

SELECTIVE ELECTROCHEMICAL FLUORINATIONS

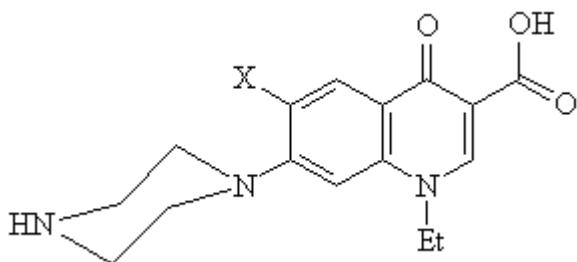
by Guillermo Daniel Zappi

New applications for fluorinated compounds are continuously being found. In areas such as agrochemicals, pharmaceuticals and fine chemicals, the enhanced activity of compounds in which one or more hydrogen atoms have been replaced by fluorine is the subject of a large body of research in universities and companies around the world. It is estimated that between 40 and 45% of all new agrochemicals being developed contain fluorine¹. The physical, chemical and biological properties of chemical compounds, including boiling points, surface energies, polarity, acidity and reactivity can be greatly altered by substitution with one or more fluorine atoms. These effects are in general result of the following facts:

- The size of fluorine is similar to that of hydrogen. Fluorine can, therefore, imitate hydrogen in enzymatic processes.
- The strength of the C-F bond leads to increased thermal stability.
- Fluorine is highly electronegative.

Striking examples of these effects can be found in the enhancement of the biological activity of pharmaceutical and agrochemical compounds brought about by the presence of a single fluorine atom in the molecule, as shown by the example below:

Table 1: Antibacterial activity of 6-Substituted 7-piperazin-1'-yl-quinolones towards E.coli²



X	Minimum Inhibitory Concentration $\mu\text{g ml}^{-1}$
H	15.6
F	1.0
Cl	4.0
Br	7.8
Me	7.8

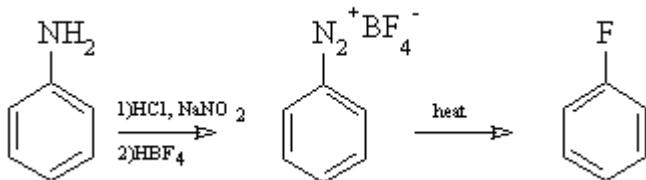
Fluoroorganic compounds: their chemical preparation

Partially fluorinated organic compounds are prepared by two different approaches: (i) by insertion of a group already containing C-F bonds into an existing molecule (the **building-block** approach), or (ii) by creating new C-F bonds by fluorination. The building-block approach makes use of the traditional methods of organic synthesis, and small molecules such as fluoroalkyl iodides and bromides and hexafluoroacetone are used mainly in the synthesis of fluoroaliphatic compounds. For the synthesis of fluoroaromatic compounds important commercial building blocks include monofluorobenzene and benzotrifluoride. Hexa- and pentafluorobenzene are also used for the synthesis of polyfluorinated compounds by nucleophilic substitution :



CF_3 is the most common fluorinated side-chain found in aromatic compounds, and its introduction is usually conducted by Friedel-Crafts alkylation or substitution by fluoride of benzotrichlorides.

The formation of new C-F bonds can be achieved with a variety of fluorinating agents such as fluorine, silver difluoride, hydrogen fluoride and halogen fluorides. For the introduction of fluorine into aromatic rings the most widely used process is the Balz-Schiemann reaction, in which aromatic NH_2 groups are replaced with fluorine via the diazonium salt:



In many cases, the use of these reagents can be highly hazardous and selectivities are low. In addition to these drawbacks, both inorganic and organic byproducts can be produced in large quantities. Despite recent advances in these synthetic techniques, the search for new technology continues.³

Enter Electrochemical Fluorinations

Electrochemistry has for almost 50 years made a significant contribution in the area of fluorination of organic compounds with the development and commercialization of the Simons⁴ process. By this route, it is possible to produce *perfluorinated* compounds (compounds in which all the hydrogen atoms are replaced by fluorine) and at the same time some functional groups are unaffected. Although in many ways analogous to complete fluorination with fluorine, in which C-C bond cleavage and rearrangements also take place to a great extent, usually with poor selectivities and yields, the electrochemical approach offers the considerable advantages of not having to handle fluorine gas and being able in many cases to conserve molecule functionality.

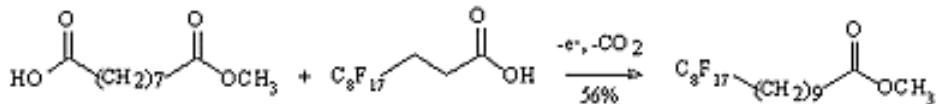
Electrochemical methods are now being used to achieve highly selective fluorinations. The examples below show some of the various electrochemical methods that can be used for the introduction of either single fluorine atoms or small fluorinated groups into organic molecules of interest. Much effort has been spent in the past three to four decades to increase the selectivity and yield of this type of reactions, and many synthetically useful results have been reported.

Fluorinated building blocks: oxidative routes

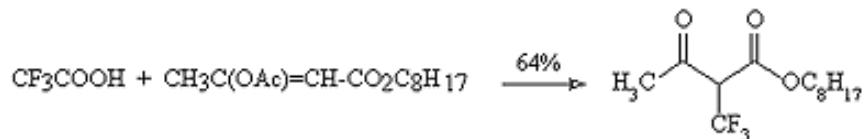
The Kolbe electrolysis is one of the best known electrosynthetic reactions; it has been studied and characterized for the last 150 years. The so-called "Kolbe products" are formed by dimerization of the radicals produced by anodic oxidation of carboxylate ions, as shown below:



where R_F is a fluorinated alkyl chain. If the carboxylate is, for example, trifluoroacetate ion, CF₃COO⁻, 93% yields of hexafluoroethane can be obtained⁵. Other examples of fluorine-substituted carboxylates include trifluoromethyl-substituted phenylacetic acid. The possibilities are numerous if "cross-coupling", i.e. Kolbe reaction between two different carboxylates, is taken into account. The example below⁶ shows how partially fluorinated esters can be obtained in this way.

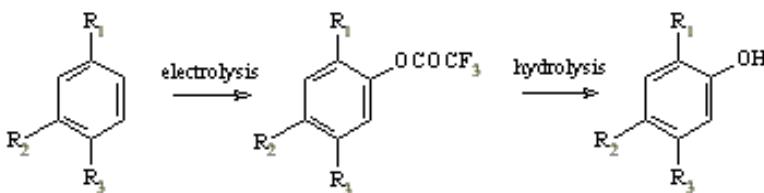


Kolbe radicals can also be added to olefins⁷:



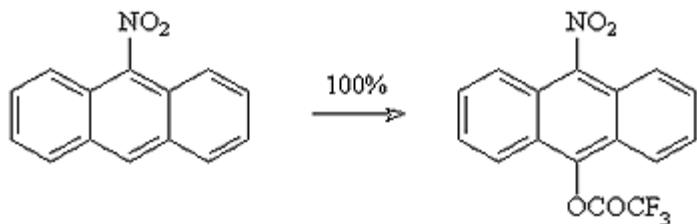
Anodic nucleophilic substitution of aromatic compounds is a well-characterized family of reactions. Typical examples include acyloxylations, alkoxylations and cyanations, among others. If the nucleophilic species is CF_3CO_2^- , fluorinated esters can be prepared in high yields. Their facile hydrolysis provides a very convenient route to a variety of phenols, as shown in Table 2. The electrolysis step was conducted in a mixture of nitromethane - trifluoroacetic acid.

Table 2: Synthesis of phenols by electrochemical trifluoroacetoxylation¹⁰.

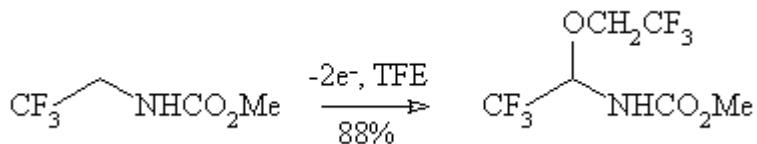


R ₁	R ₂	R ₃	Yield %
H	H	H	65
Cl	H	H	18
Cl	H	Cl	80
Cl	Cl	H	70
COCH ₃	H	H	50
COCH ₃	H	Cl	51
COCH ₃	H	CH ₃	33
CO ₂ Et	H	H	47

The equation below shows another example of a trifluoromethoxylation; it was conducted⁸ in acetonitrile - trifluoroacetic acid solution, using Bu₄NBF₄ as a supporting electrolyte:



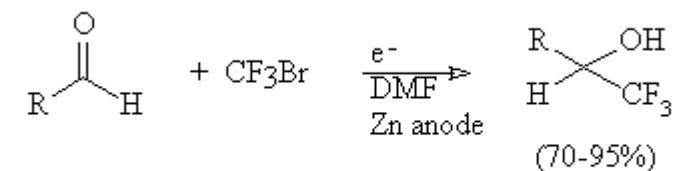
Alcohols have also been used for the synthesis of fluorinated ethers; the excellent yields obtained in the reaction shown below demonstrates that 2,2,2-trifluoroethanol (TFE) can be used as an effective medium for the introduction of the 2,2,2-trifluoroethoxy group:



These reactions take place under mild conditions⁹, in mixtures of TFE / CH₃CN.

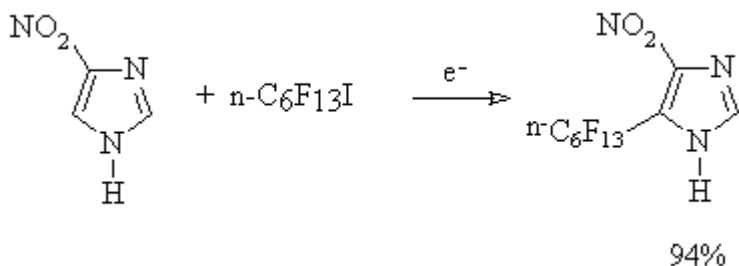
Fluorinated building blocks: reductive routes

Addition or substitution of trifluoromethyl groups into organic compounds can be achieved by direct electrochemical reduction with bromotrifluoromethane¹¹. Different types of compounds have been trifluoromethylated in this way, including carbonyl compounds, aromatic halides and olefins:

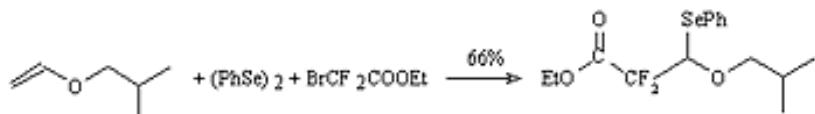


R = Ph, p-ClC₆H₄, p-PhOC₆H₄, t-Bu, n-C₆H₁₃, cyclo-C₆H₁₁

Longer fluorinated alkyl chains have also been substituted with excellent yields¹²:



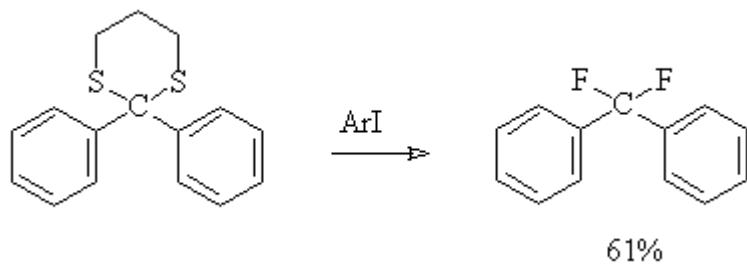
Other fluorinated groups introduced by reductive methods include -CF₂COOR; as shown below:



The reactions proceed smoothly in DMF solution, and the proposed mechanism is via cathodic reduction of (PhSe)₂ followed by electron transfer to the bromodifluoroacetate¹³.

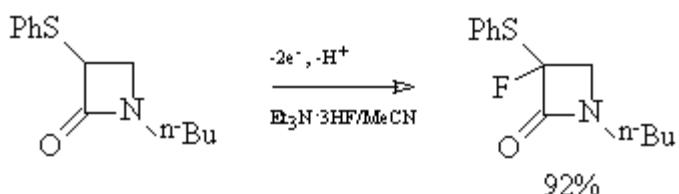
C-F bond formation: oxidative routes

The selective direct attachment of fluorine to aliphatic or aromatic carbon atoms by electrolysis has been the subject of a large amount of research. The sources of fluorine used include fluoride salts, anhydrous hydrogen fluoride and, more recently, media such as relatively low-hazard complexes Et₃N·nHF or pyridine·nHF, where n=1 to 10. These have been used as solvents either alone or in the presence of co-solvents like acetonitrile. Electrochemical reactions have been reported recently for the gem-difluorination of dithioketals in high yields. Redox mediators were used¹⁴, and the reactions were also demonstrated and scaled-up using flow-cells¹⁵:



The success of these reactions relies on the use of substituted iodobenzenes as mediators (used as stoichiometric fluorinating agents in the past¹⁶), and this new electrochemical approach offers the considerable advantage of only requiring them in catalytic amounts.

The selective α -monofluorination of aromatic sulfides bearing electron withdrawing substituents can be achieved in good yields^{17,18}:



The reactions are conducted at constant current in $(\text{CH}_3\text{CH}_2)_3\text{N}\cdot 3\text{HF}$, and the method has been extended to a large variety of organosulfur compounds. The suggested mechanism involves initial oxidation at the sulfur atom followed by loss of a proton and further oxidation. The electrophilicity of the resulting cation radical is enhanced by the presence of the electron-withdrawing group, facilitating attack by fluoride ion.

Conclusions

The reactions shown above represent only a small fraction of the research reported in the area of selective electrochemical fluorinations. Many other processes are also possible, and their feasibility must in general be determined on a case by case basis by both economic and technical considerations. The value added of the potential products is generally very high, and even in cases where improved selectivities or yields cannot be achieved by electrochemical reactions, the electrolytic routes are likely to offer intrinsically "cleaner" processes, as required by increasingly stringent environmental regulations.

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Dr. Guillermo Daniel Zappi was a Senior Scientist at the Electrosynthesis Company from 1993-2001. His research interests include electroorganic chemistry as well as a wide range of other applications of electrochemistry in synthesis. Dr. Zappi holds a Ph.D. from the University of Southampton UK and has over 10 years experience in electrochemistry.

For further information on electrochemical fluorinations or other applications of electroorganic chemistry, please call (716) 684-0513, ex. 111 or send e-mail to info@electrosynthesis.com.