Doctoral network for microprocess engineering for electrosynthesis

DELIVERABLE REPORT

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1. Introduction

Fluorination reactions are a way for synthetic chemists to explore the structure-activity relationship of a given compound as C-H and C-F bonds are sterically similar but electronically different, which gives rise to a different bio-availability of the molecule.[1] Moreover, the integration of ^{18}F isotopes in the target compounds represents an interesting labelling agent to probe the activity of the synthetized active ingredient.[2] As fluorinated compounds are of high added-value, adding a scalable and more sustainable path to achieve fluorination to the toolbox of the organic chemist represents a goal of interest. To this day, a number of methods still rely on nucleophilic or electrophilic sources of fluorine in the form of reagents (e.g Selectfluor ®, NFSI) which can be costly or limit the overall atom efficiency of the process.[3] Recent advances in the field of photochemically driven fluorinations has allowed for milder activation methods while expanding the scope of substrates amenable.[4] More recently, with the advent of electrochemistry as an alternative activation method replacing chemical redox additives, new fluorination methods emerged.[5]

Additionally, as electrochemistry is an inherently heterogenous process, it benefits from a highly efficient mixing. Therefore, the implementation of electrochemical activations in continuous flow setups is of interest to develop efficient and scalable processes.[6] The purpose of this deliverable is therefore to answer the following question: how can an electrochemical fluorination method be designed as an atom economical, safe, scalable and robust process in continuous flow?

2. Report of attempts concerning an electrochemical fluorination methodology

2.1. Attempts to develop a novel biphasic electrochemical benzylic fluorination method

This methodology was designed taking inspiration from works from Ackermann and co-workers and Noël and co-workers.[7] Oxidation potential of benzylic positions respectively.[8] An oxidative manifold to functionalize benzylic positions of (hetero)aromatics with a wide variety of nucleophiles is a well-known reactivity.[9] However, as fluoride is a notoriously poor nucleophile, expensive fluorination agents are required in thermal/photoredox catalysis (e.g NFSI, Selectfluor) and electrochemically, to the best of our knowledge, only one precedent exists in the literature,[7b] requiring harsh conditions ($3HF{\cdot}Et_3N$) and expensive electrode material (Pt), both factors leaving little to no room for a scalable process. Therefore, a novel approach would aim to switch the fluoride source for a more affordable and sustainable one: KF (cf. Figure 1). The organic phase is to contain the starting material while the aqueous phase is to contain the KF source. This process would be highly scalable because the use of this fluoride source in aqueous HCl has been reported in segmented flow,[10] so the methodology could be easily translated from batch to continuous flow.

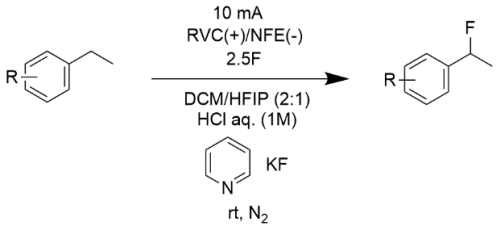

Figure 1: General scheme for an electrochemical benzylic fluorination method

For now, after attempts (8) of changing the electrode material (Platinum instead of Nickel Foam electrode) changing substrate (phenyl cyclohexane instead of 4-Biphenylethyl), degassing solvents and lowering the total amount of charges exchanged: a maximum of 9% of the desired product could be observed, the starting material remains largely untransformed.

Detailed results:

Unless otherwise stated, degassed solvents are used and the balloon of nitrogen is subsequently quenched in Na_2CO_3 sat. aq. Solution to prevent any release of HF.

In a 5 mL IKA eletrolytic cell connected to a balloon of nitrogen, Potassium fluoride (2 mmol) was dissolved in the required amount of stock solution (4 mL, 1:1 v/v DCM-HFIP-2:1/HCl_{aq} 1 M) and followed by the addition of pyridine (1.6 mmol). The solution was stirred until complete dissolution of the solids (biphasic mixture). The SM (0.4 mmol), was dissolved in the mixture. The reaction flask was equipped with an RVC anode and a Nickel Foam cathode. At room temperature, the electrolysis was carried out at a current of 10 mA for 2.5 nF (2.68 h), 500 rpm stirring.

Upon reaction termination the results were analyzed using ^{19}F NMR comparing against the literature reference value for the desired fluorine shift. The following table details the experiments conducted to investigate the usefulness of the methodology (cf. Table 1).

Experiment code	Deviation from initial conditions	^{19}FNMR yield (%)
MR152	None	0
MR153	Platinum cathode	0
MR158	No HFIP	0
MR159	Glassy carbon anode / Stainless steel cathode	0
MR161	No nitrogen, 5 mL total solution	0
MR171	Phenylcyclohexane starting material	9
MR205	Ethylbenzene	0
MR206	Ethylbenzene	0

Table 1: screening of conditions to develop an electrochemical benzylic fluorination

Work is under progress to unveil better conditions in order to be able to improve conversion and selectivity of the transformation.

2.2. Attempts to develop a novel trifluoromethylation of arenes

Trifluoromethylation of arenes represent an important transformation as this motif is present in a wide variety of drug-like molecule. A streamlined access to such moieties is then highly attractive. A recent work in the field of photo-electrosynthesis reported that oxidative decarboxylation of tri/difluoroacetic acid could and addition onto the arene could be achieved by lowering the oxidation potential of the acid through irradiation,[11] also showing that the reaction also worked only with electricity with a slightly different selectivity. Therefore, after recent works showed that rapid alternating polarity also promoted decarboxylative

generation of radicals,[12] experiments were carried out to investigate if an interesting selectivity could be obtained (cf. Figure 2).

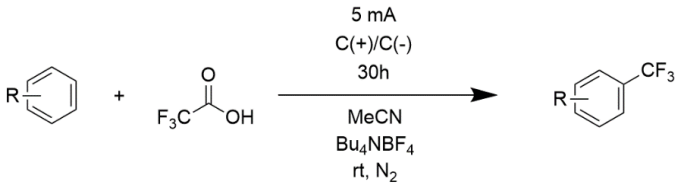

Figure 2: General scheme for an electrochemical trifluoromethylation methodology

After a few attempts (4), the starting material remains mainly untouched in these conditions, therefore the next experiments will aim at harshening the reaction conditions to push the decarboxylative addition to occur.

Detailed results

The ElectraSyn vial (10 mL volume) was charged with a magnetic stir bar, benzene (0.5 mmol, 1.0 equiv.), CF_3CO_2H (1.0 mmol, 2 equiv.), $n$$Bu_4NBF_4$ (0.5 mmol), and CH_3CN (5 mL). The graphite plate anode and graphite plate cathode were adapted on the ElectraSyn vial cap and the vial cap was screwed onto the vial tightly. A nitrogen filled balloon was adapted through the cap to bubble 1 minutes and then maintain an inert atmosphere. The vial was adapted onto the vial holder of ElectraSyn 2.0. Rapid alternating polarity electrolysis was set at 50ms (10Hz) under galvanostatic conditions (5mA), 200 rpm stirring (cf. Table 2).

Experiment code	Deviation from initial conditions	^{19}FNMR yield (%)
MR152	None	0
MR153	Constant potential rAP (3V)	0

Table 2: screening of conditions to develop an electrochemical benzylic fluorination

2.3. Trifluoromethylation from trifluoromethyl iodide

S-CF3 moieties are important motifs in bio-active molecules.[13] However their preparation mainly relies on the use of strong bases or trifluoromethylation reagents (e.g Umemoto, Togni) which limits the scalability of the process.[14] Therefore the use of trifluoromethyl iodide provides an interesting alternative as it provides an atom economical approach to trilfluoromethylation and commercial solutions of the gas are commercially available at competitive prices (cf. Figure 3).

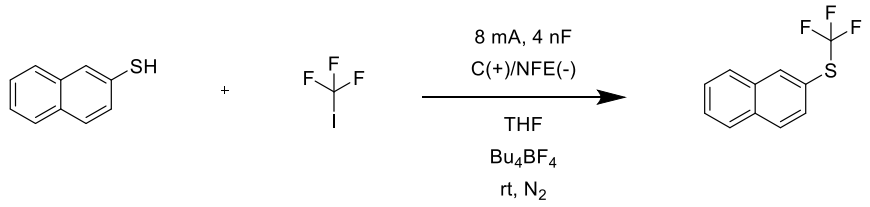

Figure 3: General scheme to achieve trifluoromethylation of thiols

Detailed results

An oven dried 5 mL electrasyn vial were loaded the thiol and supp. electrolyte. Vacuum nitrogen cycles were performed three times. Upon which 2 mL of a solution of CF_3I in THF (ca. 0.5M) and stirred until homogeneous. The electrolysis (I=8 mA) was performed at RT under a nitrogen atmosphere for 21.4 h (4 nF) (cf. Table 3).

Experiment code	Deviation from initial conditions	^{19}FNMR yield (%)
MR418	none	10
MR419	Carbon graphite anode	0
MR420	Zn anode	8
MR421	Carbon graphite anode, 1 mA	<5

Table 3: screening of conditions to develop an electrochemical trifluoromethylation of thiols

The yields remain quite low but as the cell potential is above 10V for each entry, there is a large room for optimization and attempts in continuous flow will be performed in the upcoming weeks to obtain synthetically useful yields.

3. Conclusion

In summary, the development of an electrochemical procedure to allow for a novel fluorination/trifluoromethylation remains elusive. The first methodology remained challenging due to the poor nucleophilicity of the fluoride anion, benzylic oxidation of C-H bonds is known to be straightforward electrochemically, therefore using a more nucleophilic source of fluoride would be useful but may defeat the purpose of an atom economical method. Regarding the second methodology, further attempts should be performed starting in a basic environment to allow for easier decarboxylative oxidation of the trifluoroacetic acid, as in our conditions the cell potential in galvanostatic electrolysis was very elevated. The most promising pathway to afford trifluoromethylation is, of now, starting from trifluoromethyl iodide. The selectivity of the process remains low but many optimization parameters can still be tuned, a translation to continuous flow to allow for optimal mixing is planned. Additionally, the method could be tested with difluoroiodomethane and fluoroiodomethane as their drastically different electronic properties and could allow for added value fluorinated products.

4. Outlook

The efficiency of the methods described in this report are not, as of now, synthetically useful. However, further optimization will be conducted to unveil their full potential.

5. Literature

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