SO_2NHNHBoc$), trifluoroacetic acid (F_3CCO_2H), alkaline salts of trifluoromethanesulfinate (F_3CSO_2Na/K), zinc bis(trifluoromethanesulfinate) ($(F_3CSO_2)_2Zn$), bromotrifluoromethane (F_3CBr), iodotrifluoromethane (F_3CI), trifluoromethanesulfonyl chloride (F_3CSO_2Cl), 1-trifluoromethyl-1,2-benziodoxol-3(1*H*)-one (Togni's reagent II), and perfluoroalkyl iodides.

Depending on the nature of the precursor, the fluoroalkyl radical is either generated by anodic oxidation or by cathodic reduction and subsequent fragmentation. In the following chemical step, this radical adds to an organic substrate or to a low-valent metal complex. The obtained intermediate can undergo further electron transfer or chemical steps depending on the reaction conditions and substrate, which will ultimately result in various fluoroalkylated products.



Scheme 1. Electrochemical fluoroalkyl radical formation: (a) anodic pathway; (b) Cathodic pathway.

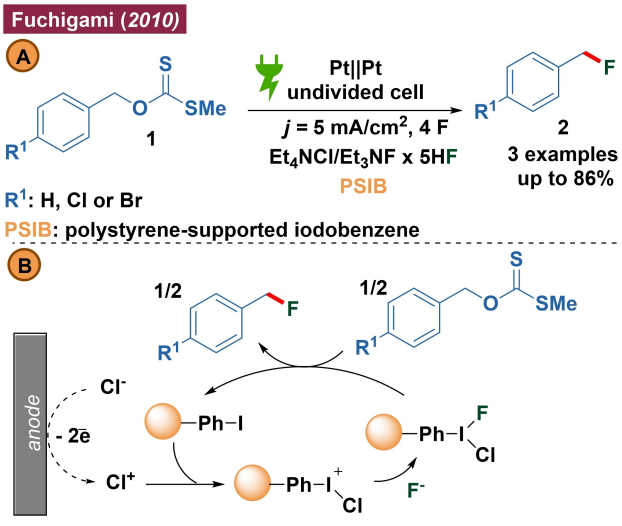
3. Monofluoromethylation

The introduction of CFH_2 moieties into small molecules by electrochemistry is a field open to exploration. To date, no examples can be found in literature. Photoredox catalysis is yet one of the best-known ways to introduce this group into organic molecules and could be used as a conceptual model for electrochemical strategies. A photoredox-catalytic approach was detailed by the Liu group, in which monofluoromethylation of isocyanides and *p*-quinone methides was performed using Mes-Acr$^+$ as catalyst and H_2CFSO_2Na as CFH_2 radical source.[22]

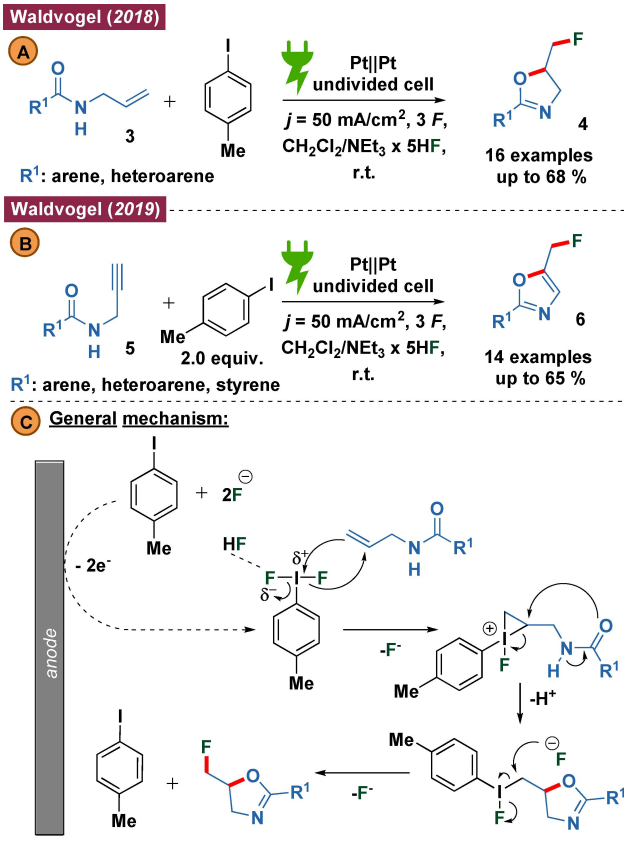
As an alternative to direct installation of a fluoromethyl group, electrochemical fluorination allows for the synthesis of fluoromethyl-bearing compounds.[23] As demonstrated by Fuchigami and co-workers in seminal contributions, most of the fluorination methods proceed via a cation radical intermediate, followed by nucleophilic substitution.[23j] The authors applied this strategy for the development of the indirect anodic fluorination of xanthates **1** with polystyrene-supported iodobenzene (PSIB) as mediator (Scheme 2).[23d]

Another example has been described by the Waldvogel group. Electrochemical fluorocyclization of *N*-allylamides **3** and *N*-propargylamides **5** results in the formation of fluoromethylated oxazoles **4** and oxazolines **6** via hypervalent iodine, in situ-generated by anodic oxidation of *p*-iodotoluene (Scheme 3).[24]

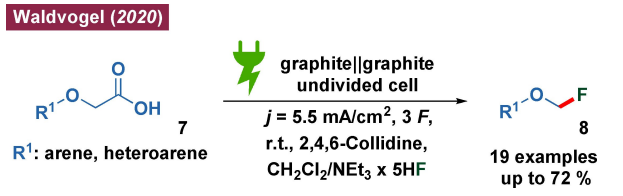
Recently, the same group showed that electrochemical decarboxylation of aryloxyacetic acids **7** followed by fluorination can be an alternative to access fluoromethyl aryl ethers **8** (Scheme 4).[25]



Scheme 2. (a) Indirect anodic fluorination of xanthates; (b) Reaction mechanism.



Scheme 3. (a) Electrochemical fluorocyclization of *N*-allylcarboxamides; (b) Electrochemical fluorocyclization of *N*-propargylamides; (c) Proposed mechanism.

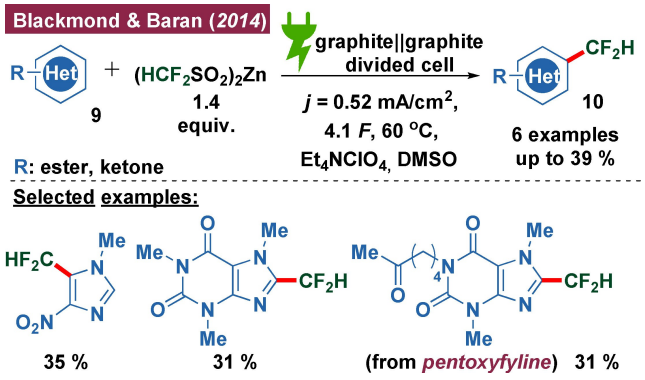


Scheme 4. Electrochemical synthesis of fluoromethoxyarene derivatives via fluorodecarboxylation.

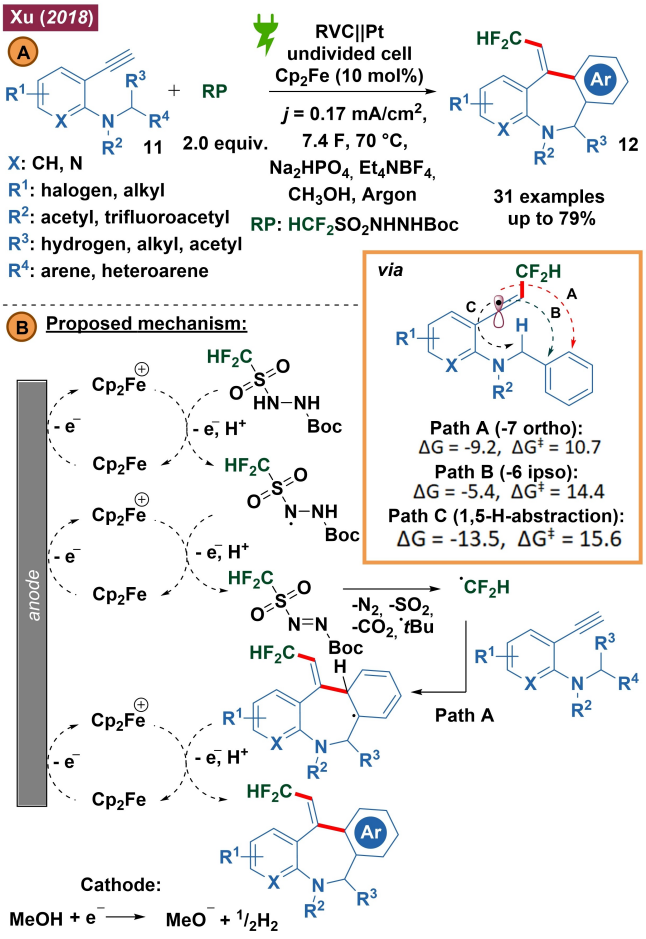
4. Difluoromethylation

Blackmond, Baran and co-workers are the pioneers of electrochemical difluoromethylation. With $(HCF_2SO_2)_2Zn$ as CF_2H radical source, they achieved the difluoromethylation of *N*-heterocycles **9**. Six examples (**10**) were synthesized with yields up to 39% (Scheme 5).[26]

Later, Xu and co-workers showed the difluoromethylation of alkynes to fluorinated dibenzazepines **12** (Scheme 6 and 7).[27] Here, the CF_2H radical was generated through ferrocene-mediated oxidation of $HCF_2SO_2NHNHBoc$.[27a]

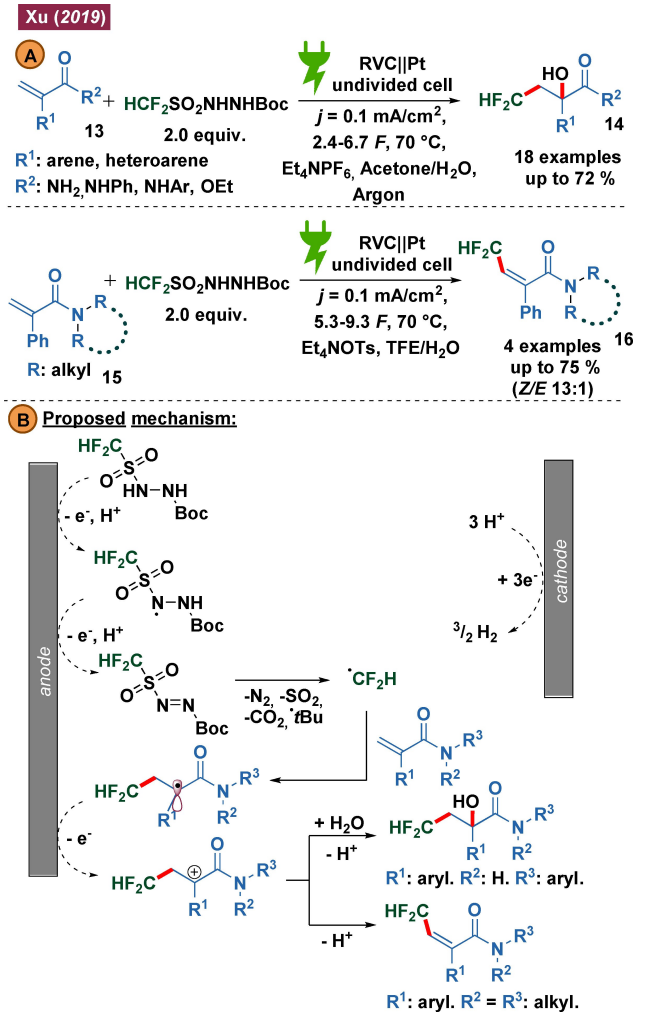


Scheme 5. Electrochemical difluoromethylation of *N*-heterocycles.



Scheme 6. (a) Difluoromethylation of alkynes using $HCF_2HSO_2NHNHBoc$; (b) Proposed mechanism.

The electrolytic process begins with the anodic oxidation of Cp_2Fe to Cp_2Fe^+, while MeOH is reduced at the cathode to generate H_2 and MeO^-. After oxidation of $HCF_2SO_2NHNHBoc$ by Cp_2Fe^+, a diazene is formed, which



Scheme 7. (a) Difluoromethylation of alkenes and alkynes using $CF_2HSO_2NHNHBoc$; (b) Proposed mechanism.

collapses to a CF_2H radical. The CF_2H radical reacts with the alkyne **11** to an intermediate vinyl radical, which immediately cyclizes to a seven-membered ring. Finally, rearomatization through elimination of an electron and a proton affords the dibenzazepine product **12** (Scheme 6B). In a second study, 1,2-hydroxydifluoromethylation and C–H difluoromethylation of acrylamides **13** and **15** were performed (Scheme 7).[27b] 22 Examples of **14** and **16** were synthesized with yields up to 75%. In this case, the ferrocene mediator system was not used, but the CF_2H radical was formed via direct anodic oxidation of $CF_2HSO_2NHNHBoc$ and subsequent fragmentation. Addition to acrylamide followed by one-electron oxidation furnishes a carbocation. Depending on the substituent at the nitrogen, the carbocation reacts with H_2O to afford the difunctionalized product **14** or undergoes proton

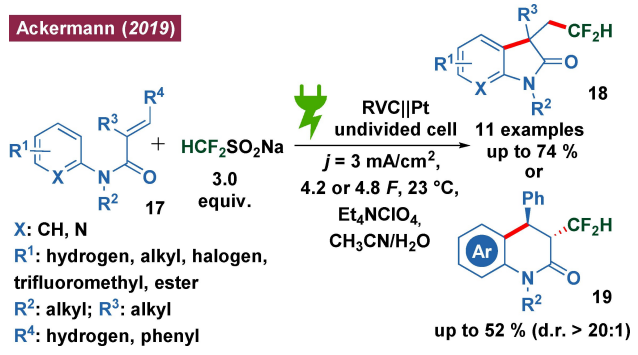
elimination to give the C–H functionalization product **16** (Scheme 7B).

Sodium difluoromethylsulfinate (HCF_2SO_2Na) has emerged as a more economic CF_2H radical precursor. The anodic oxidation of the sulfinate produces a sulfinyl radical that decomposes to the CF_2H radical. Ackermann and co-workers developed a difluoromethylation-cyclization sequence of *N*-substituted acrylamides **17** with this precursor (Scheme 8).[28]

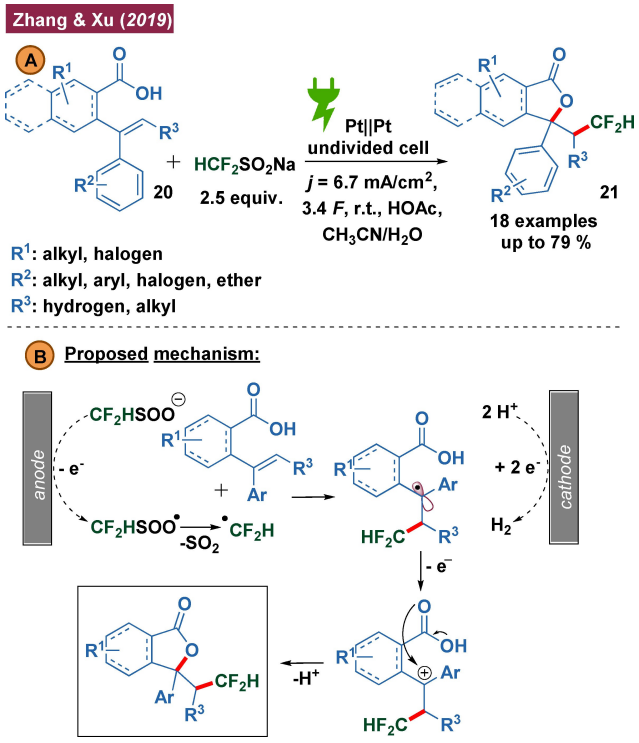
Ensuing, Zhang's and Xu's groups developed a similar electrochemical difluoromethylation-cyclization-lactonization sequence (Scheme 9A).[29] In this reaction, the carbon radical intermediate is further oxidized to a carbocation, which undergoes nucleophilic cyclization to the difluoromethylated lactones **21** (Scheme 9B).

To synthesize difluoromethylated nitrogen heterocycles **23**, Lin, Xu and co-workers used HCF_2SO_2Na as fluoroalkylating reagent. Starting from vinyl azides **22**, the desired products were obtained with yields up to 46% (Scheme 10A).[30] A plausible mechanism for this reaction starts with the CF_2H radical addition to the vinyl azide, producing an iminyl radical intermediate by liberation of N_2. Subsequently, the iminyl radical intermediate adds to the aromatic system. The resulting radical is oxidized to a carbocation, which, after deprotonation, yields the 6-fluoroalkyl phenanthridine **23** (Scheme 10B).

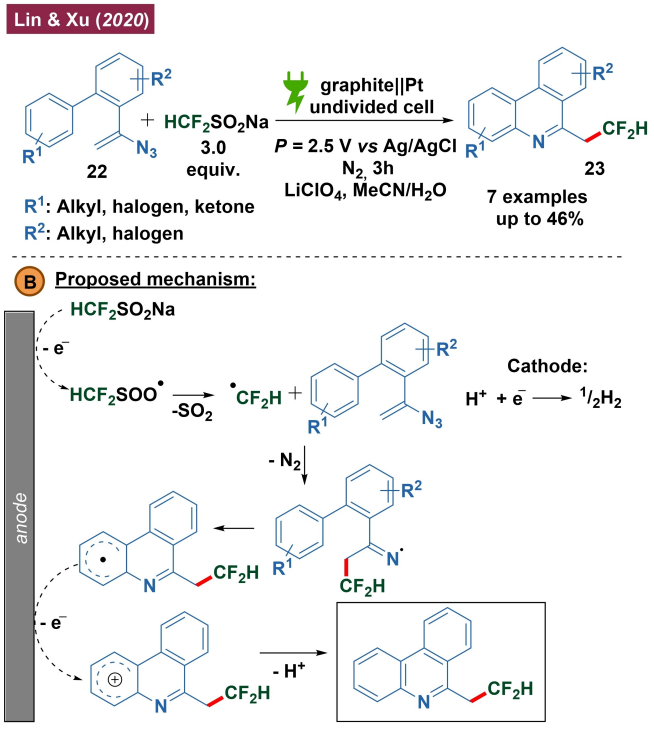
Recently, Yuan et al. demonstrated a complex cascade example consisting of difluoromethylation, cyclization, and oxidative indol cleavage of *N*-substituted 2-aryl indoles **24** (Scheme 11A).[31] This strategy exhibits a wide substrate scope with high tolerance of functionalities, in combination with the formation of a tetrasubstituted stereogenic center and an N–C axis of chirality with high stereoselectivity. 12 examples **25** were prepared with yields up to 57%. Here, the electrochemically formed CF_2H radical reacts with *N*-substituted 2-aryl indoles and triggers cyclization to form a benzo[4,5]-imidazole[2,1-a]isoquinolin-6(5*H*)-one intermediate, followed



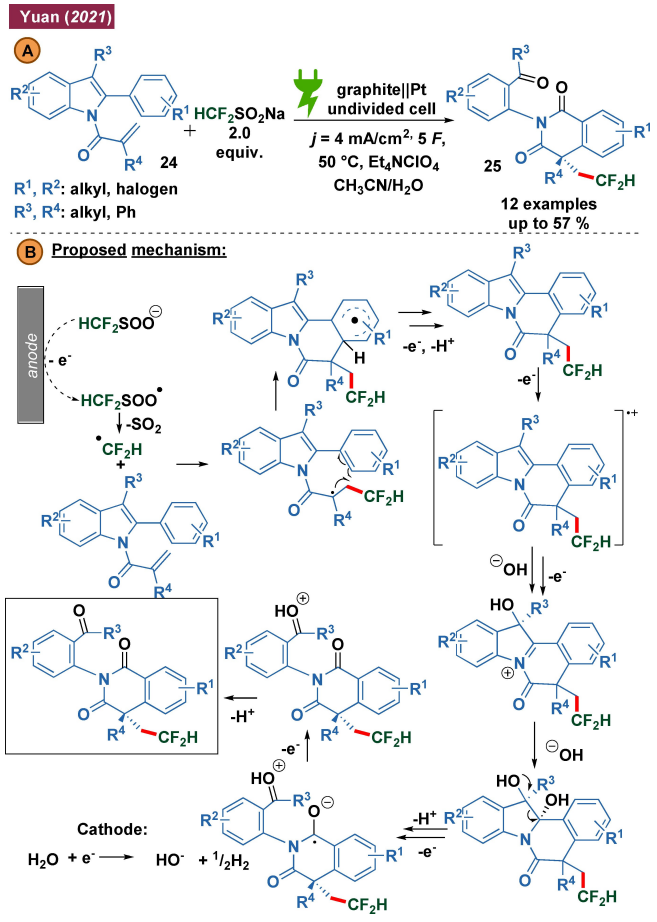
Scheme 8. Electrochemical difluoromethylation using CF_2HSO_2Na.



Scheme 9. (a) Electrochemical difluoromethylation of alkenes followed by lactonization using F_2HCSO_2Na; (b) Proposed mechanism.



Scheme 10. (a) Electrochemical difluoromethylation of biaryl vinyl azide; (b) Proposed mechanism.



Scheme 11. (a) Electrocatalytic difluoromethylation/cyclization/indole oxidative cleavage reaction; (b) Proposed mechanism.

by the selective oxidative cleavage of the C(2)–C(3) double bond of the indole skeleton to afford the difluoromethylated 2-(2-acetylphenyl)isoquinoline-1,3-diones (Scheme 11B).

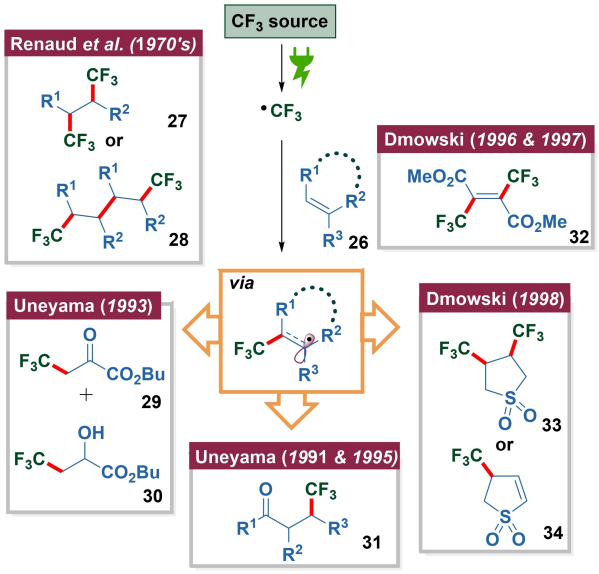
5. Trifluoromethylation

5.1 Difunctionalization of Alkenes and Alkynes

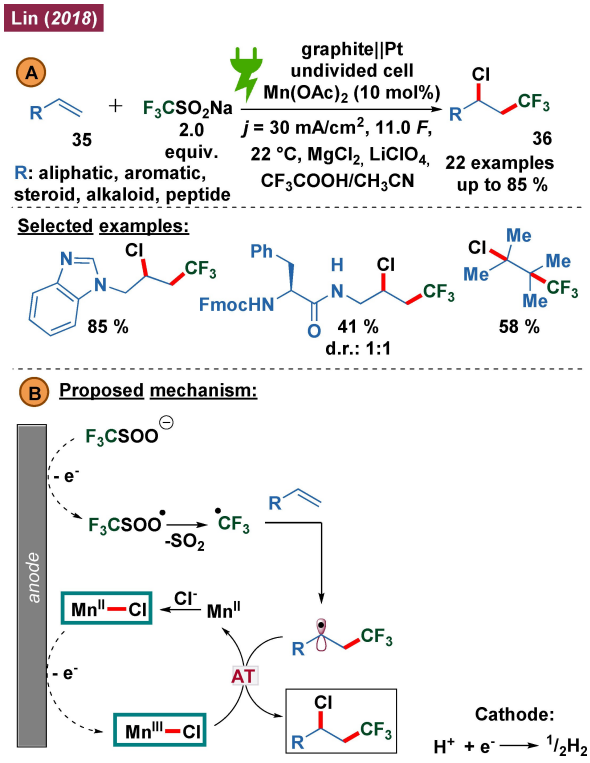
Electrochemical trifluoromethylation has been considered to be a privileged strategy for assembling trifluoromethylated compounds from a wide variety of alkenes and alkynes. In this context, trifluoroacetic acid (TFA) emerged as an attractive CF_3 radical source, because of its availability and low cost.[32] The research on such transformations started in the late 20th century. Pioneering works envisioned that electrochemical oxidation-decarboxylation of F_3CCO_2Na would generate the CF_3 radical, which could add to electron-deficient alkenes in a 1,4-fashion.

One challenge to overcome is the transient nature of the C-centered radical intermediate, which reacts fast with any available species. Under quite similar conditions, Renaud, Uneyama, Dmowski, and others demonstrated that the unstable character of this intermediate hampers its application on the development of new synthetic protocols (Scheme 12).[32–33] Mostly, mixtures of hydrotrifluoromethylation, bis-(trifluoromethylation), oxytrifluoromethylation, and dimerization products were obtained (**27**–**34**). Thus, the yields of the desired hydrotrifluoromethylated products were low. Moreover, only a few substrates could be functionalized. None of these protocols were applicable on a broad scope due to their poor selectivity and low yields. The low selectivity and limited scope likely result from high current densities – often up to 100 mA/cm^2 – and the usually large excess of the CF_3 radical precursor. Consequently, a high concentration of CF_3 radicals in close proximity to the electrode will favor bis(trifluoromethylation) over hydrotrifluoromethylation, and high electrode potentials can lead to unwanted side reactions.

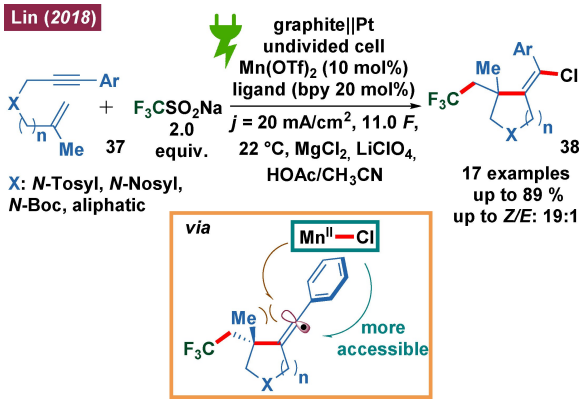
While these issues remain unsolved and there is still no general method for electrochemical hydrotrifluoromethylation of alkenes and alkynes, some advances have been made. Langlois reagent (F_3CSO_2Na), an affordable, stable and efficient CF_3 radical source, has emerged as an alternative to trifluoroacetic acid.[34] The main feature of this salt is its low oxidation potential (1.05 V *vs.* SCE).[35] In this regard, Lin and co-workers developed an electrochemical method for the regio- and chemoselective chlorotrifluoromethylation of alkenes **35** via electrolysis of F_3CSO_2Na in the presence of $MgCl_2$ and catalytic amounts of Mn(II) (Scheme 13).[36]



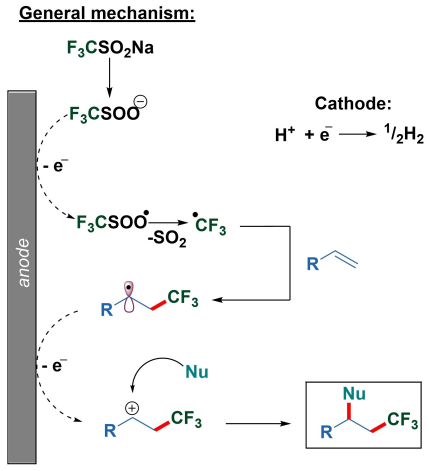
Scheme 12. Seminal reports on electrochemical trifluoromethylation of alkenes.



Scheme 13. (a) Electrochemical chlorotrifluoromethylation of alkenes; (b) Proposed mechanism, AT: atom transfer.



Scheme 14. Electrosynthesis of chlorotrifluoromethylated pyrrolidines.

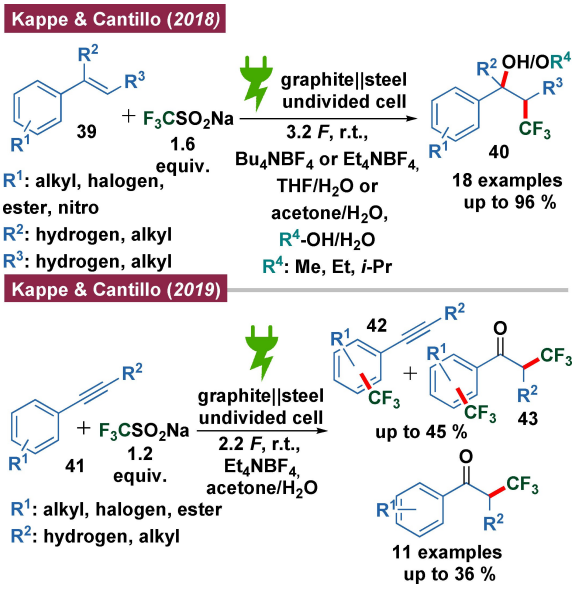


Scheme 15. General mechanism for nucleotrifluoromethylation.

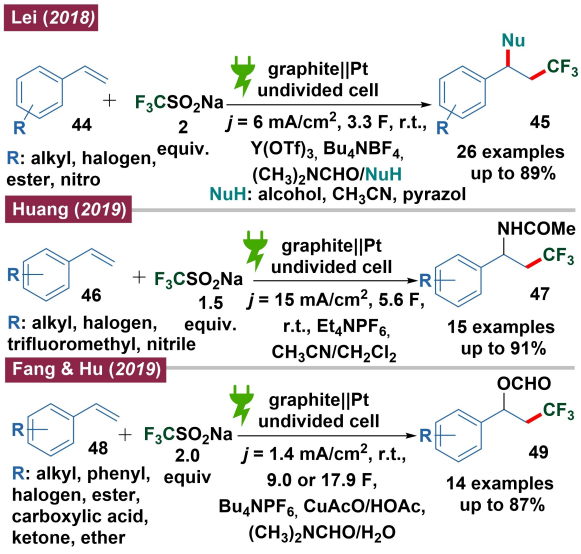
The authors designed a galvanostatic strategy to oxidize both [Mn^{II}]–Cl and F_3CSO_2Na. An anodically generated CF_3 radical adds to an alkene providing a carbon-centered radical. Cl-atom transfer from [Mn^{III}]–Cl to the carbon radical generates the chlorotrifluoromethylated product (Scheme 13B). The methodology was successfully applied to a range of alkenes with yields up to 85%. Several oxidation-labile functional groups were tolerated, and some natural product derived substrates proved to be compatible with the reaction conditions. On the other hand, electron-rich styrenes were incompatible due to competing side reactions. Additionally, they applied a similar strategy for the stereoselective synthesis of chlorotrifluoromethylated pyrrolidines **38** (Scheme 14).[37] This approach displayed a highly regio- and stereoselective ene-yne cyclization. Their study showed a broad substrate scope, showcasing 17 new compounds in yields up to 89%, as well as achieving high diastereoselectivities (up to 19:1).

The most common conceptual basis for electrochemical trifluoromethylation is depicted in Scheme 15. A CF_3 radical adds to a double bond in an anti-Markovnikov fashion giving rise to a carbon radical intermediate. Oxidation of this radical produces a carbocation, which is trapped by a nucleophile. Using this concept, Kappe, Cantillo and co-workers investigated the electrooxidative trifluoromethylation of styrenes **39** followed by vicinal oxygenation. In this process, water plays a dual role, as a sacrificial reagent for the cathodic reaction and as a nucleophile leading to oxytrifluoromethylation. A range of 1-hydroxy-2-trifluoromethyl compounds **40** was prepared in moderate to high yields (27–94%). Moreover, alcohols were evaluated as nucleophiles, but gave moderate yields (Scheme 15).[38] Although in lower selectivity and yields, the authors broadened the scope for alkynes **41**.[39] The similar nucleophilic character of the alkyne and the aromatic ring results in a competitive reaction: arenetrifluoromethylation **42** and oxytrifluoromethylation of the alkyne **43** (Scheme 16).

In 2018, the Lei group envisioned a Lewis acid-promoted strategy for oxytrifluoromethylation (Scheme 17).[40] Styrenes bearing both electron-donating and -withdrawing groups **44** were converted to the difunctionalized products **45** in yields up to 89%. The reaction exhibited a broad substrate scope with regard to the alkene. The authors expanded the scope for other *O*- and *N*-nucleophiles. Alcohols, carboxylic acids,



Scheme 16. Oxytrifluoromethylation of alkenes and alkynes.



Scheme 17. Oxy- and aminotrifluoromethylation of styrene derivatives.

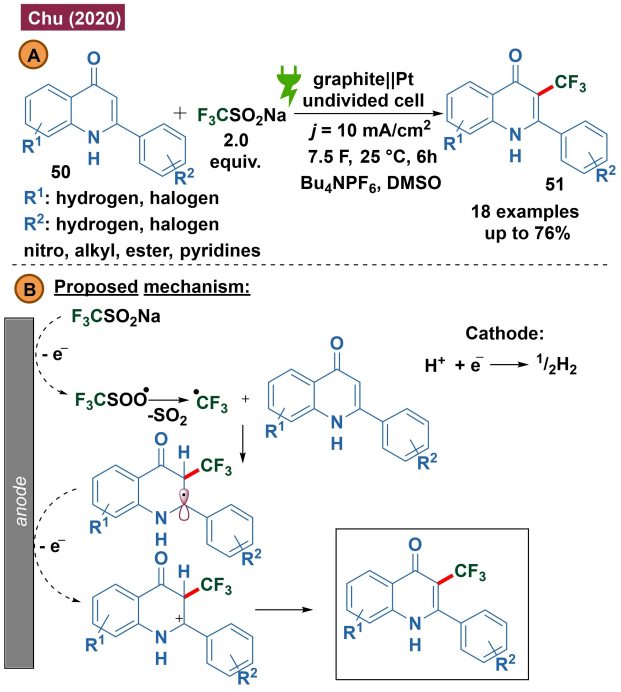
pyrazoles, and acetonitrile were evaluated, affording the corresponding alkoxy-, carboxy-, and aminotrifluoromethylated structures in moderate to high yields. Applying a similar concept, but without a catalyst, Huang's and Hu's group promoted the aminotrifluoromethylation and formyloxylation-trifluoromethylation, respectively, with acetonitrile and DMF, leading to multiple β-trifluoromethylamines and β-trifluorophenylpropyl formates (**47** and **49**).[41] The yields of both methodologies were comparable to the Lewis acid-promoted proposed by Lei, achieving yields up to 91% and 87%, respectively.

In a similar manner, Chu and co-workers performed the trifluoromethylation of quinolinones **50** (Scheme 18A).[42] This methodology differs from the previous ones because the intermediary carbocation undergoes deprotonation instead of a nucleophilic attack. In this study, 18 trifluoromethylated quinolinones **51** were synthesized in yields up to 76%.

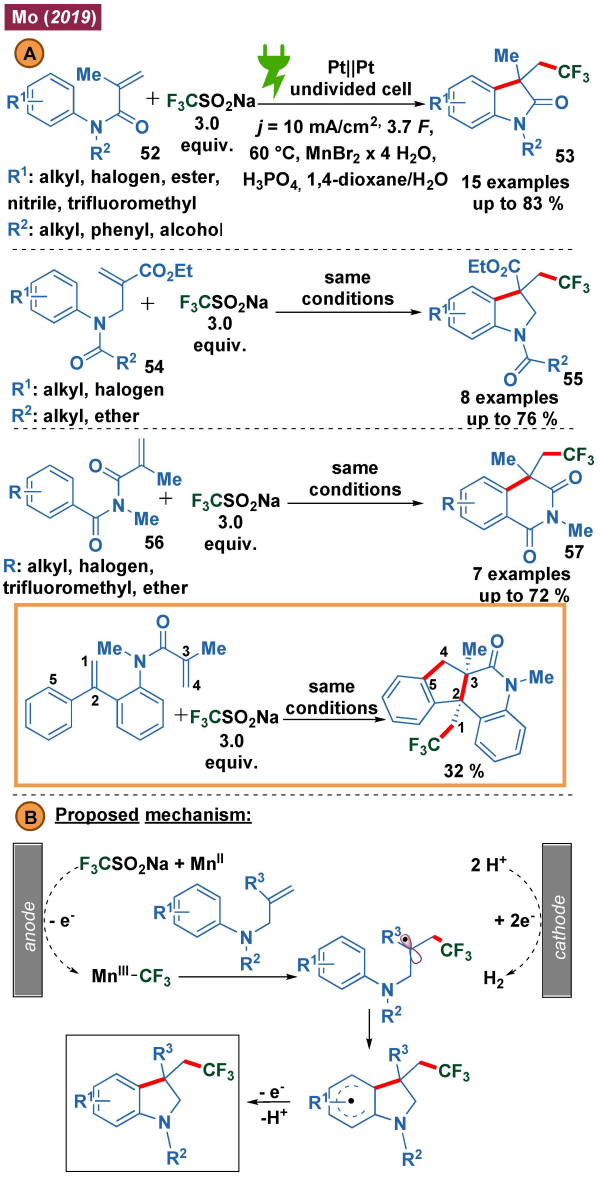
5.2 Cascade Reactions

Mo and co-workers demonstrated that electrochemical trifluoromethylation can also be completed intramolecularly.[43] By incorporating nucleophilic moieties – arenes – in the substrate (**52**, **54** and **56**), the authors achieved the synthesis of valuable trifluoromethylated *N*-heterocycles, e.g., oxindoles, indolines, and hydroisoquilolines (**53**, **55** and **57**), in yields up to 83% (Scheme 19).

Applying a similar strategy, Ackermann and co-workers developed a catalyst-free, robust, and mild procedure for direct electrochemical fluoroalkylation/cyclization of alkenes **58** to form oxindoles **59** and quinolinones **60** (Scheme 20).[28] Several *N*-aryl-acrylamides were used as substrates with electron-rich and electron-deficient substituents. Additionally, a variety of synthetically useful electrophilic functional groups were fully tolerated, including chloro, bromo, cyano and ester



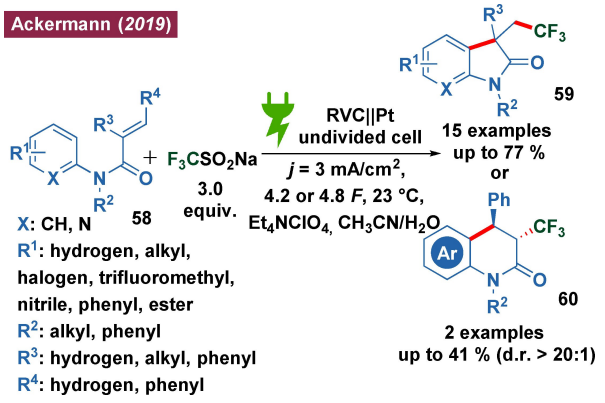
Scheme 18. (a) Electrochemical trifluoromethylation of quinolinones; (b) Proposed mechanism.



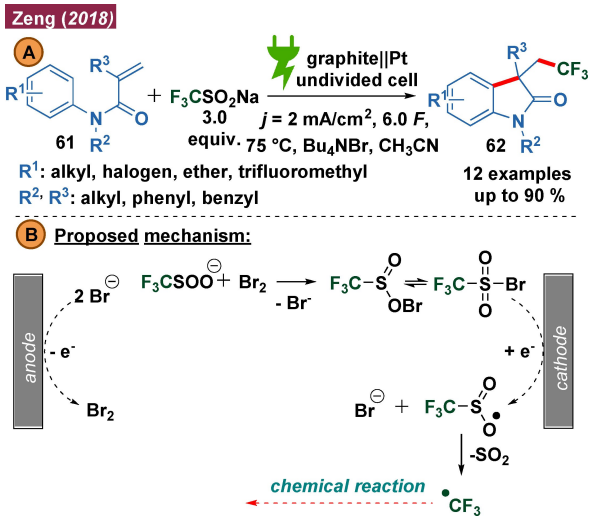
Scheme 19. Electrochemical trifluoromethylation of *N*-acrylate derivatives.

moieties. Indeed, *N*-arylcinnamamides were successfully converted to 3,4-dihydroquinolin-2-(1*H*)-ones under slightly modified conditions with yields up to 52%.

Alternatively, Zeng and co-workers developed a reductive strategy for generating CF_3 radicals from triflinate. Anodic oxidation of bromide forms Br_2, which reacts with the triflinate salt to give the triflyl hypobromite in equilibrium with sulfonyl bromide. Cathodic reduction affords the triflyl radical, which rapidly decomposes into SO_2 and a CF_3 radical. The CF_3 radicals were utilized in a trifluoromethylation/cyclization cascade, rendering oxindoles **62** from *N*-arylacrylamides **61** in high yields (59–90%, Scheme 21).[44]



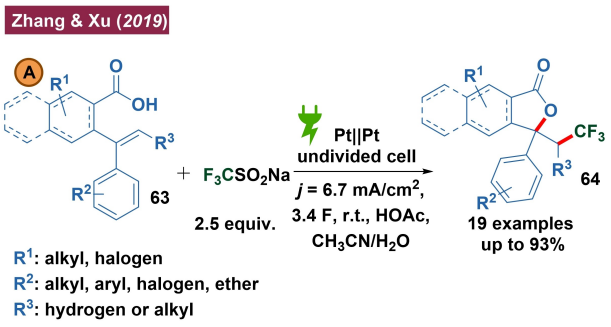
Scheme 20. Electrochemical trifluoromethylation of *N*-acrylamides.



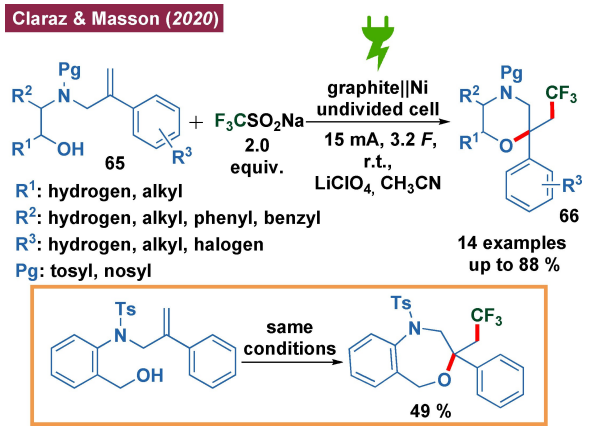
Scheme 21. (a) Electrochemical trifluoromethylation/cyclization cascade of *N*-benzylacrylamides;(b) Proposed mechanism.

Zhang's and Xu's groups developed an electrochemical trifluoro-methylation-lactonization sequence (Scheme 22).[29] Moderate to high yields of **64** were obtained regardless of the electronic nature of *para*-substituents, whilst substituents in *ortho*- or *meta*-positions diminished the yield. Fused rings, di-, and trisubstituted alkenes were tolerated, affording the desired products in high yields.

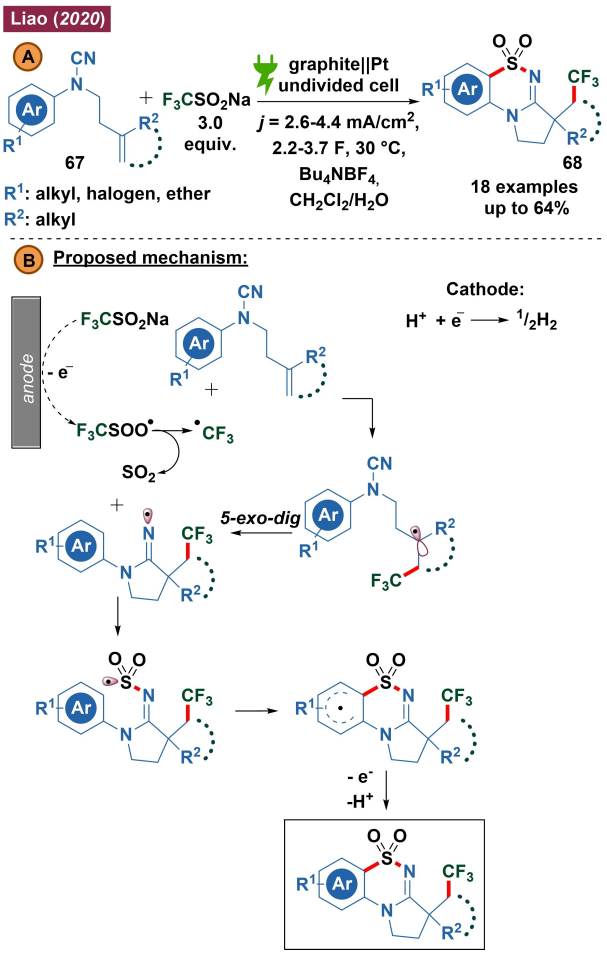
Another interesting trifluoromethylation cascade was demonstrated by Claraz and Masson (Scheme 23).[45] In this study, trifluoromethylated morpholine derivates **66** were obtained through an intramolecular electrochemical oxytrifluoromethylation of *N*-tethered alken-6-ols **65**. Thus, a set of representative *N*-tethered alken-6-ols with various substituents proved to be suitable substrates, generating the desired morpholines in yields up to 88%. This methodology can also be applied to the synthesis of bis(trifluoromethylated) morpho-



Scheme 22. (a) Electrochemical trifluoromethylation of alkenes followed by lactonization using F_3CSO_2Na.



Scheme 23. Electrochemical intramolecular oxytrifluoromethylation of *N*-tethered alkenyl alcohols.



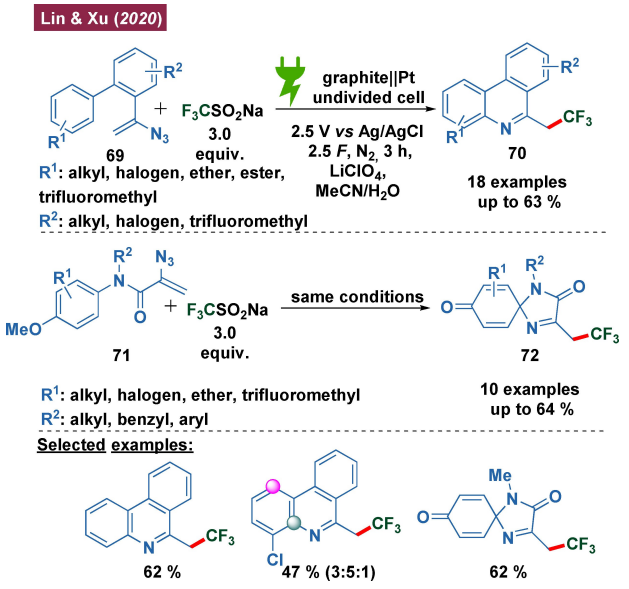
Scheme 24. (a) Electrochemical trifluoromethylation/SO_2-insertion/cyclization process by cyclization of *N*-cyanamide alkenes; (b) Proposed mechanism.

lines using more equivalents of Langlois reagent. Formation of a seven-membered oxacycle was possible in 49 % yield.

In 2020, Liao and co-workers introduced the synthesis of cyclic trifluoromethylated-*N*-sulfonylimines **68**. The authors proposed a domino cyclization of *N*-cyanamide alkenes **67** using Langlois reagent as CF_3 and SO_2 source, giving rise to fused bicyclic compounds in a single process (Scheme 24A).[46] A range of electronically distinct *N*-aryl cyanamides were evaluated. Besides, either *N*-*α*- or *β*-naphthyl substituted cyanamides can also serve as suitable substrates, furnishing the cyclic trifluoromethyl-*N*-sulfonylimines as sole regioisomers. Notably, *N*-aryl cyanamides containing a non-activated internal alkene and heterocyclic moieties, such as 5-substituted indole, were amenable to this electrochemical transformation. Further investigations revealed that this reaction was susceptive to the substitution and the length of the linkage between *N* and alkenyl moieties of cyanamides. Regarding the mechanism of this transformation, the authors proposed that the carbon radical intermediate is cyclized in a 5-exo-*dig* fashion, rendering an iminyl radical. The capture of SO_2 by this species affords a sulfonyl radical, which undergoes further cyclization to give another radical intermediate. Finally, anodic oxidation followed by aromatization affords the corresponding product (Scheme 24B).

Lin, Xu, and co-workers applied the same methodology they used for difluoromethylation of vinyl azides (Scheme 10) for trifluoromethylation and formation of diverse 6-trifluoroethyl phenanthridines **70** (Scheme 25).[30] Products with electron-donating and electron-withdrawing groups were obtained in moderate to high yields (up to 63 %). Additionally, the scope of the trifluoromethylation of a series of 2-azido-*N*-(4-methoxy-phenyl) acrylamides **71** was explored, achieving yields up to 64 %. However, possibly because of the lack of stability of trifluoromethylated products, no high yields were obtained.

In 2019, Li et al. reported the synthesis of vinyl trifluoromethyl derivatives **74** through a radical addition-de-

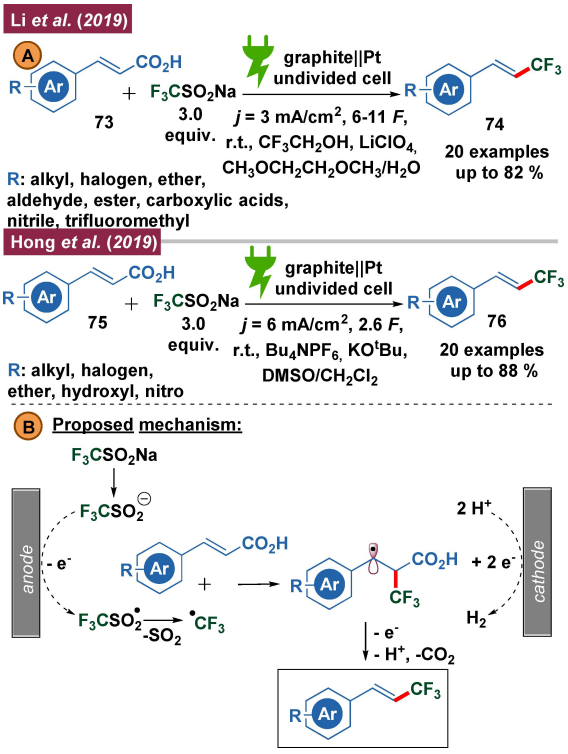


Scheme 25. Electrochemical trifluoromethylation of biaryl vinyl azide and acrylamides.

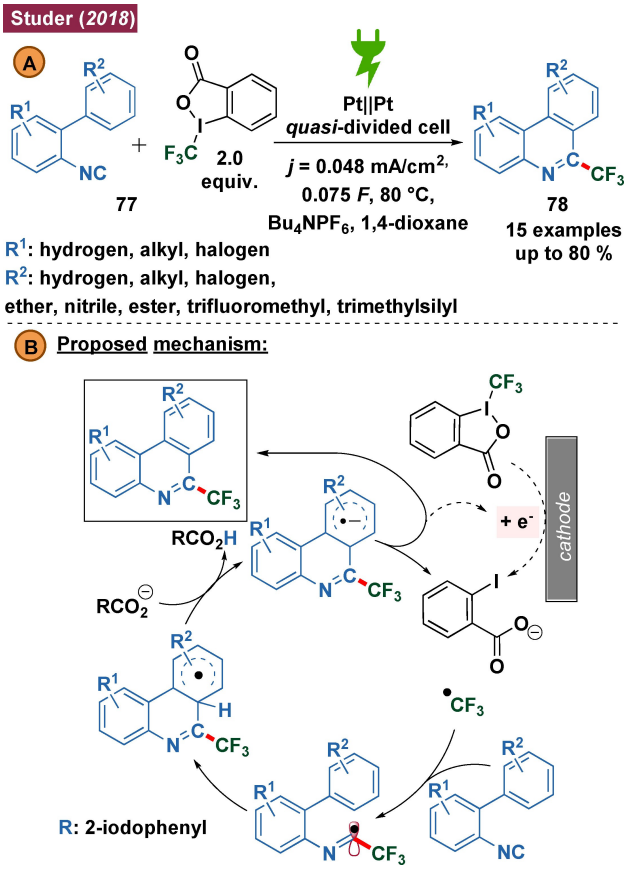
carboxylation-sequence (Scheme 26).[47] *α,β*-Unsaturated aryl carboxylic acids **73** containing heterocycles and both electron-donating and -withdrawing substituents delivered the corresponding products in yields up to 82% and with *E*/*Z* ratios higher than 99:1. However, highly electron-withdrawing groups, e.g., nitro, turned out to be a limitation of this methodology. The proposed mechanism begins with the reaction of a CF_3 radical with the vinyl carboxylic acid to form a relatively stable intermediate species, which spontaneously decarboxylates and furnishes the desired product (Scheme 26B).

Applying similar electrochemical parameters, Hong et al. proposed the decarboxylative trifluoromethylation of *α,β*-unsaturated carboxylic acids **75** (Scheme 26).[48] The protocol was applied to the synthesis of 20 examples of **76** with yields up to 88%. The reaction could be scaled-up to 0.80 g of the desired product.

Studer and co-workers described an electrocatalytic method for the preparation of 6-(trifluoromethyl)phenanthridines **78** via trifluoromethylation of biaryl isonitriles **77** (Scheme 27).[49] Here, a quasi-divided cell was used, this one combines



Scheme 26. (a) Electrosynthesis of vinyl trifluoromethyl compounds; (b) Proposed mechanism.



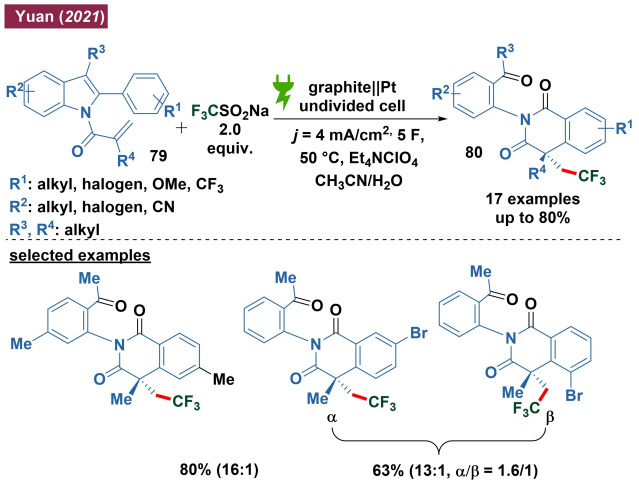
Scheme 27. (a) Electrosynthesis of trifluoromethylphenanthridines; (b) Mechanism for electrochemical trifluoromethylation of biaryl isonitriles.

characteristics of a divided and an undivided cell.[50] The method tolerates a variety of functional groups, e.g., nitriles, halogens, ethers, and esters, and substitution patterns. The most interesting aspect of this work is the catalytic amount of electric charge (0.075 *F*): One electron can induce more than 8 catalytic cycles before termination of the chain reaction occurred. The catalytic activity of the electron can be seen in the mechanism (Scheme 27B). The CF_3 radical, generated by single electron reduction of Togni's reagent II, adds to the isonitrile and affords an imidoyl radical intermediate. After cyclization, the cyclohexadienyl radical is deprotonated by the ortho-iodobenzoate. The radical anion formed can in turn transfer an electron to Togni's reagent II.

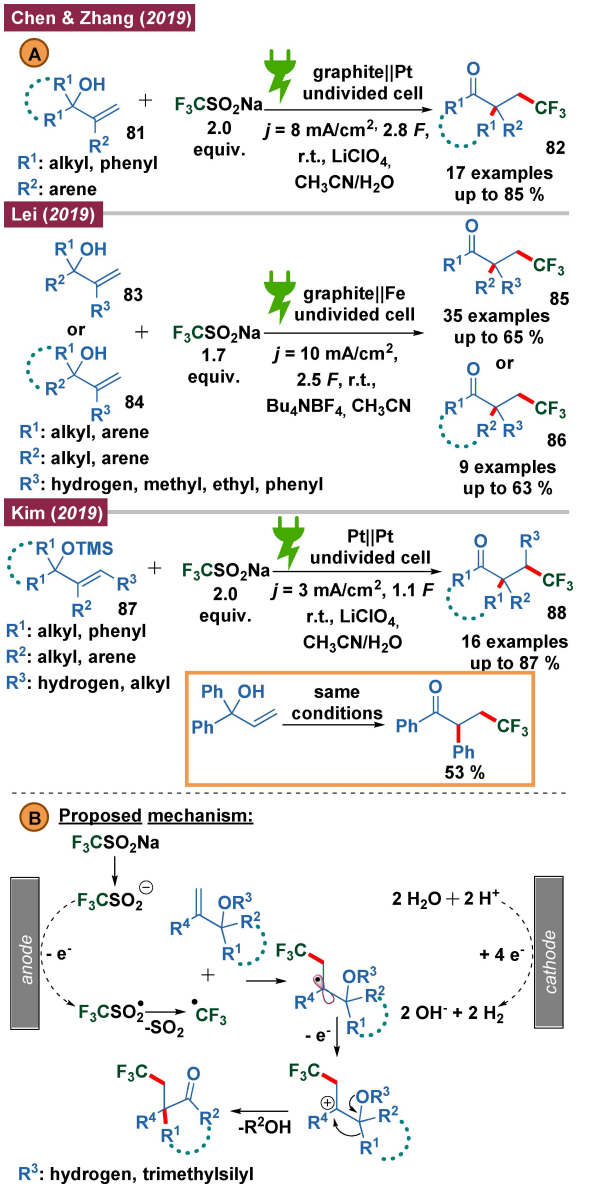
Following the methodology presented in section 4, Yuan et al. expanded their fluoromethylation/cyclization/indole oxidative cleavage of *N*-substituted 2-aryl indole to trifluoromethylation derivates.[31] 17 examples (**80**) were tested showing yields up to 80% achieving excellent stereoselectivity (Scheme 28). The variation in the electronic properties of the substituents at the para position of the 2-phenyl moiety of the *N*-substituted 2-aryl indole was found to have little influence on its catalytic efficiency. Electron-neutral substituents, electron-withdrawing groups and electron-donating group were successfully introduced into the structure. The presence of a phenyl at the C3-position of the indole ring was found to be tolerated, resulting in the formation of their corresponding products with efficiency. Various substituents at the C5-position of the indole ring were also readily tolerated in this system, delivering the corresponding products in good to moderate yields. Besides these examples, substrates containing an electron-donating methyl group at the C6-position of the indole ring were found to be similarly suitable.

5.3. Rearrangements

Addition of a CF_3 radical to a double bond can be followed by a skeletal rearrangement, which can generate retrosynthetic intersections that are not obvious on the first glance. Taking this into consideration, Chen/Zhang, Lei and Kim's groups disclosed an interesting approach based on the electrochemical semi-pinacol rearrangement of allyl alcohols (**81**, **83**, **84** and **87**) with a CF_3 radical (Scheme 29). This approach generates *β*-functionalized ketones (**82**, **85**, **86**, and **88**) with an *α*-quaternary carbon.[51]



Scheme 28. Electrocatalytic trifluoromethylation/cyclization/indole oxidative cleavage reaction.



Scheme 29. (a) Electrochemical trifluoromethylation/semi-pinacol rearrangement sequence; (b) General mechanism.

Through Chen and Zhang's methodology several derivatives were synthesized in high yields up to 85%.[51a] Lei expanded the scope of this transformation. According to their results, electronic factors of the aryl group have significant influence on the migration. Electron-rich aryl groups migrate more easily than electron-deficient, suggesting that carbocation intermediates might be present.

The α-alkyl-α-aryl allyl alcohols were found to exhibit impressive reactivity with F_3CSO_2Na. High selectivity was observed, and only aryl-migration products were obtained (yields up to 65%). Furthermore, the authors described an electrochemical ring expansion, allowing the synthesis of β-trifluoromethyl cyclic ketones in moderate yields.[51b] On the other hand, Kim and co-workers achieved high yields on a similar type of transformation, using TMS-protected alcohols. The electrolysis provides the synthesis of β-trifluoro-methylated ketones by the transformation of alkenyl alcohols into trifluoromethyl-substituted ketones. 17 substrates were successfully functionalized (yields up to 87%).[51c]

5.4. Trifluoromethylation of Arenes and Heteroarenes

Although some complex structures could be trifluoromethylated, the protocols often failed to functionalize simple and important buildings blocks such arenes and heteroarenes due the selectivity. Regioselectivity is the major problem in electrochemical arene trifluoromethylation, and many of these reactions give mixtures of regioisomers, which are hard to separate. To avoid this problem, substrates with only one replacement site have often been used. In the literature, many examples of these are seen and they are demonstrated below.

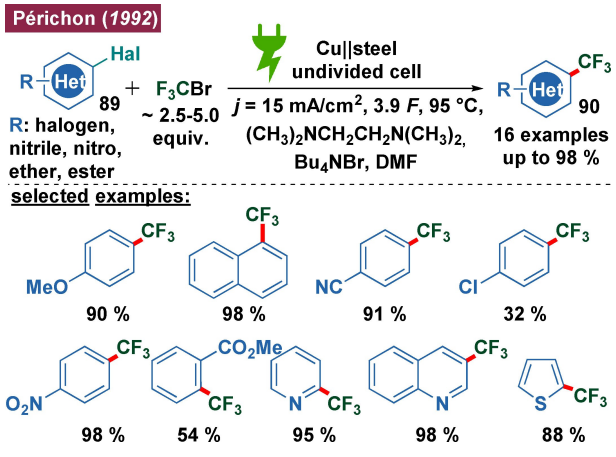
In 1989, Périchon and co-workers reported a cathodic procedure, in which a sacrificial copper anode generates $CuCF_3$ from F_3CBr (Scheme 30). In this report, the $CuCF_3$ reacts with aromatic halides **89** to achieve trifluoromethylated arenes **90** with yields up to 98%.[52] This protocol was a remarkable advance compared to prior procedures, mainly because it allows the use of less reactive F_3CBr instead of the largely employed but expensive F_3CI.[53]

In 1997, Grinberg and co-workers reported one of the first oxidative trifluoromethylation of arenes using TFA.[54] Even though moderate conversions (up to 51%) were obtained, important mechanistic features were described, such as the correlation between the absorptivity and the rate of electro-oxidation of arenes on the surface of the platinum electrode.

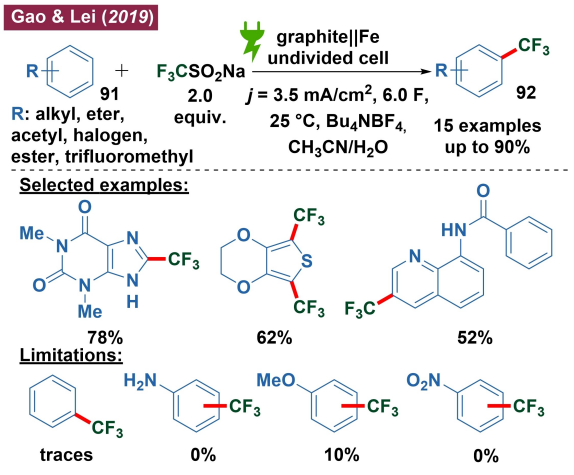
Later, Tommasino and co-workers investigated the electrochemical trifluoromethylation of electron-rich arenes by exploiting the convenient oxidation potential of F_3CSO_2K.[55] Moderate yields were obtained, which the authors attributed to side reactions such as the formation of F_3CH or dimerization to C_2F_6, as well as over-oxidation of the substrates, and formation of regioisomers.

In 2018, Raj and co-workers demonstrated that isonicotinic acid hydrazide is a suitable substrate for electrochemical trifluoromethylation, albeit with moderate conversion.[56] Gao's and Lei's groups published an analogous procedure, in which the electrochemical trifluoromethylation of aromatic compounds **91** was shown (Scheme 31).[57] More than 15 aromatic substrates **92** were evaluated achieving yields up to 90%. Here, the reactivity of the substrates depends on the substitution pattern. Electron-rich arenes gave higher yields.

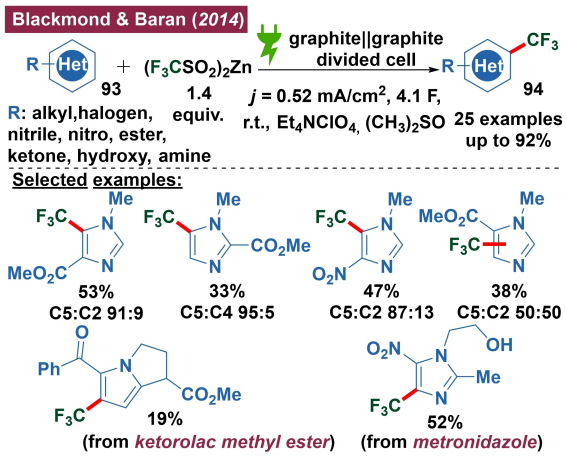
Using $(F_3CSO_2)_2Zn$ instead of Langlois reagent or TFA, Blackmond, Baran, and co-workers developed an electrochemical strategy for the trifluoromethylation of small *N*-heterocyclic pharmacophores **93** (Scheme 32).[26] Several heterocycles **94** – 25 examples – were successfully functionalized up to gram scale.



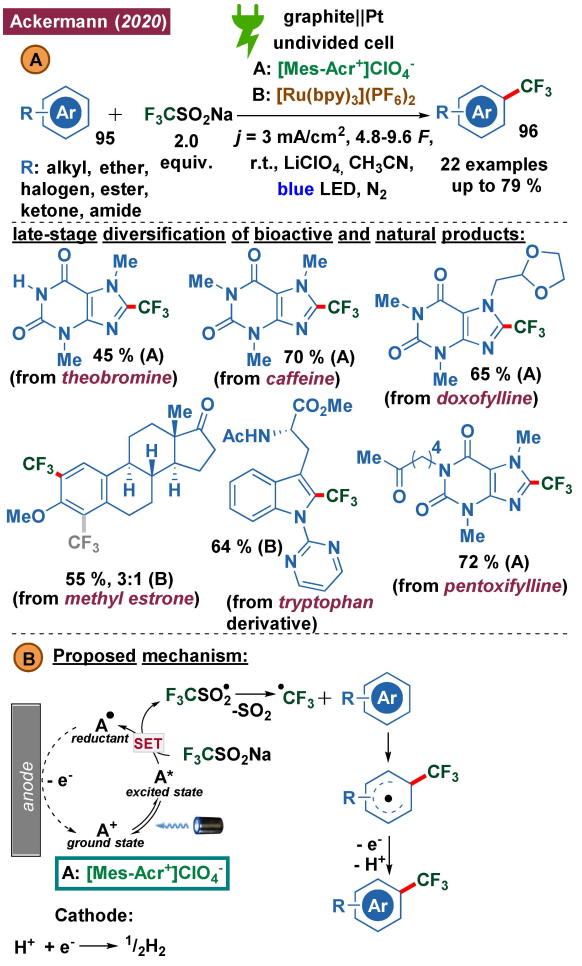
Scheme 30. Electrochemical reductive trifluoromethylation of carbonyl compounds and electrochemical trifluoromethylation of heteroaryl halides.



Scheme 31. Electrochemical trifluoromethylation of aromatic compounds.



Scheme 32. Electrochemical trifluoromethylation of *N*-heterocycles.



Scheme 33. (a) Electrophotocatalytic trifluoromethylation of arenes; (b) Proposed mechanism.

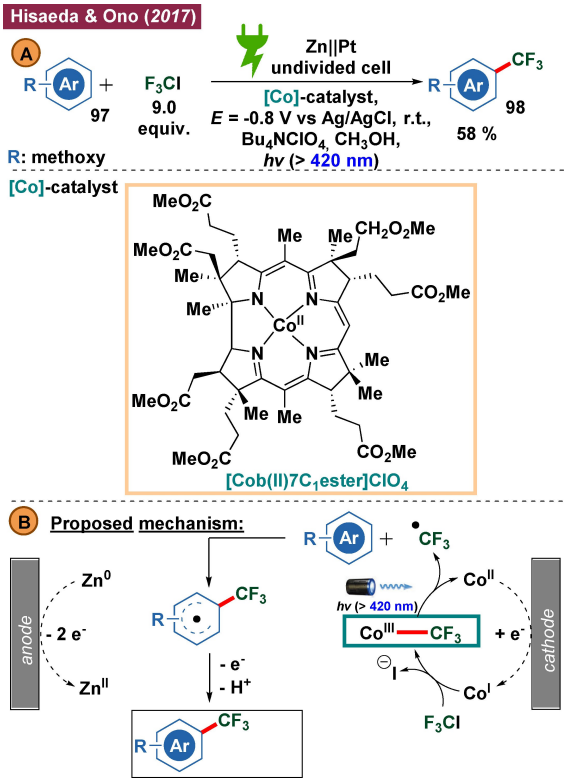
Employing a cooperative photo-electrochemical approach, Ackermann and co-workers developed a methodology for the trifluoromethylation of arenes **95** (Scheme 33A).[58] The electro-photochemical conditions allow for a maximum formation of CF_3 radicals leading to high chemoselectivity. A wide range of arenes proved to be compatible, furnishing the trifluoromethylated products **96** with high yields (up to 77 %). Notably, ester and amide moieties were tolerated. The proposed mechanism starts with the anodic oxidation of the organophotocatalyst (9-mesityl-10-methylacridinium ion, Mes-Acr$^+$) which is then irradiated to its excited state, Mes-Acr^{+*}. A SET process between Mes-Acr^{+*} and the sulfinate forms the CF_3 radical, which attacks the arene. Oxidation and loss of a proton delivers the desired product (Scheme 33B).

During studies focused on the redox chemistry of cobalamin (vitamin B12) derivatives, Hisaeda, Ono and co-workers reported a cobalt-catalyzed photo-electrochemical trifluoromethylation of arenes **97** (Scheme 34A).[59] Electron-rich (hetero)arenes could be trifluoromethylated in moderate yields (58 %). The important mechanistic step is the electrochemical reduction of Co(II) to a Co(I) complex, which acts as a supernucleophile[60] and forms a Co(III)-trifluoromethyl complex. Photoinduced homolysis of the cobalt-carbon bond releases a CF_3 radical, which reacts with the arene (Scheme 34B). While this example is interesting from a mechanistic perspective, the use of sacrificial electrodes is not desirable in terms of sustainability and economy.

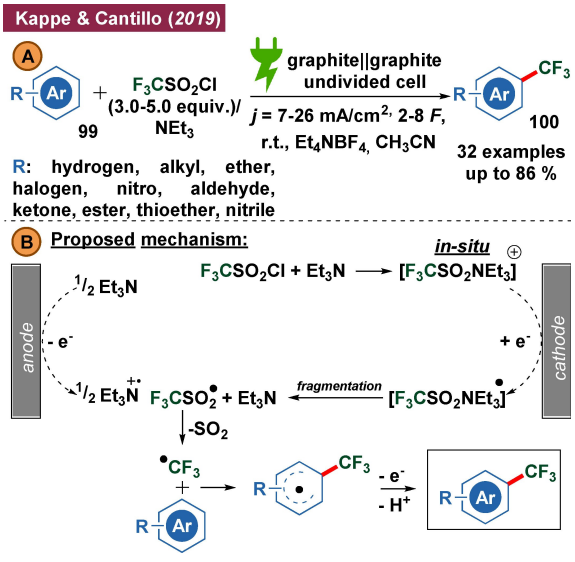
Kappe and Cantillo reported a metal-free cathodic trifluoromethylation (Scheme 35).[61] Their strategy consists of the reduction of a trifluoromethylsulfonyltrimethylammonium complex, which is formed in situ from triflyl chloride and triethylamine. Fragmentation furnishes the CF_3 radical that reacts with the arene **99** (Scheme 35B). Electron-rich arenes gave higher yields than electron-poor ones, e.g., ketone-, nitrile-, or ester-substituted. Oxidation-sensitive thioanisole and heteroarenes containing nitrogen, sulfur, and oxygen were successfully functionalized. Some complex structures such as caffeine and pentoxifylline were trifluoromethylated in moderate yields.

Applying the concept of their previous report,[44] Zeng and co-workers described the synthesis of trifluoromethylated arenes **102**. Important pharmacophores such as coumarin, thiazole, pyrimidine, and quinoxalinone were obtained in moderate yields (18–65 %, Scheme 36).[62] The examples available in literature largely circumvent formation of regioisomers since the chosen heteroarenes have only one possible substitution site. In general, the electrophilic character of the CF_3 radical can lead to an orthogonal regioselectivity in Minisci-type substitutions compared to the conventionally employed nucleophilic alkyl radicals.

To overcome problems with mass transport in paired electrolysis, alternating current electrolysis (ACE) can be used.

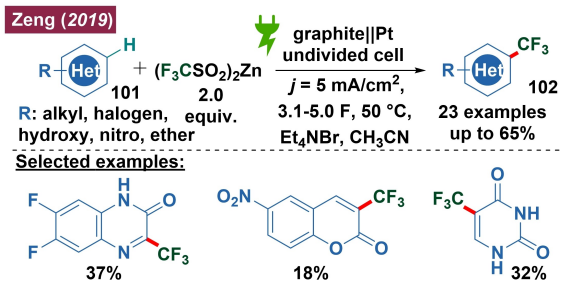


Scheme 34. a) Electrochemical trifluoromethylation of heteroarenes and structure of the heptamethyl cobyrinate perchlorate; c) Proposed mechanism.



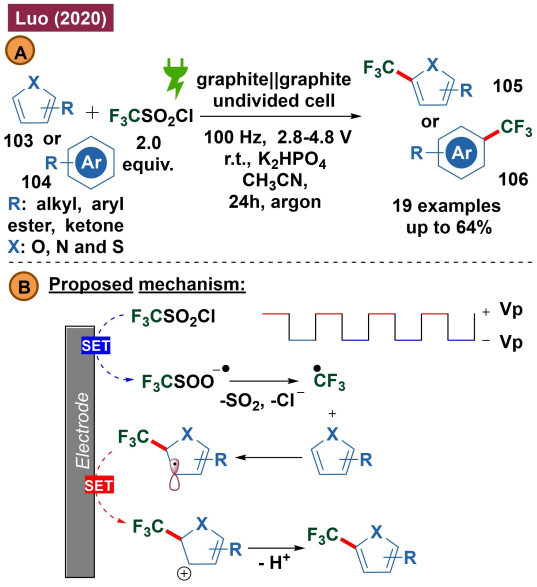
Scheme 35. (a) Electrochemical trifluoromethylation of arenes; (b) Proposed mechanism.

Here, the polarity of both electrodes is reversed by inverting the cell voltage with a set frequency. The most used voltage



Scheme 36. Minisci-type trifluoromethylation.

function is a square wave. As a result, both electrodes are alternately anode and cathode, and the reactive species do not need to diffuse to the respective counter-electrode but can stay near the electrode. As soon as the cell voltage is inverted, the electrodes change from oxidizing to reducing and vice versa. Additionally, to the parameters of an electrolysis, the frequency of the alternating current becomes important since it needs to match the rates of all interjacent chemical steps, so that the chemical species to be oxidized/reduced are present when the electrode potential switches. Using this technique, Luo and co-workers developed an ACE for the trifluoromethylation of (hetero)arenes (**103** and **104**, Scheme 37).[63] In this case, the reaction was initiated by reducing triflyl chloride to CF_3 radicals. The CF_3 radicals react with an (hetero)arene to form an intermediate radical, which is subsequently oxidized to an allylic cation at the same electrode, but at the inverted



Scheme 37. (a) Alternating current electrolysis for trifluoromethylation of (hetero)arenes; (b) Proposed mechanism.

potential. Deprotonation furnishes the trifluoromethylated product (**105** and **106**).

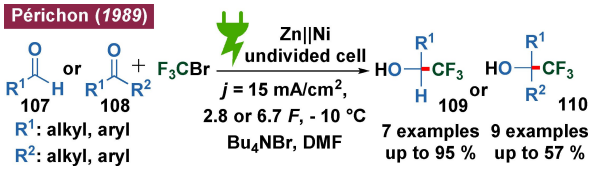
5.5 Trifluoromethylation of Carbonyl Compounds

When CF_3 moieties are added to carbonyl groups, interesting quarternary carbon-containing compounds can be formed. Thinking of that, in 1989, Périchon and co-workers reported an electrochemical trifluoromethylation of carbonyls (**107** and **108**) (Scheme 38).[64] Instead of electrochemical generation of CF_3 radicals, Zn(0) was electrolytically generated in situ from a sacrificial anode. Reaction with F_3CBr furnishes F_3CZnBr, which adds to the carbonyl.

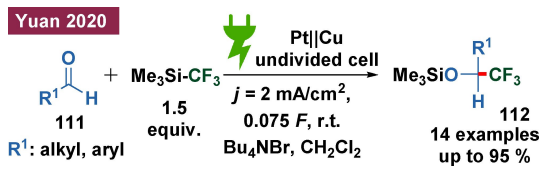
Aiming at the trifluoromethylation of aldehydes, Yuan and co-workers recently reported a direct cathodic activation of trifluoromethyltrimethylsilane (Scheme 39).[65] The authors claim that the addition products **112** could be isolated in high yields up to 95% with an average yield of 85% for 14 examples. Surprisingly, even electrochemically critical functional groups, e.g., iodo- or nitroarenes, are suggested to be tolerated under the described conditions. Disappointingly, the authors fail to discuss the catalytic behavior of the electron, which they claim in their figures (0.075 *F*). Even more alarming is the mechanistic discussion that makes the publication's claims appear questionable and will therefore not be shown here.

5.6 Trifluoromethylation of Thiophenols

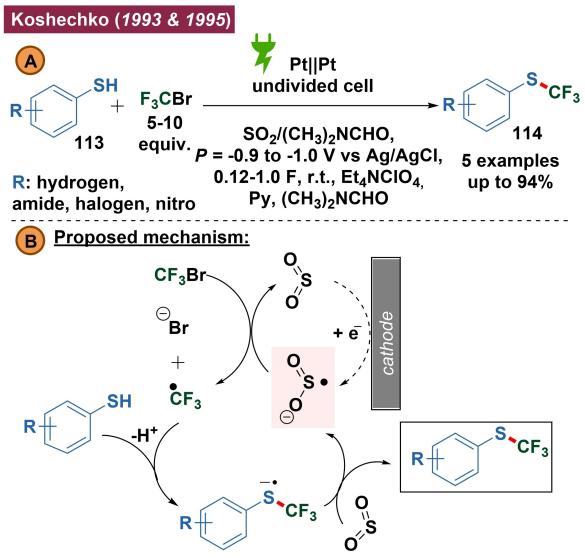
A potentially electrocatalytic trifluoromethylation of oxidation-sensitive thiophenols **113** with F_3CBr was described by Koshechko and co-workers.[66] Their potentiostatic protocol uses SO_2 as redox mediator (Scheme 40). Besides via cathodic



Scheme 38. Electrochemical reductive trifluoromethylation of carbonyl compounds and electrochemical trifluoromethylation of heteroaryl halides.



Scheme 39. Electrochemical reductive trifluoromethylation of aldehydes by cathodic activation of trifluoromethyltrimethylsilane.



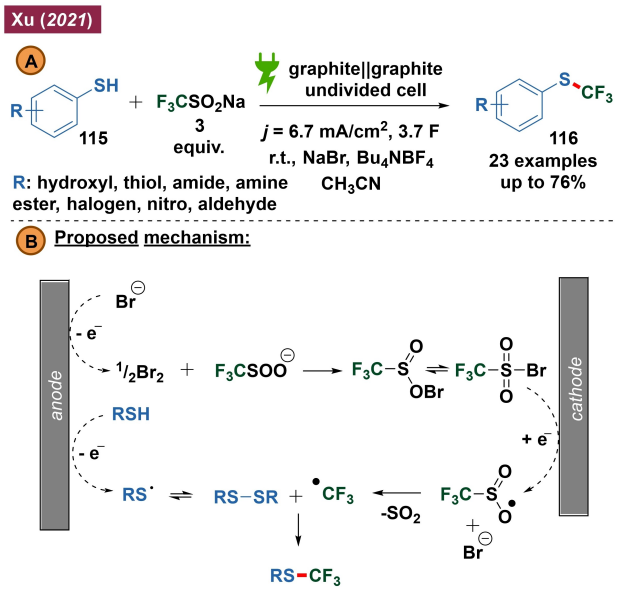
Scheme 40. (a) Electrochemical trifluoromethylation of thiophenols; (b) Proposed mechanism.

reduction, the active reducing species can be generated via SET from the trifluoromethyl-thioether radical anion.

Recently Xu and co-workers demonstrated that electrochemical trifluoromethylation of thiophenols can be achieved using a mechanism similar to Zeng's and co-workers.[67] In their approach, thiyl radicals and molecular bromine are formed at the anode. The authors claim that trifluoromethanesulfinic hypobromous anhydride, which they incorrectly named 'sulfonyl hypobromide', is formed by the reaction of molecular bromine and trifluoromethanesulfinate. While we acknowledge the equilibrium of their proposed anhydride and trifluoromethanesulfonyl bromide, the authors fail to provide any evidence for the existence of the sulfinic hypobromous anhydride or the necessity for its involvement in the reaction. In our opinion, trifluoromethanesulfonyl bromide is the more likely intermediate, formed directly by nucleophilic attack of the sulfinate on molecular bromine. Afterwards, the sulfonyl bromide is reduced at the cathode to form SO_2, bromide, and a CF_3 radical. The CF_3 radical reacts with disulfide to form the desired product **116** (Scheme 41).

6. Perfluoroalkylation

The introduction of perfluoroalkyl substituents into organic compounds is a sought-after objective in view of the applications. Most of the reactions for perfluoroalkylation described so far proceed via perfluoroalkyl radicals. The C_nF_{2n+1} radicals are produced from the parent perfluoroalkyl halides



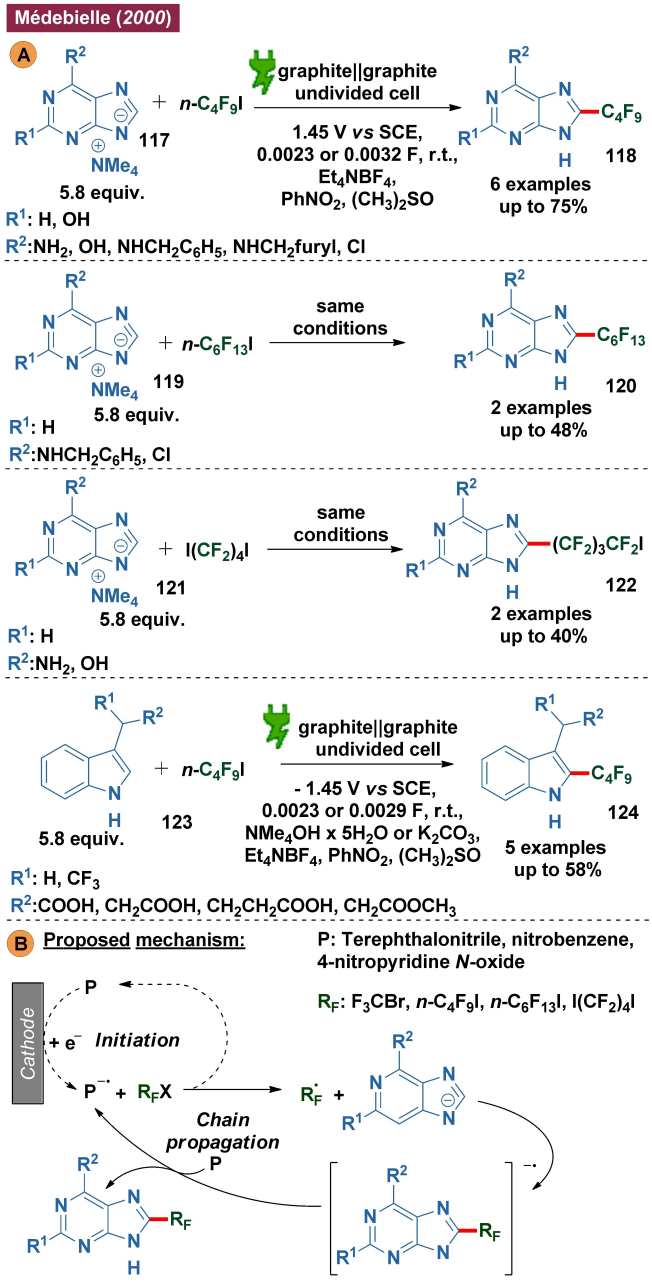
Scheme 41. (a) Electrochemical trifluoromethylation of thiophenols; (b) Proposed mechanism.

by photolysis or thermolysis.[68] Few examples for electrochemical perfluoroalkylation are reported in literature.

In 1996, Médebielle demonstrated the indirect electrochemical reduction of perfluoroalkyl halides (F_3CBr, n-C_4F_9I, n-$C_6F_{13}I$, $I(CF_2)_4I$) in the presence of imidazole, purine, pyrimidine, and indolyl anions to give perfluoroalkyl-substituted nitrogen heterocycles (**118**, **120**, **122**, and **124**).[69] This electrocatalytic method allows for one-step preparation of pharmaceutically interesting compounds (Scheme 42). The mechanism follows a $S_{RN}1$ pathway: The required perfluoroalkyl radical is generated via reduction of the corresponding perfluoroalkyl halide. The catalytic cycle is initiated by cathodic reduction of an initiator substance (**P**) to a radical anion. **P** also acts as a promoter for the catalytic cycle. Direct electrolysis of the perfluoroalkyl iodides lead to rapid passivation of the cathode (Scheme 42 B).

Budnikova et al. investigated the electrochemical perfluoroalkylation of aromatic and heteroaromatic compounds **125** with IC_6F_{13} catalyzed by $[(bpy)FeCl_3]$ or $[(bpy)FeCl_2]$ (Scheme 43A).[70] The mechanism of this reaction involves the oxidative addition of $C_6F_{13}I$ to [(bpy)Fe(II)] giving perfluoroalkylated iron complexes. Subsequently, the Fe(III) species is reduced, followed by reductive homolysis generating a perfluoroalkyl radical, that attacks the arene. Five perfluoroalkylated arenes were prepared in yields up to 83% (Scheme 43B).

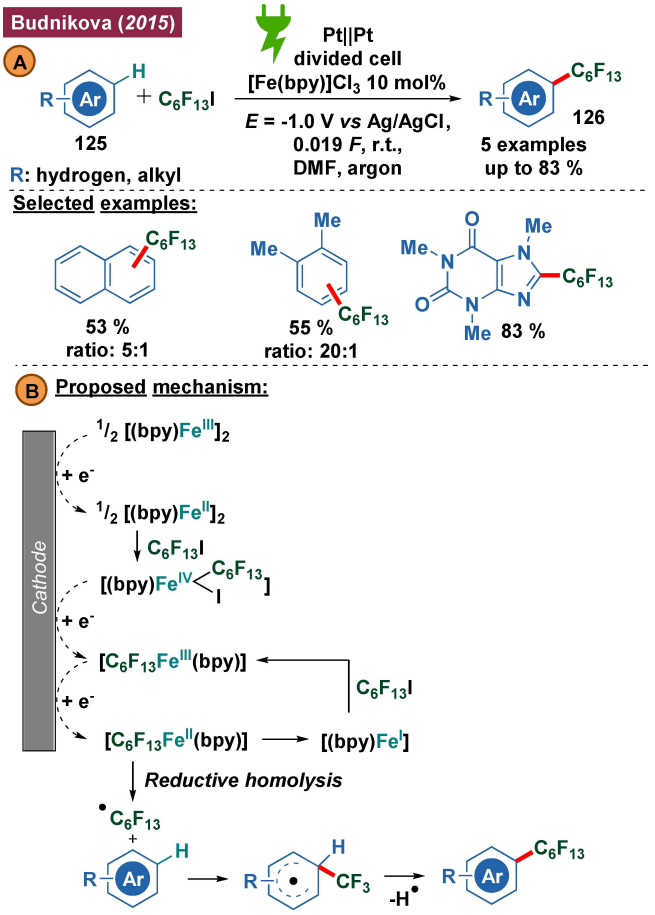
Later, Hisaeda, Ono, and co-workers used their cobalt-catalyzed photo-electrochemical approach for fluoromethylation.[59] Electron-rich (hetero)arenes **127** could be perfluoroalkylated in moderate to high yields (10–84%) (Scheme 44).



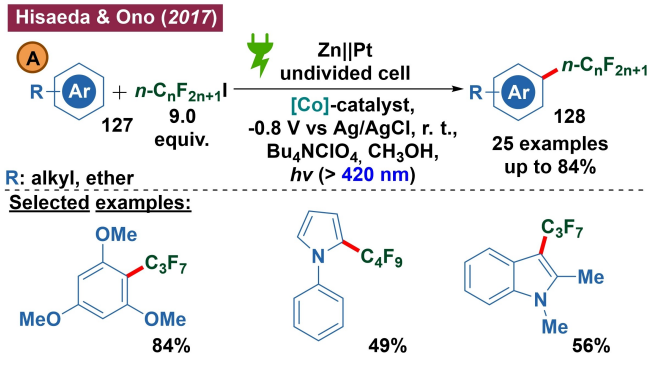
Scheme 42. (a) Electrocatalytic synthesis of perfluoroalkyl-substituted heterocycles; (b) Proposed mechanism.

7. Electrosynthetic Fluoromethylation in Flow

Electrochemical microreactors with electrodes integrated into a flow path can afford rapid and efficient electrochemical reactions due to the intrinsic properties of the flow regime. Under these conditions, the distance between the electrodes can be reduced dramatically and enable more efficient electron transfer processes.[71]

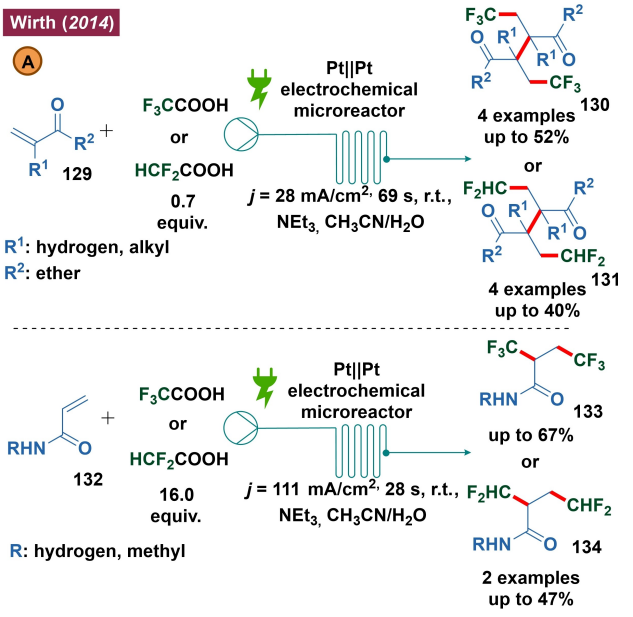


Scheme 43. (a) Electrochemical [(bpy)Fe]-catalyzed perfluoroalkylation of (hetero)arenes; (b) Proposed mechanism.



Scheme 44. Electrochemical fluoroalkylation of heteroarenes.

Taking advantage of electrochemical microreactors, Wirth and co-workers developed a continuous-flow di- and trifluoromethylation method of electron-deficient alkenes **129** through electrolysis of trifluoroacetic acid (Scheme 45). To perform this reaction, a microreactor containing a flow

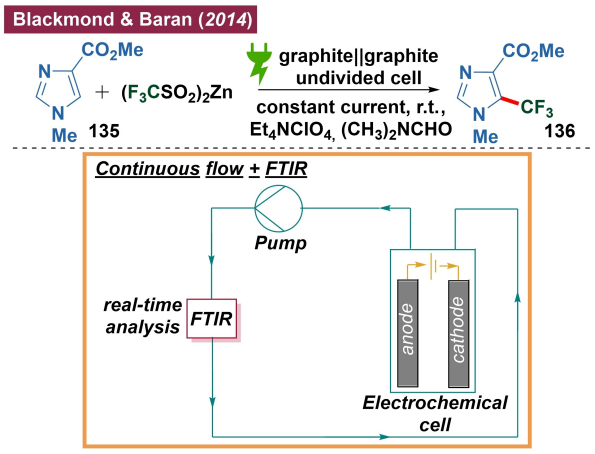


Scheme 45. (a) Trifluoromethylation/dimerization of acrylates using a continuous microreactor; (b) Bis (trifluoromethylation) of acrylamide in continuous flow.

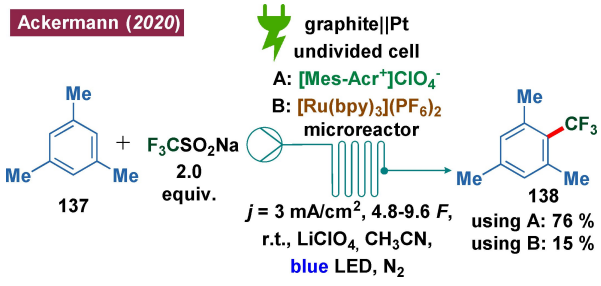
channel sandwiched with two platinum electrodes was assembled. Different acrylates were used as CF_2H and CF_3 radical acceptors within very short reaction times (69 s) under constant current reaching yields up to 52%. Later, the authors used acrylamide **132** as substrate and higher currents to obtain the desired bis(difluoromethylation) **133** and bis-(trifluoromethylation) **134** products in high chemical yield.[72]

Flow chemistry systems can be coupled to analytical tools such as NMR, FTIR, GC or HPLC for real-time monitoring of chemical reactions. In 2014, Blackmond's and Baran's groups employed this kind of approach to monitor the electrochemical trifluoromethylation of imidazole and derivatives **135** with $(F_3CSO_2)_2Zn$ (Scheme 46). The whole system consists of an FTIR flow cell and an electrochemical reaction cell with a recycle system. The reaction mixture was pumped from the electrochemical cell through the FTIR flow cell and back to the first one. The electrochemical cell was composed of carbon cloth electrodes. Monitoring the reaction in real-time provided a precise measurement of product formation when some parameters were changed, and the optimized reaction conditions could be easily obtained.[73]

Often, batch experiments are repeated using continuous flow methodologies to achieve higher yields or selectivities. Ackerman and co-workers developed a flow methodology for electrosynthetic trifluoromethylation of aromatic and hetero-aromatic compounds **137** (Scheme 47). A modular electro flow-cell followed by a looped transparent tube delivered under irradiation the desired product **138** with high efficiency in



Scheme 46. Electrochemical reactor with recycle through transmission FTIR cell to monitor the trifluoromethylation of heteroarenes.



Scheme 47. Electrophotochemical C–H trifluoromethylation in a flow setup.

yields up to 76%. This work is complementary to the study shown in section 5.2. A similar result in terms of conversion was achieved, but the reaction time was drastically shortened.[58]

8. Conclusion and Outlook

Since the end of the last century, there was a notorious evolution in the field of electrochemical fluoroalkylation. At first, trifluoroacetic acid was the most employed trifluoromethyl source. However, due to its high redox potential, over the years the electrosynthetic community has turned its attention to easier oxidizable fluoroalkyl radical sources, mostly sulfinates. This new approach broadened the scope of possible transformations and, therefore, several examples of electrochemical mono-, di- and trifluoromethylation, and perfluoroalkylation under mild conditions are described in literature. Substantial efforts have been made in this emerging field, resulting in huge advances over the last decade. The protocols present in literature allow the straightforward introduction of fluorinated alkyl groups with high selectivity and yields for a wide range of substrates, such as olefins, alkynes, aromatic and heterocyclic compounds. In addition, unusual cathodic electrochemical transformations emerge as an interesting approach for oxidation-sensitive substrates. Great advances have been made in this matter by either merging it with photocatalysis or employing mediators, allowing more feasible electrochemical procedures. Still, there are a lot of improvements to be made in this field, especially the huge excess of perfluoroalkyl radical precursors used as well as the low faradaic efficiencies need to be overcome. Interestingly, the combination of electrosynthetic fluoroalkylation and continuous-flow control generates a synergism effect that offers a valuable alternative to conventional synthesis pathways. Finally, as fluoroalkylated compounds have demonstrated their broad applicability in pharmaceutical, agrochemical, and fine chemical industries, the development of cost-effective, large-scale electrochemical protocols remains high priority and will be a challenge for the nearby future.

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