Journal of Applied Electrochemistry **34**: 357–369, 2004.

Reviews in Applied Electrochemistry. Number 53

Current approaches to the electrochemical synthesis of organo-fluorine compounds

M. NOEL[1] and V. SURYANARAYANAN[2,*]
[1]*Central Electrochemical Research Institute, Karaikudi 630 006, India*
[2]*RSIC and Department of chemistry, Indian Institute of Technology, Chennai 600 036, India*
*(*author for correspondence, e-mail: vidhyasur@yahoo.co.in)*

Received 13 November 2002; accepted in revised form 13 May 2003

Key words: defluorinative silylation, perfluoroalkylation, selective electrofluorination, triethylamine-trishydrogen fluoride

Abstract

Recent trends in the synthesis of organo-fluorine compounds using the conventional selective electrochemical fluorination (SEF) route as well as other novel synthetic approaches are presented. In the conventional SEF route, fluorinations of the active methylene group in the side chain as well as unsaturated alkenes have been achieved. In the case of heterocycles, nuclear fluorination is the predominant process. In aromatic compounds, nuclear substitution as well as addition proceeds simultaneously, leading to the formation of a mixture of products. The influence of solvents, supporting electrolytes and adsorption on product yield and selectivity has also been evaluated in recent studies. DME is found to be a superior solvent for the above processes. In the SEF process itself, redox mediators have been employed to minimize passivation and achieve better current efficiencies. Nitrogen bases containing perfluoro alkyl unit have been synthesized using redox catalysts as mediators and trifluoromethylation was achieved by the sacrificial anode technique. The introduction of the trimethyl silyl (TMS) group into the $-CF_3$ moiety to form very reactive $-CF_2$–TMS synthon, leads to the synthesis of interesting organic molecules. A brief summary of important biologically active fluoro organic molecules that have been prepared by the electrochemical route is also provided.

1. Introduction

Electrochemical fluorination has been employed for over five decades for the synthesis of perfluorinated organic compounds at the industrial scale. Recently, selective fluorination of organic compounds has received considerable attention as a potential route for obtaining useful fluoro aromatic compounds for pharmaceutical and related applications. Fuchigami and co-workers, have presented reviews relating to all aspects of selective electrofluorination [1–3], fluorination involving sulfur containing heterocycles by direct and/or and indirect electrochemical routes [4, 5] and related electrochemical techniques applied to the synthesis of fluorinated organic substances [6, 7]. A more comprehensive review of selective fluorination with particular reference to process optimization studies and historic developments was also presented from this laboratory [8]. The different electrofluorination processes, including partial fluorination of organic substances, were also described elsewhere [9]. Since then, however, considerable activity covering newer molecules as well as novel approaches are being reported in this area. Electrofluorination involving triethylamine-*n*HF complexes as fluorine source, where *n* is greater than 3, have also been reviewed [10]. Scope for further work in this area for the manufacture of pharmaceutical intermediates and products is still thought to be quite extensive [11].

In this review, a comprehensive overview of electrochemical approaches towards the synthesis of organo fluorine compounds is presented. The overview begins with recent studies related to the selective electrochemical fluorination (SEF) of a variety of organic compounds (Section 2). This is followed by the different electrochemical routes related to the synthesis of fluoro compounds by both oxidation and reduction reactions, as well as with and without redox mediators involving interesting synthetic approaches (Section 3). Finally, a brief outline of electrochemically synthesized fluoro organic intermediates and products that have considerable application in pharmaceuticals, is presented (Section 4).

2. Recent developments in the conventional selective electrochemical fluorination (SEF) process

2.1. *Fluorination at aromatic side chain*

A detailed investigation of SEF of aromatic compounds containing active methylene groups in the side chain has

been reported in 70% Py/30% HF as solvent-supporting electrolyte. Better yields are reported for organic reactants containing electron-withdrawing groups as substituents in this medium. Inhibition of electrochemical reaction on the electrode surface, due to film formation by the polymers, has been minimized by the use of pulsed current [12]. Comparison of SEF of $PhCH_2CN$ and $PhSCH_2CN$ in CH_3CN containing triethyl amine-3HF (TEA.3HF) under different operating conditions reveals that the latter compound undergoes more facile reaction than the former, leading to the formation of —CHF— and $—CF_2—$ type compounds [13]. The important reason for the successful fluorination of sulfur containing compounds is that the sulfur atom activates the electron transfer reaction, resulting in the formation of dications by the disproportionation of cation radicals.

$$ArSCH_2 \xrightarrow{-e} [ArSCH_2R]^{+\bullet} \quad (1)$$

$$2[ArSCH_2R]^{+\bullet} \longleftrightarrow ArSCH_2R + [ArSCH_2R]^{2+} \quad (2)$$

The dication appears able first, to lose a proton and second to react efficiently with F^- leading to further oxidative fluorination to yield the desired product [14].

$$[ArSCH_2R]^{2+} \xrightarrow{-H^+} Ar\overset{+}{S}{=}CHR \longleftrightarrow ArS—\overset{+}{C}—HR \quad (3)$$

$$ArS—\overset{+}{C}—HR \xrightarrow{F^-} ArSCHFR \quad (4)$$

However, the more commonly accepted mechanism involving in the SEF of sulfur containing active methylene compounds appears to be the Pummerer mechanism [6]. Among the organo sulfur compounds containing the $—S—CH_2—$ group, those compounds, which exhibit a weak and non-inhibitive adsorption, also undergo more facile fluorination. A direct correlation, for example, was found to exist between the peak currents in cyclic voltammetry and conversion efficiencies in the electro synthesis [15].

SEF of aromatic compound containing $—CH_2—S—CN—$ as the side chain in $TEA.SHF/CH_3CN$ leads to preferential fluorination at the side chain [16] (Scheme 1).

In the case of phenyl propargyl sulfide also (the side chain is $S—CH_2—C \equiv CH$ and R = H), mono and difluorination is observed only in the side chain with DME as the solvent [17]. However, the monofluorinated product is highly unstable and can be readily converted into α-fluoro allenyl sulfide by treatment with EtOH/NaOH [17].

$$Ph—S—CHF—C{\equiv}CH \xrightarrow{EtOH/NaOH} \underset{(70\%)}{Ph—S—CF{=}C{=}CH_2} \quad (5)$$

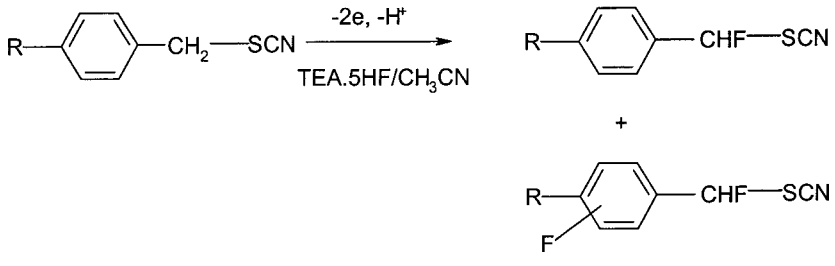
SEF of unsaturated sulfur containing carbonyl compounds such as $R^1S—CR^2{=}CH—COR^3$ undergoes addition at —CH=CH— followed by a chemical dehydrofluorination step leading to formation of α-fluoro-β-thio- α,β-unsaturated carbonyl compounds [18] (Scheme 2).

In the case of unsaturated side chain compounds without sulfur atoms fluorination, as well as acetamidation, is found to occur leading to mixture of products in CH_3CN medium [19] (Scheme 3).

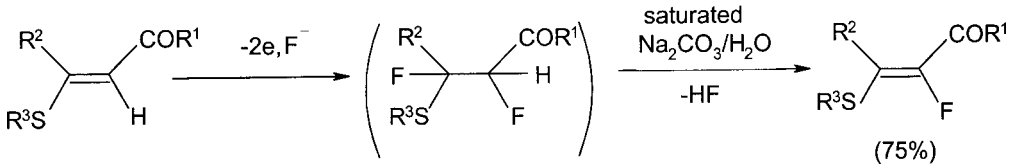
2.2. *Fluorination at the aromatic and heterocyclic ring*

Fluorination at the aromatic ring still remains a challenging problem. Some recent attempts in this direction employ solvent free tetraethylammonium fluoride-*n*HF (TEAF-*n*HF).

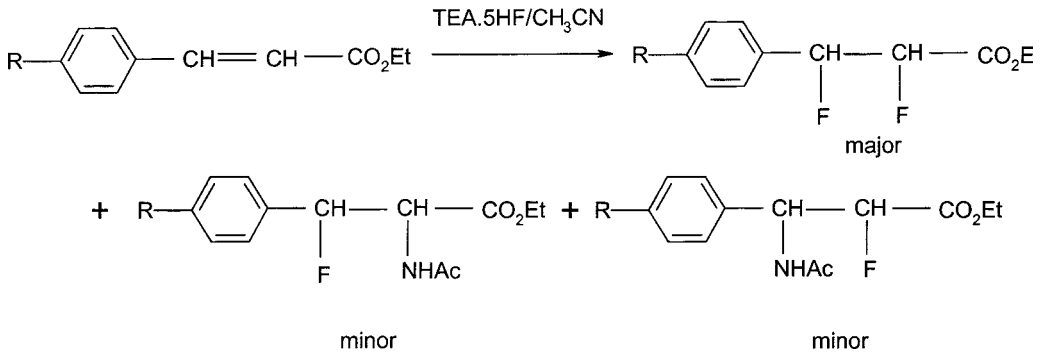
A comparative study of fluorotoluenes in the above medium indicates preferential fluorination at the side



Scheme 1.



Scheme 2.



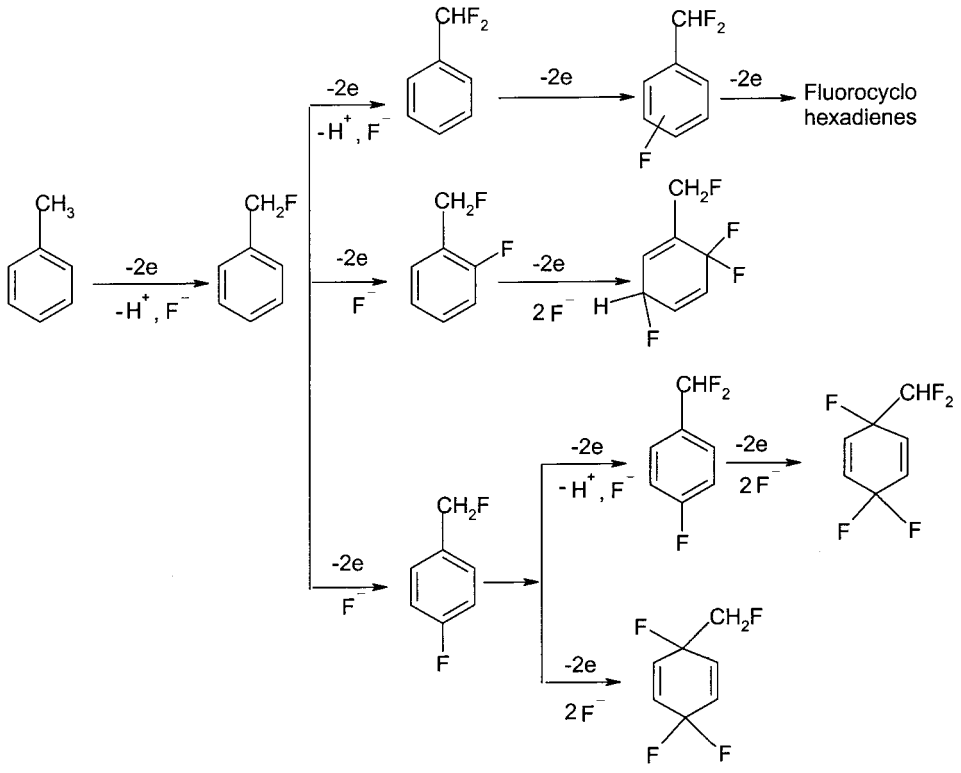
Scheme 3.

chain methyl group rather than the nuclear ring [20]. One recent study related to SEF of cumene also confirms this [21]. Similar trends are also noticed during the fluorination of monofluoro methylbenzene and difluoro methylbenzene [22]. Nuclear substitution, side chain substitution and addition products are formed as mixtures [22] (Scheme 4). An even more complicated mixture of products is formed during the fluorination of 2,6-tertiary butyl phenols [23].

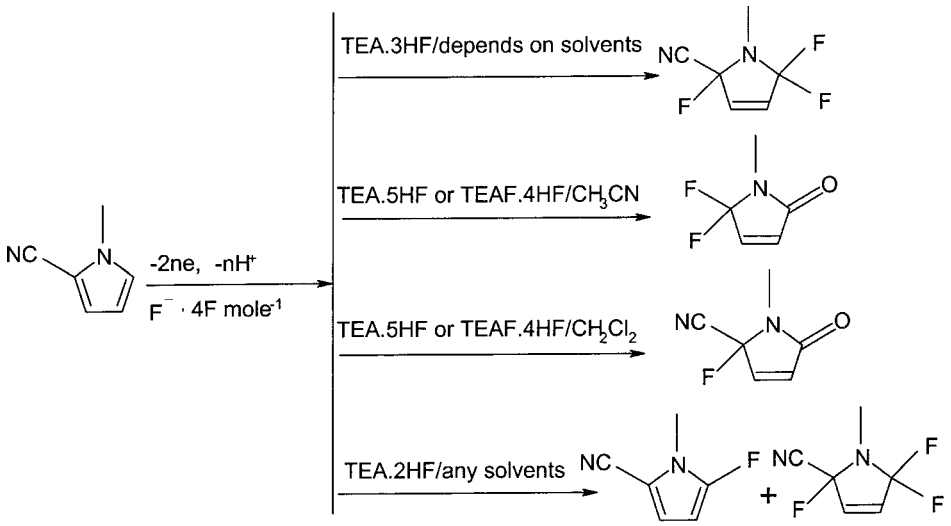
Nuclear fluorination at nitrogen containing heterocyclic appears to proceed with greater ease. In the case of substituted *N*-methyl pyrroles, for example, 2-cyano-*N*-methyl pyrrole gives 5-fluoro and 2,5,5-trifluoro-1-methyl-3-pyrrolin-2-carbonitrile in good yields. The fluoro product distribution is found to depend on the value of *n* in TEA.*n*HF as well as the solvents [24, 25]. The product distribution is described in Scheme 5. If sulfur containing a side chain moiety is present along with the *N*-heterocycle, SEF occurs preferentially at the side chain [26] (Scheme 6).

Unlike the pyridine moiety, the 4-phenyl thiazole or 4-methyl thiooxazole ring attached to the propargyl sulfide at the same position undergoes nuclear fluorination very effectively rather than the side chain [27, 28].

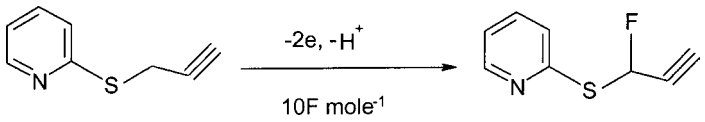
In the case of benzoxazinone, the product distribution is found to depend on whether the compound is *N*-substituted or not [29]. SEF of (E)-3-benzylidene-2,3-dihydrochroman-4-one has also been reported recently [30]. This is probably the first example of a fused oxygen containing heterocycles (Scheme 7).



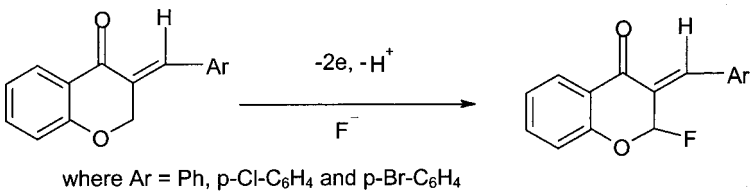
Scheme 4.



Scheme 5.



Scheme 6.



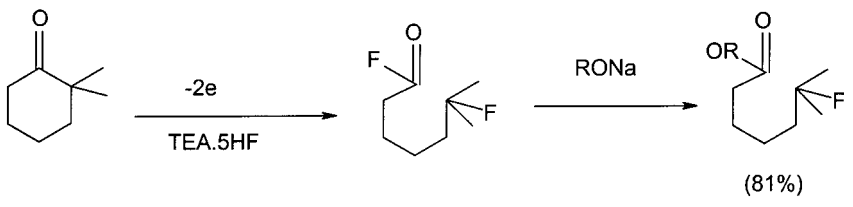
Scheme 7.

2.3. *Effect of supporting electrolytes and solvents and SEF of solvents*

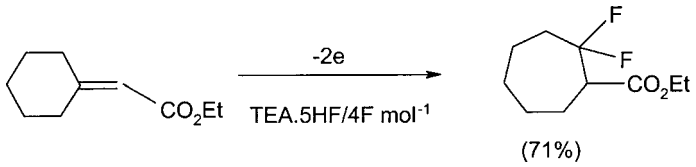
Tetraethylammonium fluoride.*n*HF (TEAF · *n*HF) has been conventionally employed as supporting electrolyte for SEF. The ease of availability of F^- as the fluoride source has confined this compound as the supporting electrolyte of choice in recent years. Fuchigami and co-workers, in a series of comparative studies, have shown that TEAF.*n*HF is a better supporting electrolyte when compared to TEA.3HF for a variety of sulfur containing compounds and aromatic heterocycles [31–33].

Yoneda and co-workers have studied electrochemical fluorination employing TEA.5HF. In the case of cyclic ketones with dimethyl substitution at the α-position, selective α-bond cleavage between the carbonyl carbon and the substituted α-carbon occurred to give fluoroacyl fluorides which are readily converted, in the presence of sodium ethoxide, to the corresponding fluorocarboxylic acid esters in good yields [34] (Scheme 8).

In the case of aldehydes, acyl fluorides are formed [35]. Cycloalkylidenes under this condition, in the presence of trifluoro ethyl acetate, exhibit ring expansion along with fluorination [36] (Scheme 9).



Scheme 8.



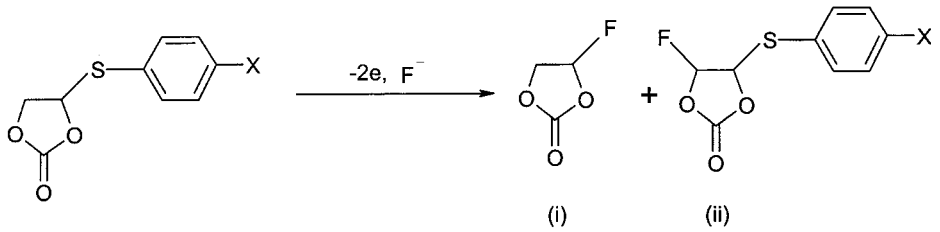
Scheme 9.

The influence of solvent on product selectivity has also been studied in recent times. Fuchigami and co-workers have found DME as a better solvent when compared to CH_3CN for the SEF of organic compounds such as benzofuranone, as well as benzothiazole derivatives [37], naphthalene and pyridine acetates [38], ethyl-α-(2-pyrimidylthio acetate) [39], α-(2-benzoxalylthio)acetates [40], *N*-benzoyl thiazolidine [41] and 2H-l,4-pyrido[3,2-b]-l,4-oxazin-3(4H)-one derivatives [42]. However, during the α-fluorination of 1,3-oxazolidines, the yield of fluoro compound is higher in CH_3CN than in DME [43]. Other solvents such as sulfolane and tetrahydrofuran (THF) are also found to be better for efficient selective electrochemical fluorination processes [44]. 4-Arylthio-l,3-dioxolan-2-one undergoes only the α-fluorination in DME leading to the formation of 4-fiuoro-l,3-dioxalone (i) (fluoroethylene carbonate, an important solvent used in Li ion batteries) as well as 4-fluoro-4-arylthio-1,3-dioxolan-2-one (ii) whereas in CH_2Cl_2, desulfurization occurs leading to the formation of the former compound [45, 46] (Scheme 10). This shows that further investigations are necessary to understand the dependence of the solvent employed on the product distribution and the yield during SEF.

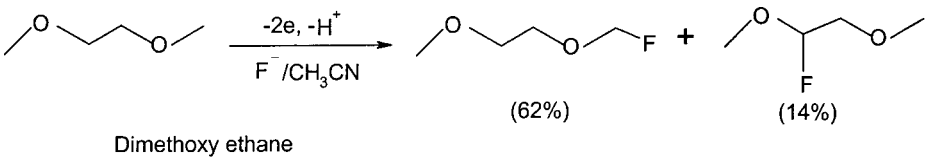
SEF of conventional solvents itself have also been attempted. For example, dimethoxy ethane undergoes fluorination at the methyl group as well as the methylene group (Scheme 11) whereas with diethylene glycol dimethyl ether, it results only at the methyl group leading to the formation of monofluoro methyl ethers [47] (Scheme 12).

On the other hand, anodic fluorination of crown ethers results in carbon–carbon bond cleavage, leading to ω,ω-difluoro product [47] (Scheme 13).

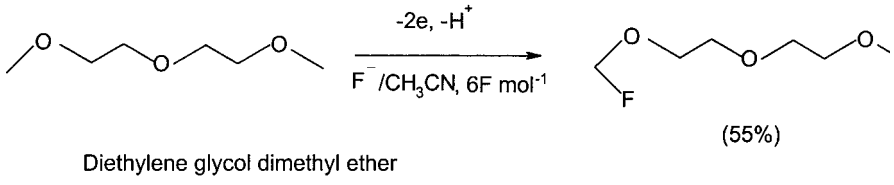
Similarly, other solvents such as tetrahydrofuran (THF), 1,3-dioxolane and 1,4 dioxane can also undergo SEF in TEAF.4HF under solvent free conditions to give the corresponding monofluoro product [48].



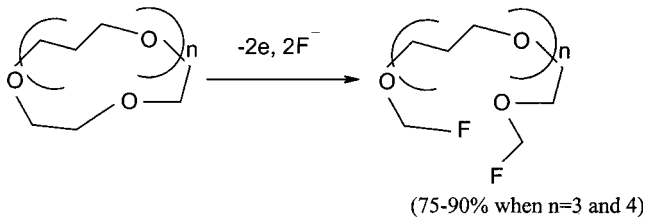
Scheme 10.



Scheme 11



Scheme 12.



Scheme 13.

As well as the above work in the conventional SEF process, organo metallic compounds are also receiving some attention. A considerable difference in the product

$$Ph_3Sb \xrightarrow{0.6\,M\ TEA.3HF/CH_3CN} Ph_3SbF_2\ (90\%) \quad (6)$$

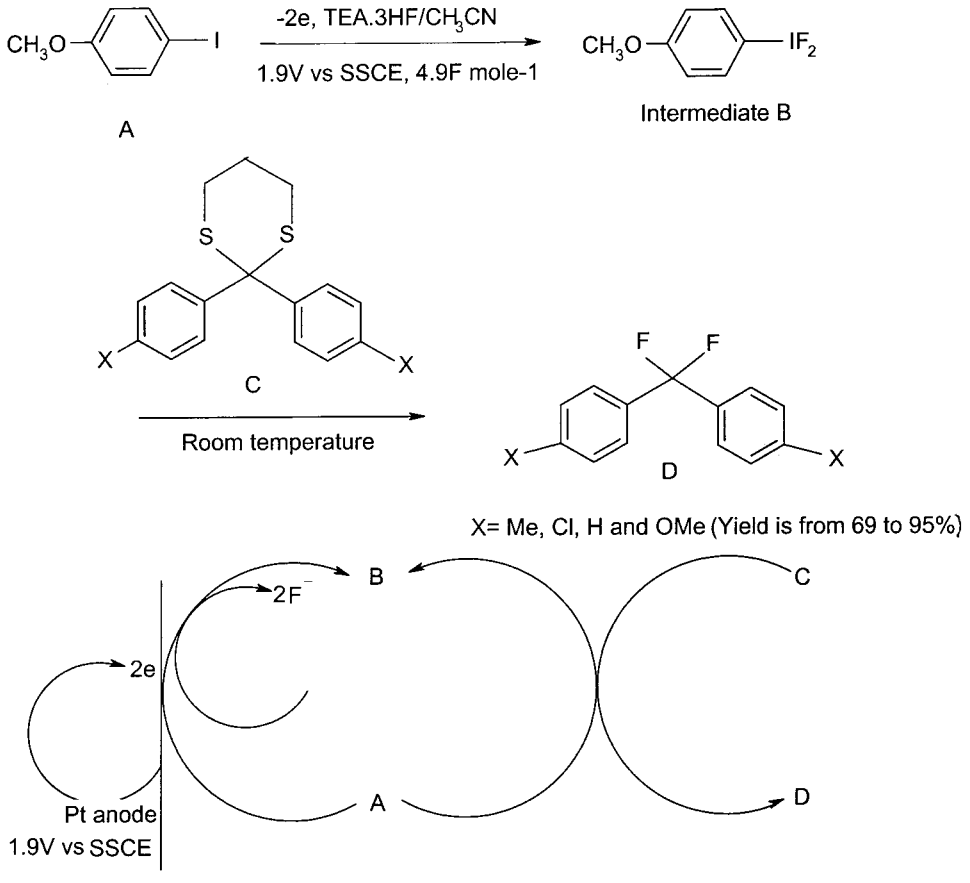
$$Ph_3Bi \xrightarrow{0.6\,M\ TEA.3HF/CH_3CN} PhNhCOCH_3 + Ph{-}Ph \quad (7)$$

pattern is noticed when Ph_3Sb and Ph_3Bi are oxidized under identical conditions. Ph_3Sb in the presence of 0.6 M TEA.3HF/CH_3CN gives the difluoro product, Ph_3SbF_2, whereas only carbon–bismuth bond cleavage products such as acetanilide and biphenyl are detected for Ph_3Bi [49].

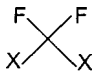
3. Other novel electrochemical strategies for the synthesis of organo-fluorine compounds

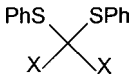
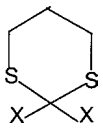
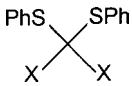
3.1. *Indirect gem-difluorination*

Apart from the conventional SEF route described above, a number of other attempts are being made to synthesize organo-fluorine compounds with greater efficiency. For example, in some SEF processes, the required applied potentials are very high, due to severe passivation of the anode. Therefore, an extremely large excess of electricity is required to complete the electrolysis, resulting in low current efficiencies. In order to avoid this, mediated synthesis of fluoro compounds has been employed. In the oxidative method, an easily oxidizable species has been electrochemically fluorinated in TEA.3HF/CH_3CN medium at very low potentials, and reacts with the organic species to give the corresponding fluoro compound. The catalyst has been regenerated easily. For example, *p*-methoxyiodo benzene undergoes electrochemical oxidative fluorination to give *p*-methoxyiodo benzene difluoride in TEA.3HF/CH_3CN medium and this system is used for the *gem*-difluorination of a variety of organic compounds [50] (Scheme 14). The results obtained when substituted and unsubstituted dithio ketals were subjected to SEF, in the presence of different mediators including *p*-methoxyiodo benzene,



Scheme 14.

Table 1. Different types of mediators used for the *gem*-difluorination of dithioketals. The final product is 

Starting materials	Mediators	X = Ph			X = *p*-F-C_6H_4		
		Potential vs SSCE /V	Charge /F mol^{-1}	Yield /%	Potential vs SSCE /V	Charge /F mol^{-1}	Yield /%
	[51]	2.6	11.0	53	6.0	6.0	79
	*p*-methoxy iodobenzene [50, 52]	1.9	4.5	98	1.9	5.9	96
Same compound	*p*-methoxy iodo benzene chlorofluoride [53]	1.3	4.0	58	1.3	5.0	58
	Et_4NBr [54]	1.2	4.5	32	1.2	3.7	43
Same compound	Ar_3N [55, 56]	1.3	4.0	58	1.3	5.0	58

are compared in Table 1. It is seen that the oxidative mediators have very beneficial influence on the potentials required, the total charge passed and the yields obtained for these processes. Fuchigami and co-workers have studied a number of oxidative mediators including *p*-methoxyiodo benzenedifluoride [50, 52], *p*-methoxyiodo benzene chlorofluoride [53], tetraethyl ammonium bromide (Et_4NBr) [54] and triarylamine [55–57].

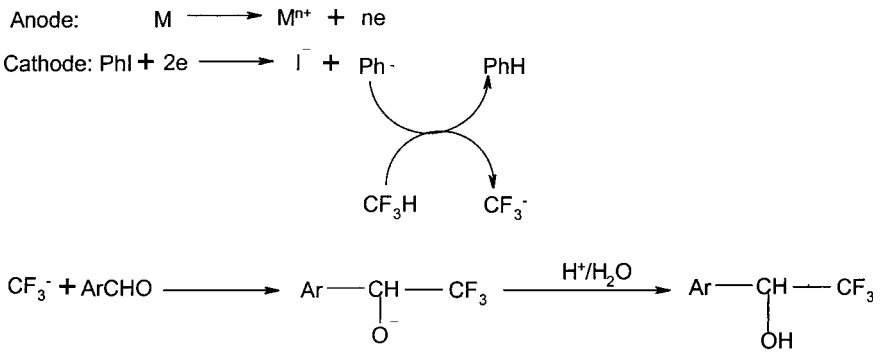
Similar types of mediators have also been employed by the other workers in recent times. These include iodo benzene for the SEF of dicarbonyl compounds [58] and $(PhSe)_2$ for the fluoroselenation of alkenes and alkynes [59]. Similarly *gem*-difluorinated heterocycles can also be obtained by the indirect electrochemical reduction of chlorodifluoro acetylated compounds in the presence of olefinic substrates followed by intramolecular cyclization of the γ,γ-difluoroalkyl radical [60].

3.2. *Indirect perfluoroalkylation*

Preparation of trifluoromethyl substituted organic compounds using Kolbe type oxidative generation of $CF_3^{\bullet}$ from CF_3COOK has been employed for some time. A recent study suggests reasonable success in trifluoromethylation of electron-rich aromatics and alkenes by the electrochemical oxidation of CF_3SO_2K [61]. Perichon and co-workers, in work involving the sacrificial anode technique, have achieved trifluoromethylation of aldehyde.

The electron released from the dissolving anode generates CF_3^- from CF_3H via the reduction of PhI through the above sequence. This CF_3^- can attack, for example, PhCHO leading to the formation PhCHOH—CF_3 [62] (Scheme 15).

A much more interesting approach for the synthesis of perfluoroalkylated nitrogen bases is the use of perfluoroalkyl halides; thereby perfluoroalkyl free radicals are reductively generated using redox catalysis as mediators demonstrating the $S_{RN}1$ process [63]. These mediators include terepthalonitrile, nitrobenzene and 4-nitro pyridine *N*-oxide. This approach is made necessary by the fact that the electrode is rapidly passivated upon direct electrolysis of perfluoroalkyl halides and also by the need to operate under less reducing conditions.



Scheme 15.

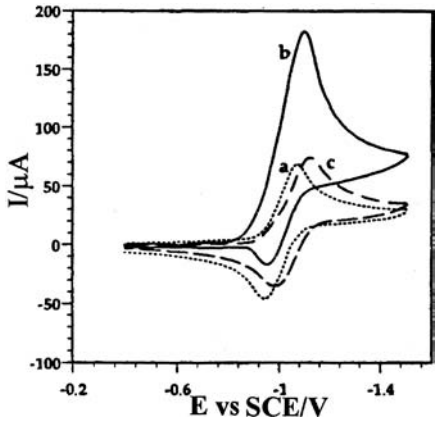


Fig. 1. Cyclic Voltammetry of the redox catalyzed reduction of n-C_4F_9I by the anion radical of nitrobenzene in DMSO + 0.1 M Et_4NBF_4 in the absence (a, b) and in the presence of 6-benzylamino purine anion (c). (a) catalyst alone, $C = 2.0$ mM, (b) a + n-C_4F_9I ($C = 6.0$ mM), (c) b + 6-benzylamino purine anion ($C = 96.9$ mM), $v = 0.2$ V s^{-1} on glassy carbon electrode, $T = 22$ °C [64].

Typical cyclic voltammograms of nitrobenzene (P, $E^\circ = -1.10$ V vs SCE) show simple one electron reversible redox characteristics (Figure (1a)) [64].

$$P + e^- \leftrightharpoons P^{\bullet -} \tag{8}$$

With the addition of alkyl halides (n-C_4F_9I (R_FX)), P loses its reversibility and the reduction of R_FX is then redox catalyzed by the $P/P^{\bullet -}$ couple resulting in an increase in the peak height of the voltammetric characteristics (Figure (1b)).

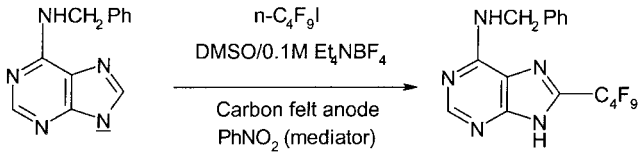
$$P^{\bullet -} + R_FX \longrightarrow R_F^{\bullet} + X^- + P \tag{9}$$

If the nucleophile is added to the solution, the peak decreases and reversibility is restored (Figure (1c))

$$R_F^{\bullet} + Nu^- \longrightarrow R_FNu^{\bullet -} \tag{10}$$

$$R_FNu^{\bullet -} + P \leftrightharpoons R_FNu + P^{\bullet -} \tag{11}$$

As an example, perfluro butyl substituted 6-benzylamino purine can be easily synthesized on carbon felt anode using nitrobenzene as mediator and the yield is 60% [64] (Scheme 16). By this method, perfluoroalkyl and fluorinated aryl substituted heterocyclics can be conveniently synthesized. These compounds have potential biological applications in medicine [64, 65].



Scheme 16.

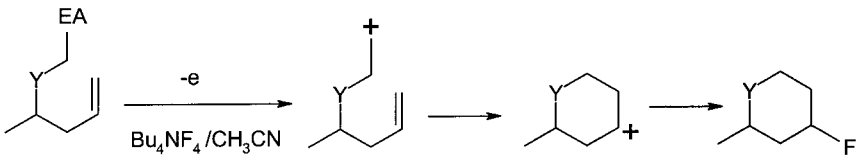
3.3. *Oxidative fluorination involving electroauxiliaries*

Another important approach involving the synthesis of organo-fluorine compounds is the introduction of an electroauxiliary on the carbon adjacent to the heteroatoms. Electroauxiliaries activate the electron transfer in the reaction, resulting in bond cleavage and generation of cation radicals so that nucleophiles can be introduced very easily. Anodic oxidation of organic compounds containing electroauxiliary leaving groups such as —$SiMe_3$, —$SnBu_3$ and —SPh can undergo one electron oxidation leading to C—F bond formation [66]. In some cases the electroauxiliary assists cyclization, in addition to C—F bond formation [67] (Scheme 17).

3.4. *Defluorinative silylation*

The introduction of a difluromethylene moiety into organic molecules is an important subject since wide ranges of difluoromethylene compounds have potential applications in drugs. The difluoromethylene unit can be easily synthesized by the selective electroreductive defluorination of trifluoromethyl compounds using trimethylsilyl chloride (TMSCl) followed by chemical reaction with electrophiles. For example, the electroreduction of trifluoromethylimines in the presence of TMSCl resulted in the defluorination of one of the three fluorine atoms in the CF_3 group, affording β,β-difluoroenamines, whose amino groups were trimethylsilylated. These fluorine-substituted enamines can be further alkylated, leading to the formation of difluoromethylene compound [68] (Scheme 18).

Similarly, the electroreductive defluorination of trifluoromethyl ketone results in the formation of difluoroenol silyl ethers. However, the same reaction with trifluoromethyl acetate yields a mixture of *tert*-butyl difluoroketene silyl acetal (A) and carbon silyated

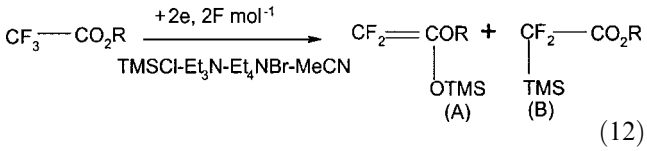


Y= OR' and NCO_2R EA= SiR_3, SnR_3 and SR"

Scheme 17.

Scheme 18.

difluoroacetate (B). The formation of B as a sole product was observed at higher temperature and with a large excess of TMSCI [69, 70].



(12)

This silyl group can also be introduced by removing the chlorine atom from the compound $CF_2ClCOOEt$ (Scheme 19) [71].

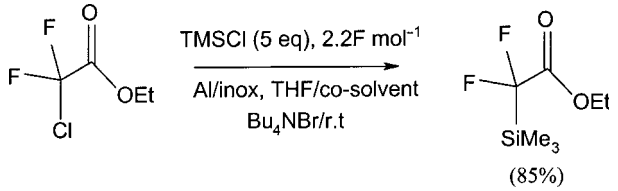
Trifluoromethyl benzene may lead to the formation $PhCF_2(TMS)$, $PhCF(TMS)_2$ and $PhC(TMS)_3$ depending on the number of Faradays passed [72]. 1,3-trifluoromethyl benzene can also give a number of TMS substituted products depending on the experimental conditions, such as solvent employed and the charge passed [73] (Scheme 20).

The difluoro silyl synthon can act as an effective CF_2 building block since it is easily available, sufficiently stable to be stored for a long time and highly reactive in the presence of fluoride ions. For example, the chemical reaction between the $-CF_2-$ synthon coupled with the trimethyl silyl group and an aromatic ketone in the presence of F^- catalysis followed by acid hydrolysis leads to the formation of difluoro tertiary alcohols (Scheme 21) [73].

C—F bonds may also be introduced by the reduction of C—Cl and C—I bonds in organic moieties. The former process has greater significance, since this can be used for the conversion of chlorofluorocarbon into hydrofluorocarbon. Electrochemical conversion of $CFC1_2—CF_2C1$ in a multi-step process leads to $CHF=CF_2$ [74].

$$CFCl_2—CF_2C1 + 2e^- \longrightarrow CF_2C1—CFHCl + CFCl=CF_2 \quad (13)$$

$$CF_2C1—CFHCl \xrightarrow{Pd^{2+}} CFH=CF_2 \quad (14)$$



Scheme 19.

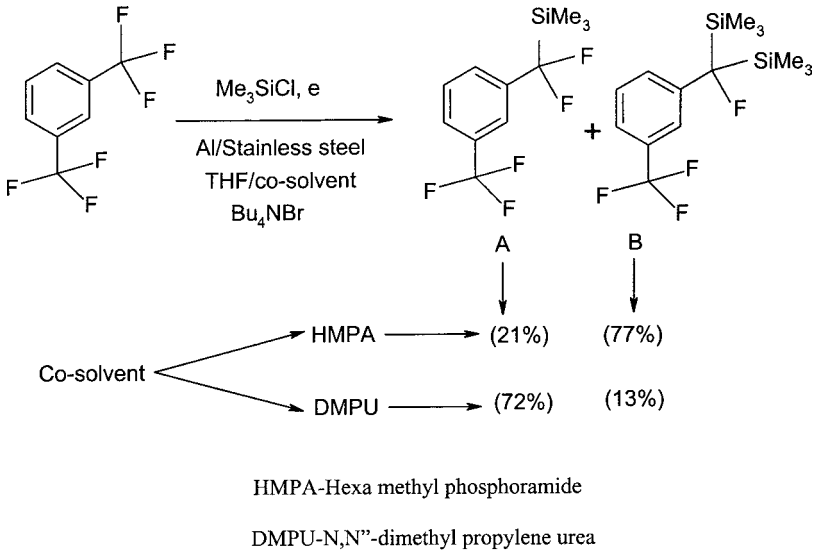
Pd^{2+} acts as a good catalyst for this process. For the conversion of C—I to C—F, however, such inorganic catalysts are not required [75].

4. Compounds of interest in bio-medical applications

SEF has been under investigations for over three decades [9]. In recent times, however, fluorinated organic compounds have received much interest due to the increased recognition of their biological importance. From a structure–activity relationship (SAR) viewpoint, the introduction of a fluorine atom into the organic moiety may provide new drugs and pharmaceuticals with increased functionality. Some typical examples of these electrochemically synthesized fluoro organic intermediates, their synthons and their potential applications towards pharmaceuticals are summarized in Table 2. A large number of these compounds are produced by a direct single step in SEF, involving conversion of C—H bonds to C—F bonds. DME appears to be a very useful solvent for many of these compounds.

Fluoro azetidin-2-ones (I) are very useful intermediates for preparation of fluorinated carbohydrates and amino acids. They can be prepared either by SEF of β-lactams [75, 76] or by the replacement of $-SiMe_3-$ by F- in 4-trimethylsilyl azetidin-2-ones [77]. Similarly fluoro caffeine (II) and flavone (III) are also important biological compounds [78, 79]. Substituted quinolines (IV) [80] and oxindoles (V) [81], where the fluorine atoms are introduced in the side chain as —S—CH—F—, have potential applications towards anti-bacterial and anti-malarial drugs. Similarly the fluoro derivative of 4(3H) quinazolinones (VI) also finds important applications as an anti-tumor agent [82].

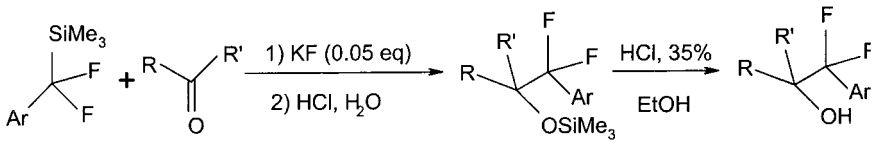
One typical example of a heterocyclic O, S-acetal ring system possessing inhibitory activities towards human type-II (non-pancreatic) secretory phospholipase A_2 (PLA_2) is fluorine substituted l,3-oxathiolan-5-one derivatives (VII) [83]. Their activities also match with the well-known PLA_2 inhibitor manoalide [83]. The nitrogen containing heterocycles which function as anti-cancer and anti-fungal agents include fluorine substituted pyrimidines (VIII) [84] and 2-benzoxazolys sulfide (IX) [85], respectively. The preparative electrolysis of 1-(4′-iodo-tetrafluorophenyl) imidazole in the presence of adenine anion results in the formation of a C-8 fluorinated aryl purine derivative (X), which are potential adenosine receptors agonists [64]. Monofluorinated α,β-unsaturated esters synthesized by



HMPA-Hexa methyl phosphoramide

DMPU-N,N"-dimethyl propylene urea

Scheme 20.



Scheme 21.

Table 2. The basic units of electrochemically-synthesized fluoro organic compounds and their potential applications in medicine

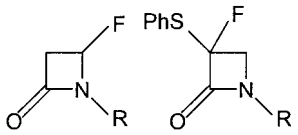
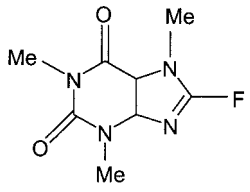
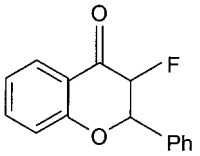
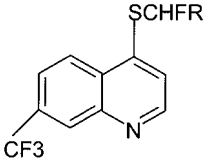
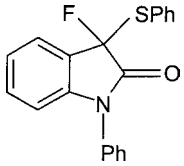
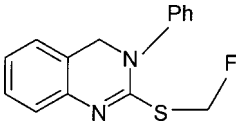
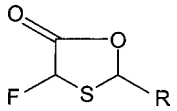
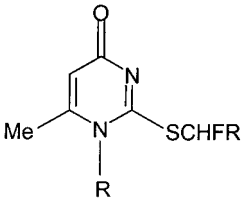
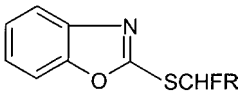
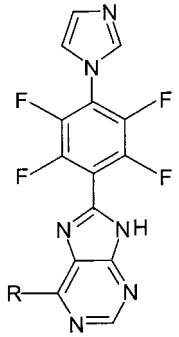
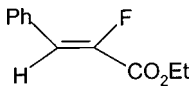
Name of the fluorine substituted basic unit	Structure of the fluorine substituted basic unit	Potential applications	Ref.
Azetidin-2-one derivatives (I)		Building block for preparation of fluorinated carbohydrates and aminoacids	[76–78]
Caffeine (II)		Biologically important compound	51
Flavones (III)		Biologically important compound	79
Quinoline moiety (IV)		Antibacterial, anti-malarial and analgesic	80

Table 2. (Continued)

Oxindole (V)		Starting materials for various drugs	81
Quinazolinones (VI)		Anti-tumor, anti-microbial and anti-lipidemic	82
1,3-oxathiolan-5-ones (VII)		Phospholipase A_2 (PLA_2) inhibitor	83
Pyridimines (VIII)		Anti-cancer	84
2-benzoxazolyl sulfide (IX)		Anti-fungal and anti-inflammatory	85
Tetrafluoro phenyl imidazole combined purine moiety (X)		Adenosine Receptors Agonists	65
α-fluorinated unsaturated ester (XI)		Monofluorinated retinoids and sex pharmones	86

electrochemical selenation, followed by chemical treatment, have been used as retinoids and sex pharmones (XI) [86].

5. Conclusion

Despite eluding commercial success, selective electrochemical fluorination continues to attract active research interest. It is one of the best methods for direct fluorination since fluorine atoms can be introduced into organic molecules in one step under safe conditions. Much effort has been directed towards synthesis of fluorine containing heterocycles, owing to their biological activity. Redox mediators are very useful for avoiding passivation and achieving higher current efficiencies. Other interesting electrochemical routes are also emerging for the synthesis of organo-fluorine compounds. Among these, the use of TMS for the synthesis of difluoro methylene compounds derivatives and anodic trifluoromethylation reaction involving $S_{RN}1$ substitution appear to be very promising. It is very important to note that the electrochemical fluorination route for the synthesis of organo-fluorine compounds has reached an interesting phase of development in the field of organic synthesis, which implies that the commercial viability of this route towards the electrosynthesis of fluorine based drugs is not far-off.

Acknowledgement

V.S. thanks CSIR, New Delhi for the award of a Research Associateship.

References

1. T. Fuchigami and A. Konno, 'Research Trends: Current Topics in Electrochemistry', Vol. 2 (Trivandrum, India, 1993) pp. 155–166.
2. T. Fuchigami, *Rev. Heteroatom Chem.* **10** (1994) 155.
3. T. Fuchigami and A. Konno, *J. Syn. Org. Chem. Jpn.* **55** (1997) 312.
4. T. Fuchigami, *Phosphor Suflur Silicon Lett.* **120** (1997) 343.
5. T. Fuchigami, S. Higashiya, Y.K. Hou and K.M. Dawood, *Rev. Heteroatom. Chem.* **19** (1999) 67.
6. T. Fuchigami, *in* P.S. Mariano (Ed), 'Advances in Electron Transfer', Vol. 6 (JAI Press Inc., Connecticut, 1999) p. 41.
7. T. Fuchigami, *in* H. Lund and O. Hammerich (Eds), 'Organic Electrochemistry', 4th edn (Marcel Dekker, New York, 2001) Chapter 25.
8. F.G. Drakesmith, *Topics Curr. Chem.* **193** (1997) 197.
9. M. Noel, V. Suryanarayanan and S. Chellammal, *J. Fluorine Chem.* **83** (1997) 31.
10. S. Hara and N. Yoneda, *J. Syn. Org. Chem. Jpn.* **56** (1999) 312.
11. P.M. Bersier, J. Bersier and L. Carlsson, *in* 'Proceedings of 14th International Symposium on Applied Electrochemistry', Clearwater Beach, Florida, 12–16 November 2000.
12. S.M. Lee, J.M. Roseman, C. Blair Zartman, E.P. Morrison, S.J. Harrison, C.A. Starkiewicz and W.J. Middleton, *J. Fluorine Chem.* **77** (1996) 65.
13. V. Suryanarayanan and M. Noel, *J. Fluorine Chem.* **91** (1998) 153.
14. P. Baroux, R. Tardivel and J. Simonet, *J. Electrochem Soc.* **144** (1997) 84.
15. V. Suryanarayanan, S. Chellammal and M. Noel, *J. Fluorine Chem.* **93** (1999) 53.
16. Y.K. Hou, S. Higashiya and T. Fuchigami, *Electrochim. Acta* **45** (2000) 3005.
17. S.M. Riyadh, H. Ishii and T. Fuchigami, *Tetrahedron* **58** (2002) 5877.
18. D.F. Andres, U. Dietrich, E.G. Laurent and B.S. Marquet, *Tetrahedron* **53** (1997) 647.
19. W. Dmowski and T. Kozlowski, *Electrochim. Acta* **42** (1997) 513.
20. K. Momota, T. Yonezawa, K. Mukai and M. Morita, *J. Fluorine Chem.* **87** (1998) 173.
21. T. Tajima, H. Ishii and T. Fuchigami, *Electrochem. Commun.* **4** (2002) 589.
22. K. Momota, K. Makai, K. Kato and M. Morita, *Electrochim. Acta* **43** (1998) 2503.
23. M. Sawaguchi, T. Fukuhara and N. Yoneda, *J. Electroanal Chem.* **507** (2001) 66.
24. T. Tajima, H. Ishii and T. Fuchigami, *Electrochem. Commun.* **3** (2001) 467.
25. T. Tajima, H. Ishii and T. Fuchigami, *Tetrahedron Lett.* **42** (2001) 4857.
26. S.M. Riyadh, H. Ishii and T. Fuchigami, *Tetrahedron* **57** (2001) 8817.
27. S.M. Riyadh and T. Fuchigami, *J. Org. Chem.* **67** (2002) 9379.
28. S.M. Riyadh, H. Ishii and T. Fuchigami, *Tetrahedron* **58** (2002) 9273.
29. M.R. Shaaban and T. Fuchigami, *SynLett* (2001) 1644.
30. K.M. Dawood and T. Fuchigami, *J. Org. Chem.* **66** (2001) 7691.
31. A. Konno and T. Fuchigami, *J. Org. Chem.* **62** (1997) 8579.
32. T. Fuchigami, S. Narizuka, A. Konno and K. Momota, *Electrochim. Acta* **43** (1998) 1985.
33. A. Konno, M. Shimojo and T. Fuchigami, *J. Fluorine Chem.* **87** (1998) 137.
34. S. Hara, S.-Q. Chen, T. Hatakeyama, T. Fukuhara, M. Sekiguchi and N. Yoneda, *Tetrahedron Lett.* **36** (1995) 6511.
35. S-.Q. Chen, T. Hatakeyama, T. Fukuhara, S. Hara and N. Yoneda, *Electrochim. Acta* **42** (1997) 1951.
36. S. Hara, S.-Q. Chen, T. Hoshio, T. Fukuhara and N. Yoneda, *Tetrahedron Lett.* **37** (1996) 8511.
37. S. Higashiya, K.M. Dawood and T. Fuchigami, *J. Fluorine Chem.* **99** (1999) 189.
38. S. Higashiya, T. Sato and T. Fuchigami, *J. Fluorine Chem.* **87** (1998) 203.
39. Y. Hou and T. Fuchigami, *Electrochem Commun.* **1** (1999) 445.
40. Y.K. Hou and T. Fuchigami, *J. Electrochem Soc.* **147** (2000) 4567.
41. D. Baba, H. Ishii, S. Higashiya, K. Fujisawa and T. Fuchigami, *J. Org. Chem.* **66** (2001) 7020.
42. N. Iwayasu, M.R. Shabaan and T. Fuchigami, *Heterocyclics* **57** (2002) 623.
43. D. Baba and T. Fuchigami, *Tetrahedron Lett.* **43** (2002) 4805.
44. V. Suryanarayanan and M. Noel, *J. Fluorine Chem.* **92** (1998) 177
45. H. Ishii, N. Yamada and T. Fuchigami, *J. Chem. Soc. Chem. Commun.* (2000) 1617.
46. H. Ishii, N. Yamada and T. Fuchigami, *Tetrahedron* **57** (2001) 9067.
47. Y.K. Hou and T. Fuchigami, *Tetrahedron* **56** (2000) 8877.
48. M. Hasegawa, H. Ishii and T. Fuchigami, *Tetrahedron Lett.* **43** (2002) 1503.
49. T. Fuchigami and M. Miyazaki, *Electrochim. Acta* **42** (1997), 1999.
50. T. Fuchigami and T. Fujita, *J. Org. Chem.* **59** (1994) 7190.
51. M. Sano, N. Toyada, Y. Shizuri and M. Torri, *Tetrahedron Lett.* **35** (1994) 9237.
52. T. Fuchigami, T. Fujita, S. Higashiya and A. Konno, *J. Chin. Chem. Soc.* **45** (1998) 131.
53. T. Fujita and T. Fuchigami, *Tetrahedron Lett.* **37** (1996) 4725.
54. T. Fuchigami and M. Sano, *J. Electroanal. Chem.* **414** (1996) 81.
55. T. Fuchigami, K. Mitomo, H. Ishii and A. Konno, *J. Electroanal. Chem.* **507** (2001) 30.
56. T. Fuchigami, M. Tetsu, T. Tajima and H. Ishii, *Synlett.* **8** (2001) 1269.
57. Y. Shen, K. Suzuki, M. Atobe and T. Fuchigami, *J. Electroanal. Chem.* **540** (2003) 189.
58. S. Hara, T. Hatakeyama, S.-Q. Chen, K. Ishii, M. Yoshida and M. Sawaguchi, T. Fukuhara and N. Yoneda, *J. Fluorine Chem.* **87** (1998) 189.
59. K. Uneyama, H. Asai, Y. Dah-oh and H. Matha, *Electrochim. Acta* **42** (1997) 2005.
60. P. Hapiot and M. Medebielle, *J. Fluorine Chem.* **107** (2001) 285.
61. J.B. Tommasino, A. Brondex, M. Medebielle, M. Thomalla, B.R. Langlois and T. Billard, *Synlett.* (2002) 1697.
62. R. Bahdadi, M. Troupet and J. Perichon, *J. Chem. Soc. Chem. Commun.* (1998) 1251.
63. M. Medebielle, M.A. Oturan, J. Pinson and J-.M. Saveant, *J. Org. Chem.* **61** (1996) 1331.
64. M. Medebielle, S. Fujii and K. Kato, *Tetrahedron* **56** (2000) 2655.
65. M. Medebielle, J. Pinson and J.-M. Saveant, *Electrochim. Acta* **42** (1997) 2049.
66. J. Yoshida, *in* W.V. Childs (Ed), 'Proceedings of Electro Chemical Society Symposium Series' Vol. 97 (Pennington, 1997) pp. 106.
67. J. Yoshida, Y. Ishii and S. Isoe, *J. Amer. Chem. Soc.* **114** (1992) 7594.
68. K. Uneyama and T. Kato, *Tetrahedron Lett.* **39** (1998) 587.
69. K. Uneyama, G. Mizutani, K. Maeda and T. Kato, *J. Org. Chem.* **64** (1999) 6717.
70. K. Uneyama and G. Mizutani, *J. Chem. Soc. Chem. Commun.* (1999) 613.
71. P. Clavel, C. Biran, M. Bordeau, N. Roques and S. Trevin, *Tetrahedron Lett.* **41** (2000).
72. P. Clavel, M.P. Leger-Lambert, C. Biran, F. Serein-Spirau, M. Bordeau, N. Roques and H. Marzouk, *Synthesis* **5** (1999) 829.
73. P. Clavel, G. Lessene, C. Biran, M. Bordeau, N. Roques, S. Trevin and D. Demontanzon, *J. Fluorine Chem.* **107** (2001) 301.

74. P.L. Cabot, M. Centells, L. Sagarre and J. Casado, *J. Electroanal. Chem.* **435** (1997) 255.
75. M. Sawaguchi, S. Ayuba, Y. Nakamura, T. Fukuhara, S. Hara and N. Yoneda, *Synlett*. (2000) 999.
76. T. Fuchigami, S. Narizuka and A. Konno, *J. Org. Chem.* **57** (1992) 3755.
77. S. Narizuka and T. Fuchigami, *J. Org. Chem.* **58** (1993) 4200.
78. K. Suda, K. Hotoda, M. Aoyagi and T. Takanami, *J. Chem. Soc. Perkin Trans. I* (1995) 1327.
79. Y. Hou, S. Higashiya and T. Fuchigami, *Synlett* **9** (1998) 973.
80. K.M. Dawood and T. Fuchigami, *J. Org. Chem.* **64** (1998) 138.
81. Y. Hou, S. Higashiya and T. Fuchigami, *J. Org. Chem.* **62** (1997) 8773.
82. K.M. Dawood, S. Higashiya, Y.K. Hou and T. Fuchigami, *J. Org. Chem.* **64** (1999) 7935.
83. S. Higashiya, S. Narizuka, A. Konno, T. Maeda, K. Momota and T. Fuchigami, *J. Org. Chem.* **64** (1999) 133.
84. M.R. Shaaban, H. Ishii and T. Fuchigami, *J. Org. Chem.* **65** (2000) 8685.
85. K.M. Dawood, S. Higashiya, Y. Hou and T. Fuchigami, *J. Fluorine Chem.* **93** (1999) 159.
86. T. Fuchigami, T. Hayashi and A. Konno, *Tetrahedron Lett.* **33** (1992) 3161.