



C-F bond formation

Organofluorine chemistry has a wide variety of applications, from the manufacture of pharmaceuticals and agrochemicals through to polymers and fuel cells. The presence of fluorine atom(s) in an API can provide beneficial effects through increased efficacy, due to for example improved metabolic stability; lipophilicity and/or improved bioavailability through changes to its pK_a .^[1] Although fluorination remains a critical technology for the pharmaceutical industry, very little is done in house – at least in process and manufacturing.^[2]

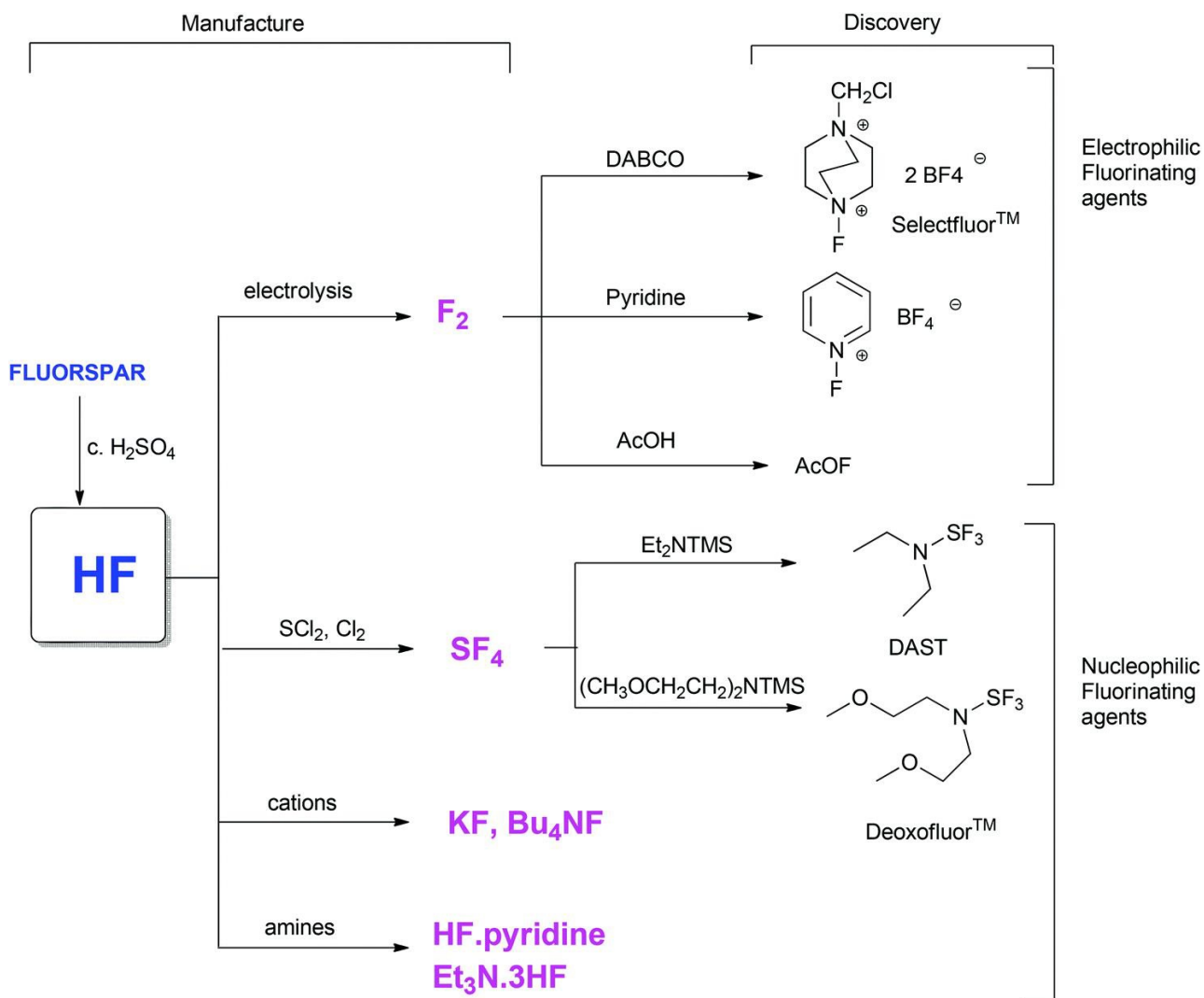
In 2015 members of the CHEM21 project, Harsanyi and Sandford, based at Durham University published a perspective for the Green Chemistry Journal on fluorine sources, applications and sustainability.^[3]

Organofluorine compounds are extremely rare in nature, and therefore the construction of carbon-fluorine bonds requires the use of synthetic fluorinating agents. The range of fluorinating agents used in chemical synthesis (see Figure 1) are ultimately all derived from the mineral fluorospar (CaF_2) which is used to make anhydrous hydrogen fluoride (aHF), (see Figure 1).^[3]

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Preparation of fluorinating agents. Reproduced from A. Harsanyi and G. Sandford, *Organofluorine chemistry: applications, sources and sustainability*, Green Chem., 2014, 17, 2081–2086. with permission from the Royal Society of Chemistry

Figure 1

There is a threat to the long term sustainability of organofluorine chemistry, as estimated reserves of fluorospar are set to last for approximately only another one hundred years. Therefore alternative sources of fluorine need to be explored. One route that has been suggested is the exploitation of a byproduct of the fertiliser industry ‘fluorosilic acid’, which is formed during the production of phosphoric acid from widely abundant phosphate rock.^[3]

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Fluorinating agents

This page reproduces content from G. Pattison, 'Green' and Sustainable Halogenation Processes, in *Green and Sustainable Medicinal Chemistry: Methods, Tools and Strategies for the 21st Century Pharmaceutical Industry*, The Royal Society of Chemistry, 2016, ch. 17, pp. 203-217..

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Fluorinating agents are, by their inherent highly reactive nature, not generally regarded as green or sustainable due to associated hazards and toxicity issues. However modern alternatives are being developed alongside safer handling techniques that facilitate safer halogenation reactions, with minimal impact on the environment.[1] Table 1 provides a summary of the main advantages and disadvantages of various fluorinating agents.[1]

Fluorinating Agent	What is it used to fluorinate?	Why is it green? Advantages	Why is it not green? Disadvantages
Elemental Fluorine	Carbonyl compounds Aromatics C-H bonds	Excellent atom economy	Highly reactive, toxic Specialist handling needed Often generate HF byproducts
HF	Halide Displacements (S_N2)	Excellent atom economy	Extremely corrosive and hazardous
Fluoride Salts (e.g. KF, CsF)	Halide Displacements (S_N2)	Safe and easy to handle Excellent atom economy Few by-products produced	Very hygroscopic but often needs to be dry for good reactivity

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Fluorinating Agent	What is it used to fluorinate?	Why is it green? Advantages	Why is it not green? Disadvantages
N-F Reagents (e.g. Selectfluor, NFSI)	Carbonyl Compounds Aromatics Alkenes Thioethers Organometallic reagents (e.g. organotin)	Safe and easy to handle Low toxicity	Derived from elemental fluorine Expensive Amine waste generated
Ruppert Reagent (CF ₃ SiMe ₃)	Carbonyl compounds (nucleophilic) Aromatics	Safe and easy to handle	Silicon-containing waste generated Expensive
Electrophilic trifluoromethylation reagents (e.g. Togni)	Carbonyl compounds (electrophilic) Aromatics Alkenes Alcohols/sulfides	Few other ways of doing many of these transformations	Iodoarene waste generated Expensive Reports of explosions
DAST / SF ₄	Alcohol → CF Carbonyl → CF ₂	Few other ways of doing many of these transformations	Corrosive Explosive byproducts at high temperatures
Fluoroform (CHF ₃)	Carbonyl compounds	Using byproduct of Teflon production which otherwise needs to be disposed of	Very potent greenhouse gas Normally incinerated producing H ₂ O, CO ₂ , HF

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Fluorinating Agent	What is it used to fluorinate?	Why is it green? Advantages	Why is it not green? Disadvantages
Trifluoroacetate Salts	Aromatics Carbonyl compounds	CO ₂ is only byproduct produced on decarboxylation	CO ₂ is greenhouse gas Produced using corrosive HF

Table 1: Advantages and disadvantages of range of fluorinating agents. Reproduced from [1] with permission from The Royal Society of Chemistry.

1. G. Pattison, '[Green' and Sustainable Halogenation Processes](#), in *Green and Sustainable Medicinal Chemistry: Methods, Tools and Strategies for the 21st Century Pharmaceutical Industry*, The Royal Society of Chemistry, 2016, ch. 17, pp. 203-217.

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Case studies

This case study was provided by [Prof. Graham Sandford](#) from the [Centre of Sustainable Processes](#) at Durham University.

Although many pharmaceutically relevant molecules contain fluoro- or trifluoromethyl-aromatic functionalities, drug development now has evolved to require chemical entities that contain fluorine functionality at unaccessible sites and thus there continues to be a demand for the development of efficient, selective and economically viable methods for fluorination on industrial scale.[\[1\]](#)[\[2\]](#)[\[3\]](#)[\[4\]](#)

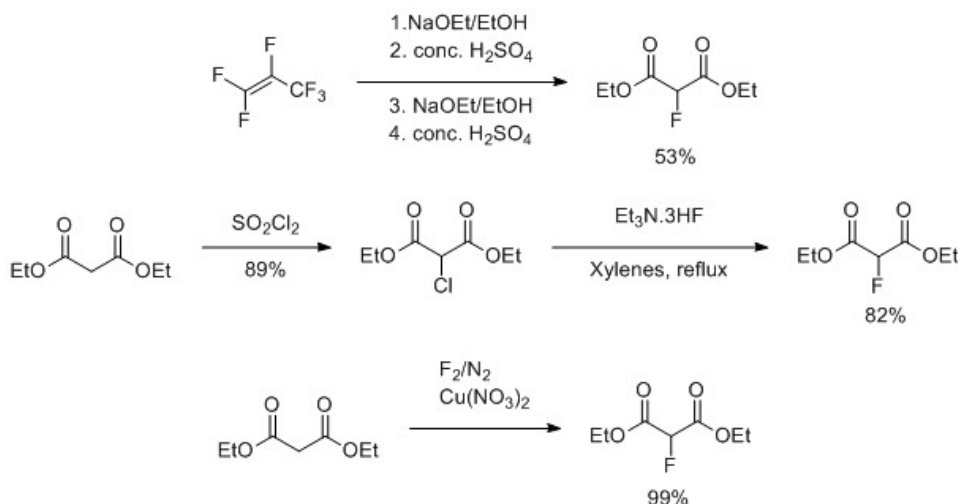
Large scale manufacture of fluorinated compounds are carried out using expensive anhydrous hydrogen fluoride (aHF). However, the highly corrosive nature of this reagent limits fluorination reactions to structurally simple organic substrates, which have to be pre-functionalised with nitro- or chloro- groups through multistep procedures.[\[5\]](#) Ideally, the most efficient and direct way of achieving fluorination on large scale would be the selective conversion of a carbon-hydrogen bond to a carbon-fluorine bond using inexpensive fluorine gas.[\[6\]](#) Despite the recent advances seen in selective fluorination methods for both batch and flow processes, the use of fluorine gas for life science product manufacture has thus far been limited to the production of 5-fluoracil[\[7\]](#) as well an intermediate in the synthesis of Voricanazole (V-Fend, Pfizer).[\[8\]](#)

2-Fluoromalonate esters represent a class of potentially versatile building blocks for the synthesis of fluorinated compounds; various alkylations,[\[9\]](#) Michael additions,[\[10\]](#)[\[11\]](#)[\[12\]](#) and heterocycle formation reactions[\[13\]](#)[\[14\]](#) have been reported for them, which gives a good indication of their utility in organic synthesis. There are three reasonable, low-cost synthetic strategies available for large scale manufacture of diethyl 2-fluoromalonate; the reaction of ethanol with hexafluoropropene (HFP),[\[15\]](#) halogen exchange (Halex)[\[16\]](#) and a selective direct fluorination process[\[17\]](#) (**Scheme 1**).

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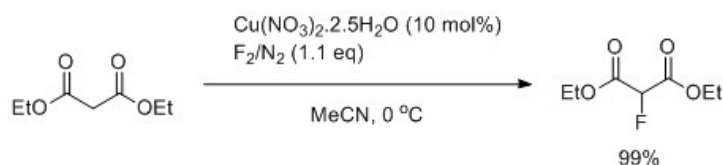
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Scheme 1: Three reasonable, low-cost synthetic strategies available for large scale manufacture of diethyl 2-fluoromalonate [5] Reproduced under license: [Creative Commons Attribution 3.0](#)

CHEM21 researchers have assessed and optimised the direct fluorination of diethyl malonate, catalysed by copper nitrate in flow, with the goal of intensifying the transformation and reducing its environmental impact. The optimised system for the selective fluorination process is shown in **Scheme 2** and was applied successfully to related malonate esters in excellent yields.[13]





















Scheme 2: Optimised copper nitrate catalysed direct fluorination of diethyl malonate [5] Reproduced under license: [Creative Commons Attribution 3.0](#)

The CHEM21 researchers went further and investigated the green metrics of the optimised direct fluorination process as well as the other two approaches shown in **Scheme 1**. The group applied [the CHEM21 metric toolkit \[18\]](#) at first pass to all three approaches, the results for which are shown in **Table 1**.

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Route	HFP method	Flag	Halex method	Flag	Cu catalyst direct fluorination	Flag
Yield	52%		77%		99%	
Atom Economy	39.1		39.0		89.9	
Reaction mass efficiency	20.6		33.0		88.6	
MI/PMI total	62.1		6.9		9.0	
MI/PMI Reaction	18.0		5.5		4.6	
MI/PMI Solvents	48.8		3.3		6.7	
MI/PMI workup	44.1		3.3		4.3	
Solvents	MeOH		Xylenes		MeCN	
	Et ₂ O				EtOAc	
Catalyst	N/A		N/A		Cu(NO ₃) ₂ ·2.5H ₂ O	
Critical Element	N/A		N/A		Cu (recoverable)	
Energy	High		High		Low	
Workup/purification	Extraction		Multiple		Extraction	
	Vac.-Distill.		Extractions			
Health and Safety	Corrosive		Corrosive		Corrosive	
	Toxic		Toxic		Toxic	
	Flammable					
Availability	Expensive		Good		good	

The resultant metrics for the direct fluorination approach shows low material intensity with a PMI value of below 10, and other green metrics for this approach compare favourably with those of the HFP and Halex method in terms of environmental impact. These results demonstrate that the new optimised direct fluorination approach serves as an excellent benchmark figure for an efficient, effective and environmentally benign approach to the synthesis of fluoromalonates.

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Summary and further reading

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