SALVATORE RE

# Fluorination toolkit – From reagents to bulk chemicals*

## INTRODUCTION

The introduction of fluorine into fine chemicals has a long distinguished history. Fluorine has been incorporated directly, selectively, as well as via fluorochemical intermediate "building blocks". The high electronegativity and relatively small size make it useful in a variety of fine chemical applications. Molecules containing C-F bonds have been designed for major pharma applications including anaesthetics, anti cancer, antidepressants, anti malarials, antifungals and steroids. Commercial agrochemicals, include insecticides, herbicides and formicides. Other areas of interest include liquid crystals, battery materials and flame retardants. However, as many synthetic chemists have found over the decades, fluorine is extremely difficult and dangerous to work with. Elemental fluorine is extremely reactive, corrosive and difficult to control; in fluorination using hydrofluoric acid the hazards are self evident.

In today's fine chemical industry, there is a clear trend to focus increasingly on core skills, whilst outsourcing key stages of the manufacturing to process specialists. This has been the driving force behind the holistic approach to fluorination developed by Daikin, and supported by key technology expertise and a growing body of intellectual property.

The basic philosophy is rather simple.

1. **Discovery** – Understanding that in the discovery phase molecular structures are highly confidential, a range of fluorinating agents have been developed. These are safe and give consistent and reliable results, with a high level of selectivity.

This rather exotic chemistry is of course rather expensive.

2. **Scale Up and Bulk** – Daikin chemists can easily identify effective methods of manufacturing target compounds in bulk using well established standard fluorination methods, practiced by Daikin for decades, or newer patented technologies. In all cases the cost of this bulk fluorination is significantly lower than that of the more exotic fluorinating agents.
3. **In House Manufacture** – For those who prefer to keep their process in house, a limited range of fluorinating agents is available in bulk safe, bulk handling.

## DISCOVERY WITH FLUORINATING AGENTS

The most commonly used Daikin fluorinating agent is the

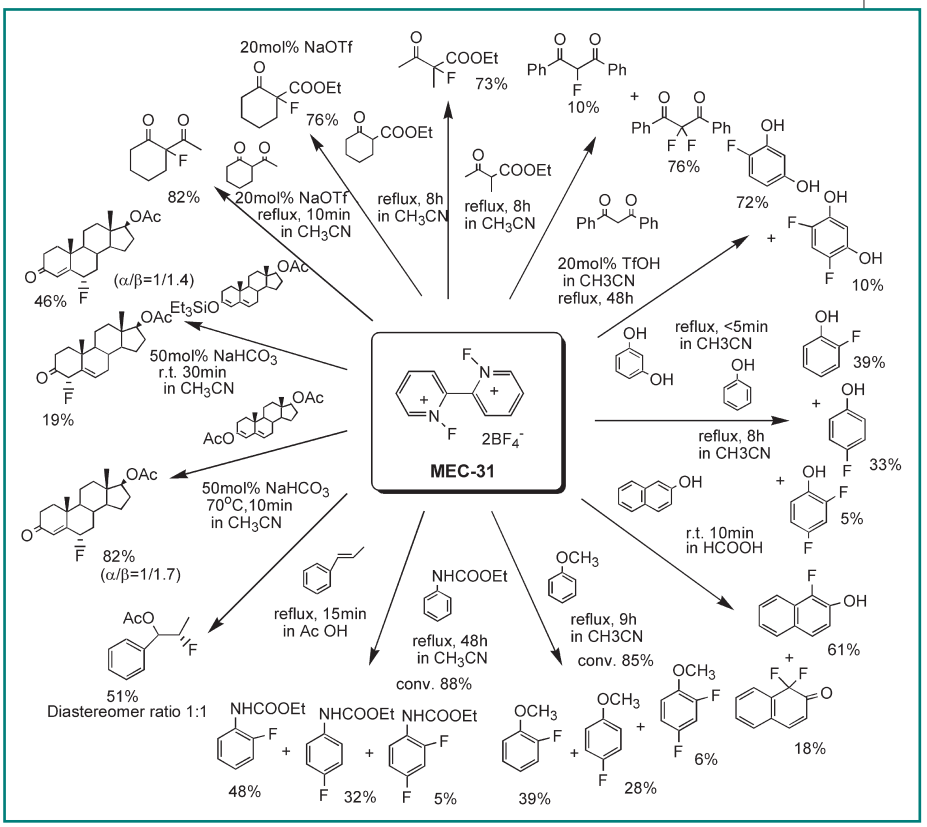


Figure 1 – Electrophillic fluorination using MEC-31

* Based on original work compiled by Kenji Adachi, Daikin Industries Ltd, Japan

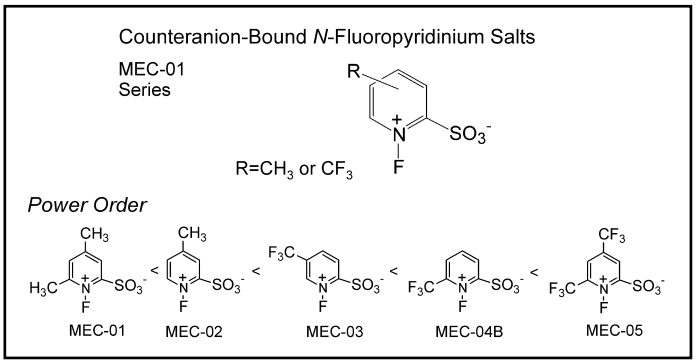


Figure 2 – Relative fluorinating of MEC reagents

salts shown in Figure 2.
The main practical difference between these reagents is their reactivity with MEC-31 in the middle of the range. Clearly this reactivity of the reagent and substrate is one of the major factors to be considered in the selection of the grade. MEC-01 in particular displays high regio-selectivity.
In the fluorination of phenol, N-fluoropyridinium salt gave the mixture of ortho and para

electrophilic agent, MEC-31. Figure 1 shows the structure and several examples of fluorination reactions achievable using MEC-31.
You can see tat MEC-31 has two N-fluoropyridinium salts combined at the ortho position, making a highly reactive compound. It has also the highest effective fluorine in it's class (103 g/kg) almost double that of the most commonly used electrophilic fluorinating agents. As we will see later, MEC-31 is also available in bulk.
The fluorination examples shown include 1,3-dicarbonyl compounds, phenol derivatives, activated aromatic compounds such as anisole and phenylurethane, olefin and conjugated enol ethers.
The electrophilic range of the MEC series is completed by four other counterionbound N-fluoropyridinium

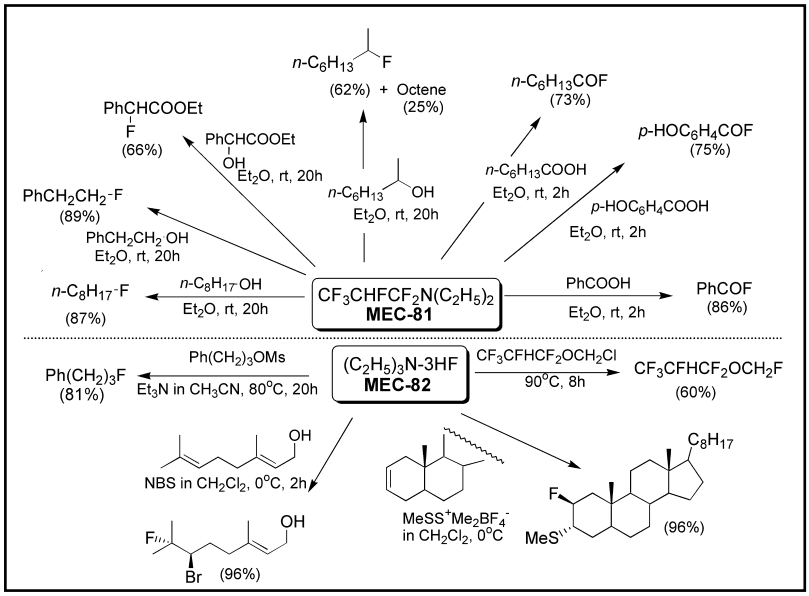


Figure 4 – Nucleophillic fluorination using MEC-81 and 82

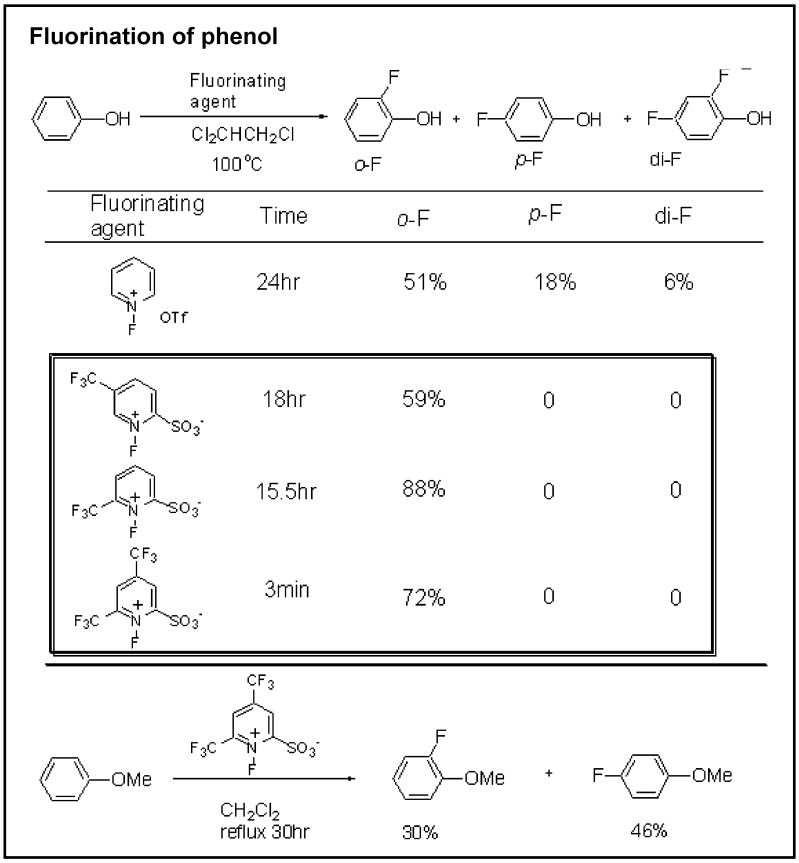


Figure 3 – Selective fluorination of phenol and anisole using different MEC reagents

fluorophenol and difluorophenol, as illustrated in Figure 3.
However, these counteranion-bound MEC fluorinating reagents gave the ortho-isomer only. Para-fluorophenol was not detected. The reaction time attributes to the reactivity of fluorinating reagents.
In the case of fluorination of anisole, such an ortho-selectivity wasn't found. The mixture of ortho and para fluoroanisole was generated at this ratio.
This exclusive ortho fluorination can be explained by the formation of π-complex fixed by hydrogen bonding between the OH and the bound $SO_3$ anion, so that the N-F part is situated near the ortho-position during the reaction.
Similarly, phenylurethane was fluorinated selectively at ortho-position to give the ortho-fluorophenylurethane mainly with counteranion-bound MEC fluorinating reagents.
MEC-81 and MEC-82 are well-known reagents as nucleophilic fluorinating reagent.
MEC-81 is able to substitute the hydroxyl group with fluorine under mild conditions in the same way as diethylaminosulfur trifluoride (DAST).
MEC-82 is triethylamine-3HF salt and is easy to handle as a source of HF.

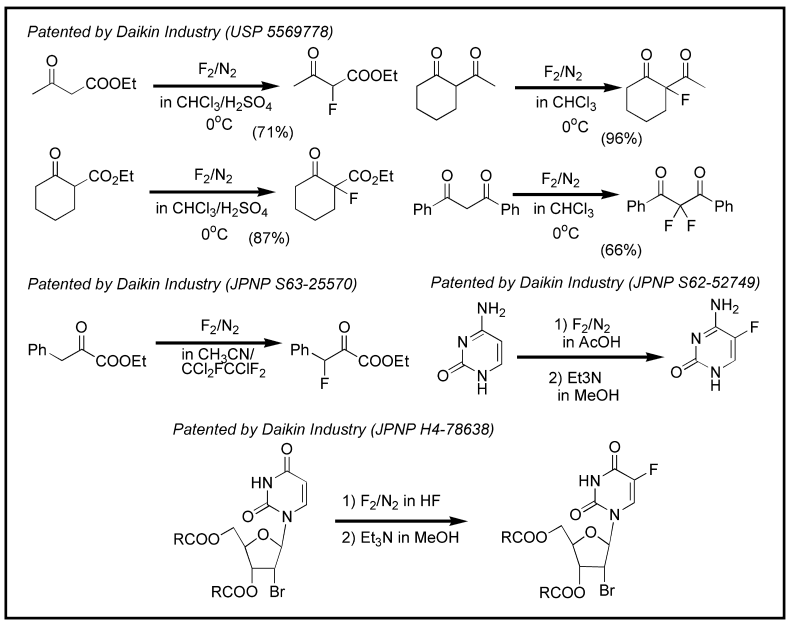


Figure 5

Reaction examples are shown in Figure 4.
In some cases it was found that the combination of MEC-81 and MEC-82 improves the selectivity and yield of the substitution of hydroxyl group to fluorine.

## BULK FLUORINATION

Direct fluorination by fluorine gas is one of the most cost effective methods, for those who are able to control this savage element.
Examples of patented fluorinations are shown in Figure 5.
Note especially that the direct fluorination of 1,3-dicarbonyl compounds gave the various 2-fluoro-1,3-dicarbonyl compounds in high yield. These 2-fluoro-1,3-dicarbonyl compounds are the key intermediates for the synthesis of many useful heterocyclic compounds as shown in this figure.
The same molecules can also be synthesized on a lab or bulk scale using MEC-31 as shown in Figure 6.
An exciting new development is in the use of $IF_5/Et_3N$-3HF complex for bulk fluorination. Iodine pentafluoride has been rarely used in the fluorination of ordinary organic compounds until recently because of the difficulty in controlling its reactivity. However, professor Yoneda discovered that the combination of $IF_5$ and $Et_3N$-3HF salt significantly becomes a unique and versatile fluorinating reagents for ordinary organic compounds.
The amazing point of this reagent is that the fluorination occurs at both nucleophilic and electrophilic sites, as shown in Figure 7.
These examples are nucleophilic fluorination as those with DAST or $SF_4$.

In fluorination at electrophilic position, this $IF_5$ complex is able to substitute hydrogen to fluorine. Especially, the industrial production of this kind of compound, $-COCF_2S-$ part was too difficult until this $IF_5$ complex was found.
The fluorination by $IF_5/Et_3N$-3HF complex at nucleophilic position will follow the same mechanism as that by DAST. They are both conventional nucleophilic fluorination reactions. The surprising result is the fluorination at the electrophilic position.
We believe that this mechanism is essentially nucleophilic fluorination as shown in Figure 8. It can be thought $IF_5$ will act as an oxidant. This figure is electrophilic fluorination by MEC-31.
The interesting point is you can get the same fluorinated compounds from the same substrate by the opposite reaction path.
Another method used frequently is the well-known versatile, fluorinating reagent, sulfur tetrafluoride,$SF_4$.
As with elemental fluorine, fluorination with $SF_4$ requires considerable expertise, as it is a highly toxic gas.
For example, the fluorination by $SF_4$ gave difluoro compounds from carbonyl compounds, and trifluoromethyl compounds from esters, carboxylic acid, carbohalide and amide, and so on.

## INTERMEDIATES – THE BUILDING BLOCK APPROACH

A long established route to incorporation of fluorochemistry is the use of fluorinated intermediates. Key intermediates in pharmaceutical, agrochemical and industry applications include hexafluoropropanol (HFP), hexafluoropropene oxide (HFPO), tetrafluorooxetane (TFO) as well a large range of fluoroalcohols and fluoroiodides, all available in bulk.

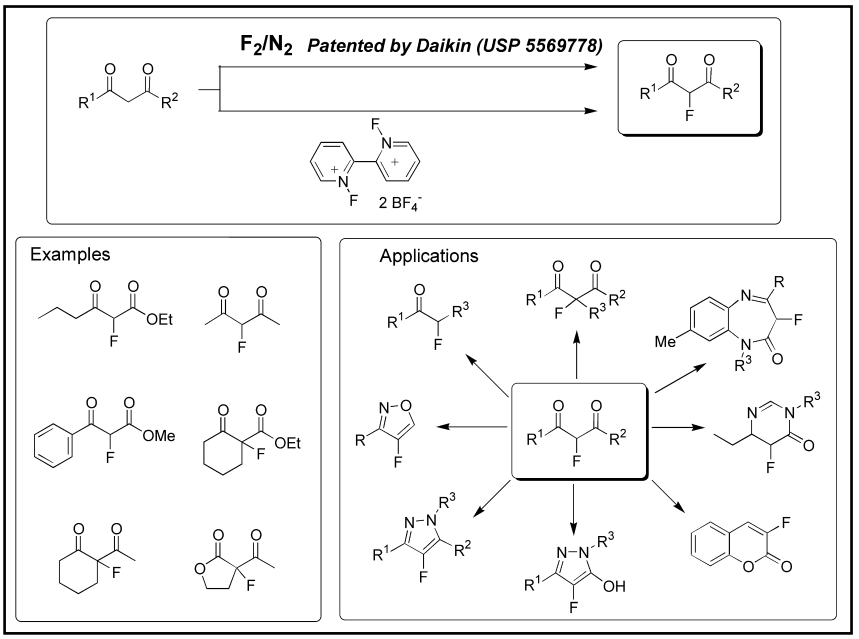


Figure 6 – Use of $F_2/N_2$ bulk fluorination

Uniquely TFO can be used to insert -$CH_2CF_2CO$- groups.
In this way difluoromalonic acid ester can be prepared form tetrafluorooxetane via oxidation and esterification. Meanwhile HFPO can be used to prepare hexafluoroacetone, which in turn is used to make pentafluoropropionic acid and key intermediates derived from it.

## CONCLUSION

Fluorination on a lab scale is now a practical and safe option using a comprehensive toolbox of fluorination reagents available to the modern chemist.
Target molecules can then be produced cost effectively in bulk,using a vast range of fluorination methods, new and traditional, and expertise developed over decades of handling fluorine.

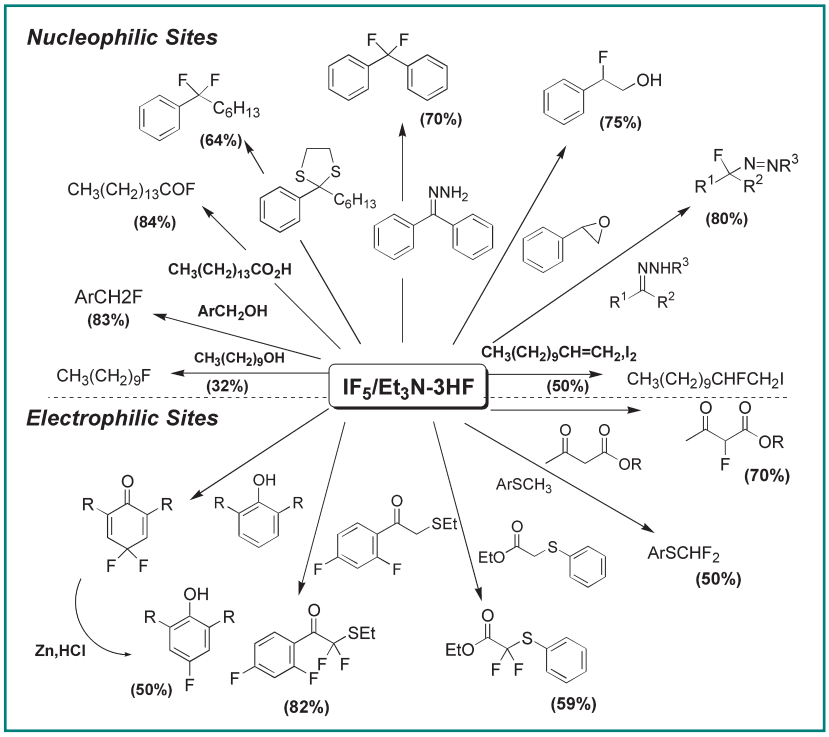


Figure 7 – Bulk fluorination with $IF_5/Et_3N$-3HF

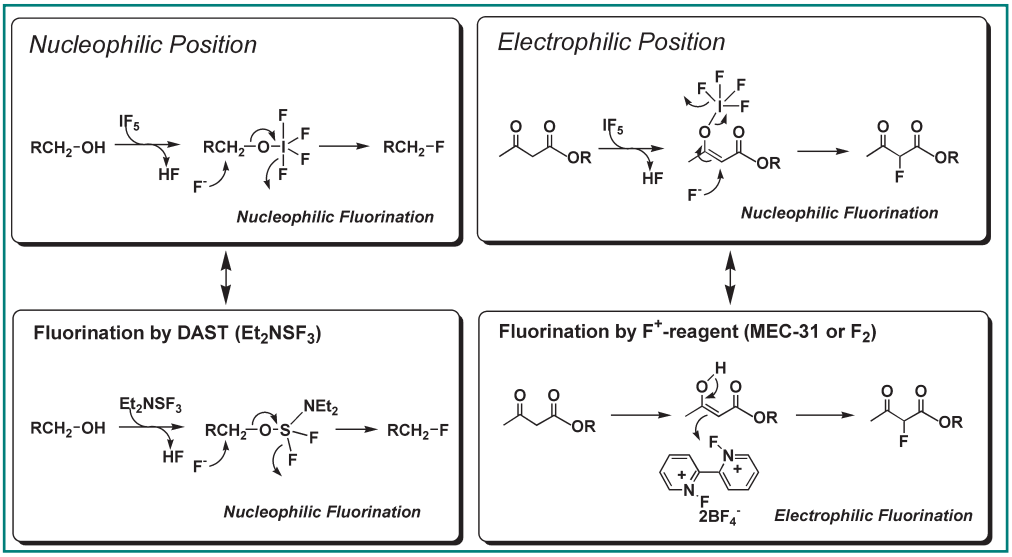


Figure 8 – Proposed fluorination mechanisms of $IF_5/Et_3N$-3HF

## REFERENCES


- T. Umemoto, M. Nagayoshi, K. Adachi, G. Tomizawa, *J. Org. Chem.*, 1998, *63*, 3379
- K. Adachi, Y. Ohira, G. Tomizawa, S. Ishihara, S. Oishi, *J. Fluorine Chem.*, 2003, *120*, 173
- T. Umemoto, G. Tomizawa, *J. Org. Chem.*, 1995, *60*, 6563
- Takaoka, A.; Iwakiri, H.; Ishikawa, N., *Bull. Chem. Soc. Jpn.*, 1979, *52*, 3377
- M.A. McClinton, *Aldrichimica Acta*, 1995, *28*, 31.; O.A. Mascaretti, *Aldrichimica Acta*, 1993, *26*, 47
- S.T. Purrington, B.S. Kagan, T.B. Patrick, *Chem. Rev.*, 1986, *86*, 997
- B. Baasner, "*Houben-Weyl, Organo-Fluorine Compounds*", 2000, 159, Thieme
- Japan Registration Number: 3220986 (Daikin Industries, LTD.)
- Carl L. Bumgardner, Joseph C. Sloop, *J. Fluorine Chem.*, 1992, *56*, 141
- N. Yoneda, T. Fukuhara, *Chem.Lett.*, 2001, 222
- S. Ayuba, N. Yoneda, T. Fukuhara, S. Hara, *Bull. Chem. Soc. Jpn.*, 2002, *75*, 1597
- G.A. Jr. Boswell, W.C. Ripka, R.M. Schribner, C.W. Tullock, "*Org. Reactions*", 1974, *21*, Chap. 1
- C-L. J. Wang, "*Org. Reactions*", 1985, *34*, Chap. 2
- B. Baasner, "Houben-Weyl, Organo-Fluorine Compounds", 2000, 321, Thieme.


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