A QUICK GUIDE TO THE SYNTHESIS OF ORGANOFLUORINE COMPOUNDS

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Preamble

Approaching one million compounds containing one or more carbon-fluorine bonds are known, and since barely more than ten of those occur naturally, organofluorine chemistry is virtually a completely man-made branch of organic chemistry. Given these statistics, and the fact that none of the natural C-F compounds are isolated for utilisation, newcomers to the area will not be surprised to find that synthetic routes to a wide variety of fluoro-organic molecules have been developed, and that an impressive array of reagents exists for creating a C-F bond (the strongest single bond involving carbon, incidentally).

Basic Strategy

Two approaches are open to chemists planning routes to novel fluoro-organic targets: (**A**) purchase a starting material already containing the C-F bond(s) required (*the `building block' method)*: and (**B**) create the C-F bond(s) at a convenient stage using the most appropriate of the numerous fluorinating agents available commercially (*en-route fluorination*). Depending on the target molecule, only one of these methods may be applicable; and sometimes both may be needed, as in the following route to the inhalation anaesthetic 'Sevoflurane':

$$(CF_3)_2CHOH + (CH_3)_2SO_4/NaOH \rightarrow (CF_3)_2CHOCH_3$$

$$\rightarrow \text{(with } Cl_2/uv) \ (CF_3)_2CHOCH_2Cl$$

$$\rightarrow \text{(with KF) } (CF_3)_2CHOCH_2F$$

It becomes necessary sometimes, of course, to face up to two challenges, the synthesis of a novel or non-commercial fluorinated building block and then its conversion to the final target molecule.

Buying C-F bonds in the form of `building blocks' or synthons (strategy **A**) is much more appealing than actually making C-F bonds (strategy **B**) to experimentalists who don't specialise in fluorine chemistry because often it avoids having to manipulate hazardous fluorinating agents and/or use unfamiliar techniques or special equipment. When *en-route* fluorination (**B**) is mandatory, the C-F bond(s) are preferentially constructed at as late a stage in the synthetic route as possible; this minimizes loss of fluorinated intermediates through side-reactions, purification procedures, *etc*.

Availability of Intermediates and Reagents

Very impressive ranges of both fluoro-organic building blocks and fluorinating agents are available commercially nowadays from companies like SynQuest Laboratories. Should any intermediate (or reagent) not be listed, SynQuest's chemists will make every effort to manufacture or locate it; perhaps even your target molecule can be provided!

Examples of the Building-Block Approach

Even a cursory glance through recent tomes such as *Chemistry of Organic Fluorine Compounds II*, (editors M. Hudlicky and A.E. Pavlath; (ACS Monograph 187, 1995) and *Organofluorine Chemistry : Principles and Commercial Applications* (editors R.E. Banks, B.E. Smart and J.C. Tatlow; Plenum Press, 1994) will reveal that a vast body of information bearing on the construction of fluoro-organic target molecules from already fluorinated precursors is available. The examples displayed here in Figures 1-5 can only scratch the surface of the subject. All of the building blocks/starting material shown are available from SynQuest Laboratories.

A concise structured account of mechanistic principles which underpin the synthesis and reactions of fluoro-organic building blocks can be found in chapter 11 (`A guide to Modern Organofluorine Chemistry') in *Fluorine - The First Hundred Years, 1886-1986* (edited by R.E. Banks, D.W.A. Sharp and J.C. Tatlow; Elsevier Sequoia, 1986).

Common Selective Fluorination Methods

Important reaction types (*e.g.* C-H → C-F; C-Cl → C-F; C-OH → C-F; C=O → CF_2; C=C → CH-CF) commonly used in the laboratory for producing C-F bonds at *specific* molecular sites are presented and exemplified in Table 1. Only reagents which any competent chemist ought to be able to use safely are listed; footnotes give information about equivalent reagents which properly-equipped well-practised fluorine chemists are happy to use (*e.g* HF, F_2). All chemists working with fluorine and its compounds need to know about the hazards arising from contact with hydrogen fluoride (perhaps produced inadvertently); liquid HF (bp 19.5 ^oC), its vapour (to a lesser degree) and aqueous HF (hydrofluoric acid) can cause serious skin burns and sensible *prior* arrangements must be made for medical treatment.[1]

Information, such as the use of F_2, high-valency metal fluorides (*e.g.* CoF_3), and Simons electrochemical fluorination (ECF) for the synthesis of perfluorocarbons and their

[1]Contact SynQuest for information about dealing with HF burn treatments.

derivatives, can be found in *Chemistry of Organic Fluorine Compounds II* and *Organofluorine Chemistry : Principles and Commercial Applications* (see the section on the building-block approach to C-F compounds. `Hudlucky and Pavlath (*Chemistry of Organofluorine Compounds II*) presents a plethora of conventional synthetic uses for these synthons.

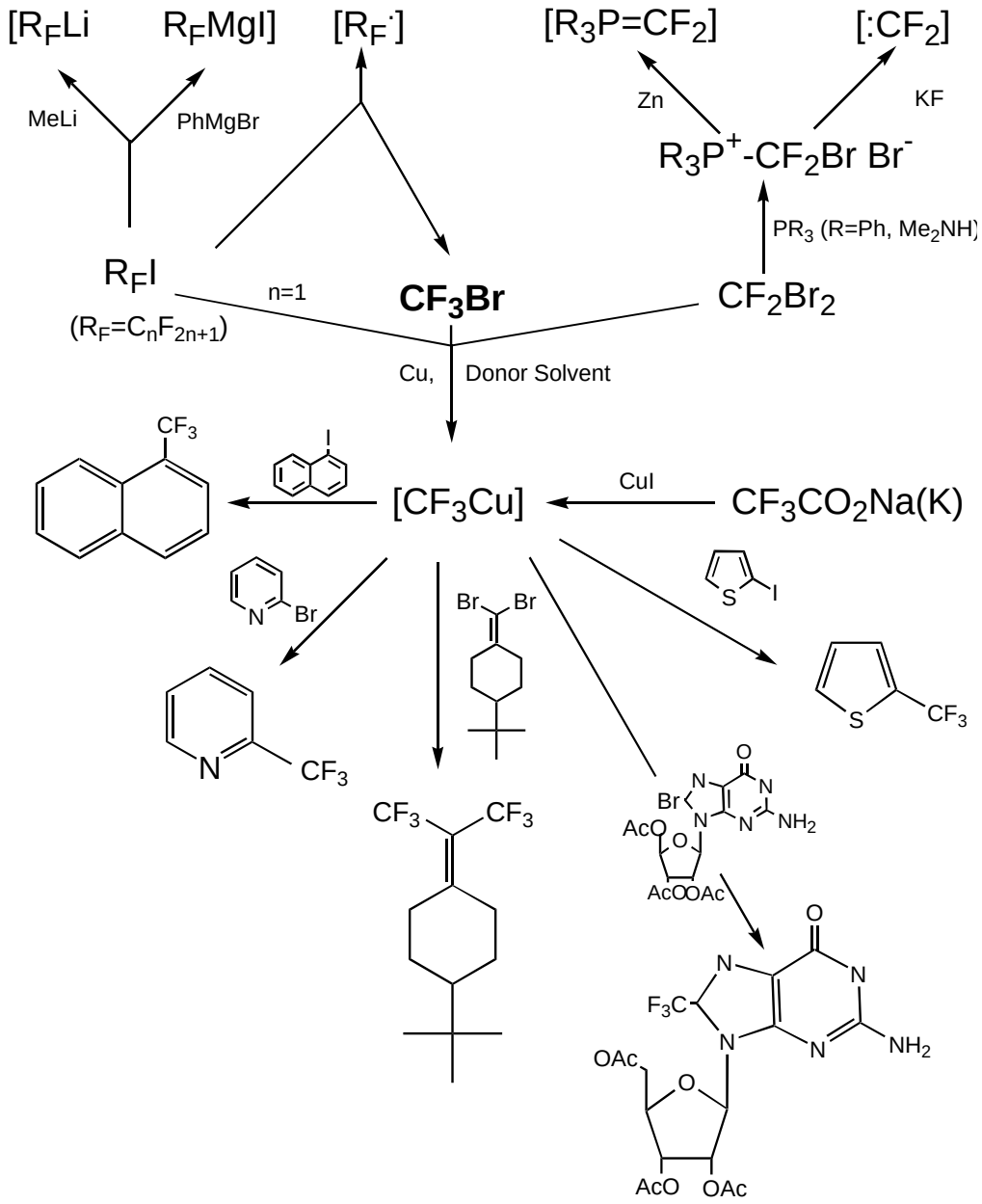

Figure 1: *Important uses for some simple perfluorinated alkyl halides*

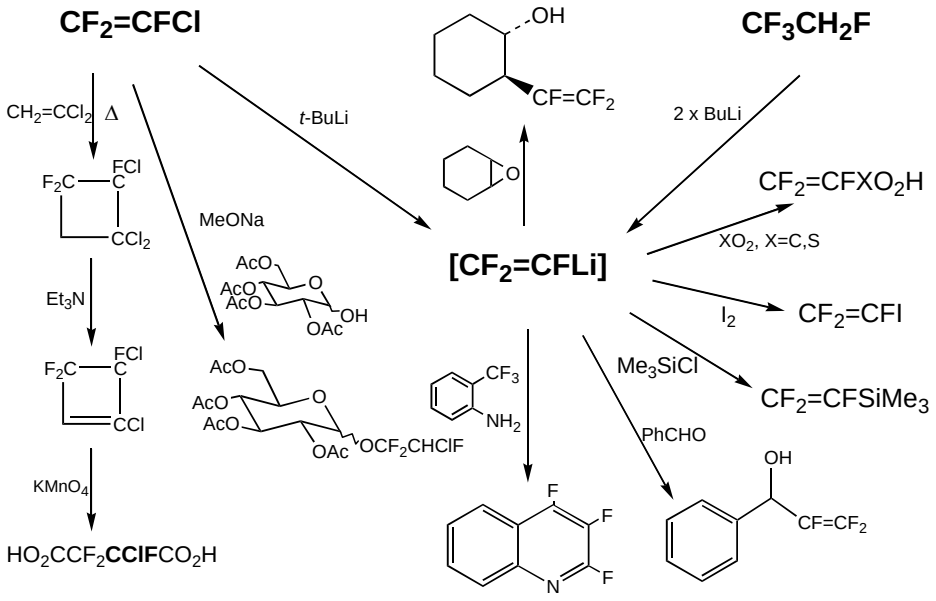

Figure 2 The `ozone friendly' CFC replacement 1,1,1,2-tetrafluoroethane (HFC-134a is proving to be a useful synthetic equivalent of the trifluorovinyl anion (J. Burdon *et.al., J.Chem.Soc., Chem.Commun.,* **1996**, 49-50; *J.Fluorine Chem*., **1997**,*85*, 151-153). Chlorotrifluoroethylene (CTFE, commercially important in fluoropolymer circles) is a well-established precursor of trifluorovinyllithium and a host of other fluorinated intermediates and target molecules.

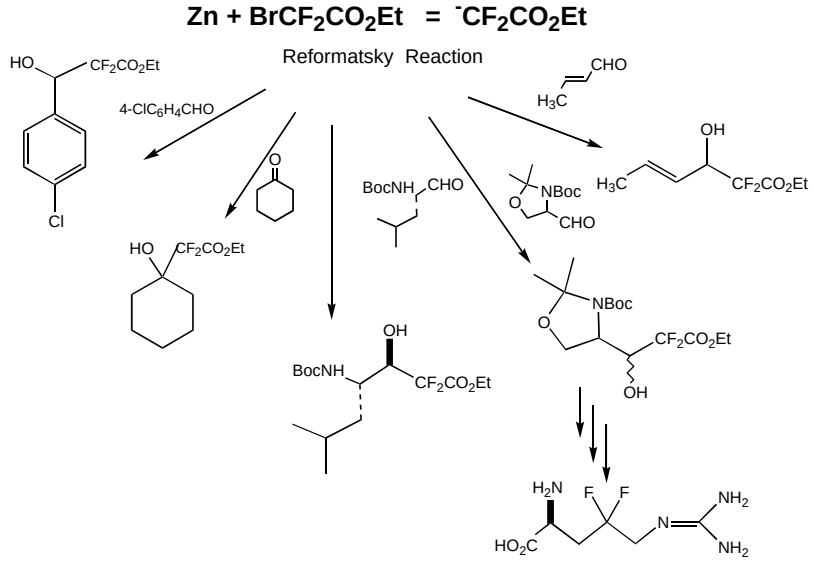

Figure 3 The Reformatsky reaction involving (most commonly) ethyl bromodifluoroacetate as a nucleophilic CF_2 synthon (synthetic equivalent) is widely used in work on difluorinated biologically active compounds (see `Methods for the Synthesis of *gem*-Difluoromethylene compounds' by M.J. Tozer and T.F. Herpin, Tetrahedron, **1996**, *52*, 8619-8683).

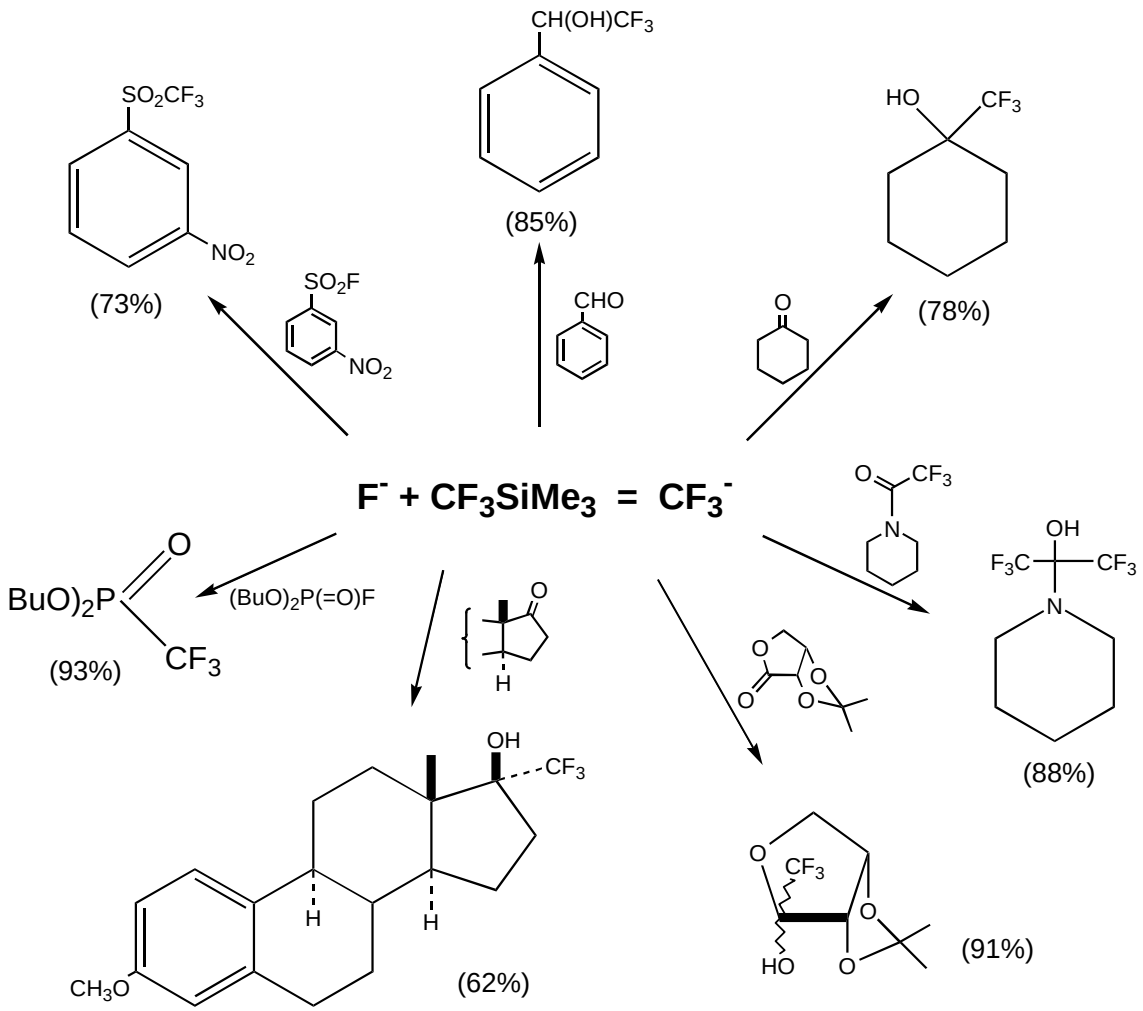

Figure 4 Examples of silicon-assisted trifluoromethylation of electrophilic substrates via fluoride-triggered "CF_3^-" transfer from (trifluoromethyl)trimethlsilane (CF_3TMS, Ruppert's Reagent). Tetrabutylammonium fluoride ($Bu_4N^+F^-$, TBAF), often in `catalytic' amounts is generally used as the F^- source. (For a recent detailed review, see G.K.S. Prakash and A.K Yudin, Chem.Rev. **1997**, *97*, 757-786)

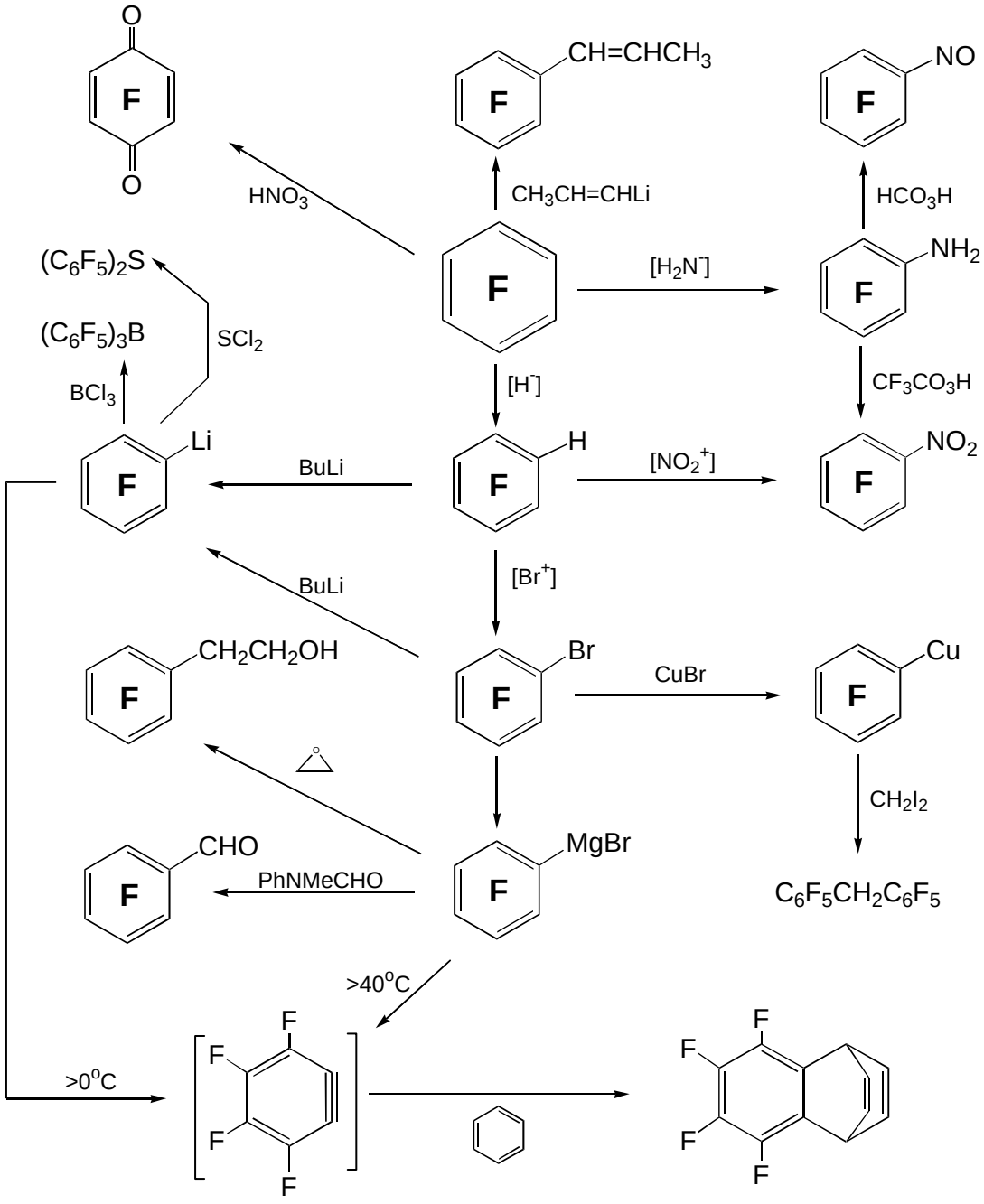

Figure 5 Hexafluorobenzene, pentafluorobenzene or bromopentafluoro-benzene, provide access to an impressive and structurally wide-ranging host of $C_6F_5^-$ derivatives, as contemplation of the reactions shown here should reveal. For a comprehensive account of the preparation and reactions of polyfluorinated aromatic and heteroaromatic compound, see G.M.Brookes' review in a recent issue of *J.Fluorine Chem*., (**1997**, *86*, 1-76)