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Fluoroalkylation of organic compounds †

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Abstract. Data on fluoroalkylation and perfluoroalkylation methods in organic synthesis are analyzed, summarized and described systematically. The most practically important properties of compounds with fluoroalkyl substituents are illustrated. The key trends and the potential of this field of organic chemistry are considered. Electrochemical syntheses of perfluoroalkyl derivatives that are inaccessible or experimentally difficult to prepare by regular chemical techniques are presented. Particular attention is paid to processes involving organometallic compounds as well as to prospects for the development of this field of research. The bibliography includes 226 references.

I. Introduction

Organofluorine compounds possess unique physical and biological properties and, therefore, they are widely used in medicine, agrochemistry and materials science.[1–3] Today, at least 30% – 40% of agricultural chemicals and 20% of marketed pharmaceuticals contain fluorine; these include three of the eight top medical drugs sold in 2010. However, rather few such compounds have been detected in nature.[4] The replacement of hydrogen atoms by fluorine, the most electronegative element, changes the steric and electronic properties of the molecule by affecting the acidity or basicity of neighbouring groups, the dipole moment and the general reactivity.[2,3] Due to the high reactivity of elemental fluorine, initially, the progress in the synthesis of new fluorinated compounds was held up by the requirement of special conditions and procedures. The subsequent development of approaches using electrophilic fluorinating agents initiated the activity of synthetic chemists along this line. Since the evolution of new pharmaceutical drugs will be related to increasing percentage of fluorinated molecules, elaboration of new, more perfect and efficient methods for the synthesis of organofluorine compounds is expected to become a highly important area of health-related research. A new empirical rule of pharmaceutical chemistry states that the introduction of fluorine into a potential drug structure increases the probability of hitting the target almost 10-fold. Numerous examples of the efficiency of this strategy are confirmed by the ability of fluorinated analogues to be recognized *via* macromolecular binding by natural substrates. High electronegativity of fluorine is utilized for the development of enzyme inhibitors or for enhancing the stability of molecules against chemical degradation.[5] It was found that the introduction of fluorine atoms or fluoroalkyl groups into a molecule sharply (by several orders of magnitude) enhances the anticancer, antiviral and anti-infectious properties of approved drugs or drugs that are under clinical trials: nucleosides, macrolides, alkaloids, steroids, amino acids and prostaglandins. In the USA, second-generation epothilones (antitumour agents) are modified by introducing CF_3 and C_nF_m groups; this increases the cell growth inhibition 100-fold, while the lack of toxicity for the body is retained.

Compounds containing highly fluorinated $(CH_2)_z(CF_2)_yF$ chains attract considerable interest as stoichiometric reagents and as catalysts for highly selective chemical transformations. Unique dissolving properties of highly fluorinated compounds open up the way for using these compounds in organic synthesis in innovative reaction media such as 'fluorinated two-phase systems' or in supercritical carbon dioxide. Highly fluorinated reagents and

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† The review is dedicated to the memory of Professor L M Yagupolskii (1922 – 2009).

substrates are also useful for the synthesis in traditional solvents as they are readily separable from non-fluorinated compounds.

Thus, the role of fluorine derivatives in various fields is generally recognized. However, a problem is the lack of selective and convenient fluoroalkylation methods tolerant to various substituents, especially at the last stages of synthesis of complex molecules. The existing methods of introduction of perfluoroalkyl groups into various substrates have low selectivity and a number of drawbacks. Development of a new synthetic strategy of fluoroalkylation is obviously a topical task. This task may be accomplished by using organometallic compounds.[6] The first attempts at the synthesis of fluoroalkylated organometallic derivatives were made back more than 30 years ago. Among the first synthesized derivatives were trifluoromethyl derivatives of mercury, which were later successfully used for trifluormethylation. However, organic compounds of mercury are highly toxic and induce irreversible changes of the nervous system, which reduces the scope of their applicability. Fluoroalkyl Grignard reagents are thermally very unstable. Zinc fluoroalkyl reagents, which are more stable than Mg compounds, are also fairly difficult to prepare and isolate, and they often function as difluoromethylating and nucleophilic fluorinating reagents. Copper(I) compounds are prepared and isolated rather easily and react over a broad temperature range. The key difficulty of trifluoromethylation involving copper is the formation of perfluoroethyl derivatives, which are difficult to separate during the workup of the reaction mixture and purification.

It is noteworthy that there are very few catalytic reactions of trifluoromethylation and perfluoroalkylation. Stoichiometric reactions were studied long ago, while the first copper-catalyzed trifluoromethylation of aryl iodide was described only in 2009. Unfortunately, there are hardly any effective catalytic processes in this area or they are very expensive. For example, many ligands used in Pd-catalyzed reactions are often more expensive than the metal. This is the case for the ligand Brett Phos, which is used in the only currently available Pd-catalyzed nucleophilic aromatic trifluoromethylation reaction. Furthermore, most metal-promoted perfluoroalkylation reactions are suitable for introduction of trifluoromethyl groups rather than long fluoroalkyl substituents. Very few studies were concerned with Ni-catalyzed trifluoromethylation and perfluoroalkylation. This may be related to the difficulty of preparing compounds with $Ni-R_F$ bonds (R_F is the fluorine-containing group), their low reactivity in oxidative addition and reductive elimination and to the lack of knowledge of the redox properties, *i.e.*, the lack of understanding of how these compounds could be activated towards the target reactions. The further development of metal complex approaches to the synthesis of organofluorine compounds by available catalytic reactions is required.

Many lines of research in this area are still poorly developed and require further exploration. Trifluoro- and perfluoroalkylation of alkenes under mild conditions has not yet been accomplished.

The use of electrochemically generated catalysts in organic reactions has recently been aquiring increasing importance as regards new opportunities for organic synthesis and for more in-depth studies of electron transfer, bond cleavage, substitution, addition and other reactions. This line of research is being actively developed, and the results are being used in quite a few areas of physical, organic and analytical chemistry. The interest in electrochemical reactions is caused by a number of factors: mild conditions (moderate temperature, ambient pressure), the possibility of closed-loop implementation with a minimum amount of the catalyst reactant that is repeatedly recycled. This is supplemented by high environmental safety of the synthesis, especially in comparison with traditional organic chemistry techniques. New selective methods for introducing perfluorinated organic groups into various alkenes in the presence of redox-active nickel catalysts have appeared in recent years, these methods combining the advantages of synthetic organic chemistry and electrochemistry. For the understanding of mechanisms of such processes, EPR spectroscopy is a valuable tool.

The present review gives account and analysis of the developing synthetic approaches to the selective introduction of perfluoroalkyl groups into various substrates, first of all, approaches involving metal compounds. Particular attention is given to the advances in determining the nature and reactivity of organometallic intermediates and to the electrochemical synthesis of compounds with carbon–perfluoroalkyl or metal–perfluoroalkyl bonds.

The last decades have seen rapid progress in the fluorine and organofluorine chemistry, which is tightly connected with practical demands of, most of all, medicine, power engineering, chemical industry, agriculture and military and space research. The vigorous growth of the fluorine chemistry was reflected in the literature: numerous publications devoted to theoretical and applied aspects of fluorine chemistry appeared, the number of synthesized compounds that contain fluorine atoms increased. This is related first of all to unique properties of organofluorine compounds. Since only few such compounds occur in nature, a topical issue is still the search for new effective synthetic approaches to the synthesis of organofluorine products.

Section II of the present review deals with the chemistry of organofluorine compounds and their properties that account for the high interest in this area. The application of some representatives of this class in various fields is described.

Sections III and IV give an account of the methods used to introduce perfluoroalkyl groups into various substrates. Particular attention is devoted to trifluoromethyl and perfluoroalkyl derivatives of metal catalysts including synthesis, binding and reactivity.

Section V considers the potential of the electrochemical approach to the investigation of functionalization of unsaturated bonds catalyzed by complexes of transition metals in low oxidation states.

II. The chemistry and applications of fluorine compounds

The fluorine chemistry originated in the second half of the 19th century owing to experiments of Henri Moissan, who was the first to isolate elemental fluorine in 1886. Initially, the progress in investigating fluorine reactions was quite slow; however, the last decades witness the 'fluorine boom', which is caused by exceptional importance and high value of fluorine-containing products. The fluorine chemistry played an important role in numerous notable and fairly diverse technological achievements during the last 80 years starting with the discovery of Freons in the 1930s, which

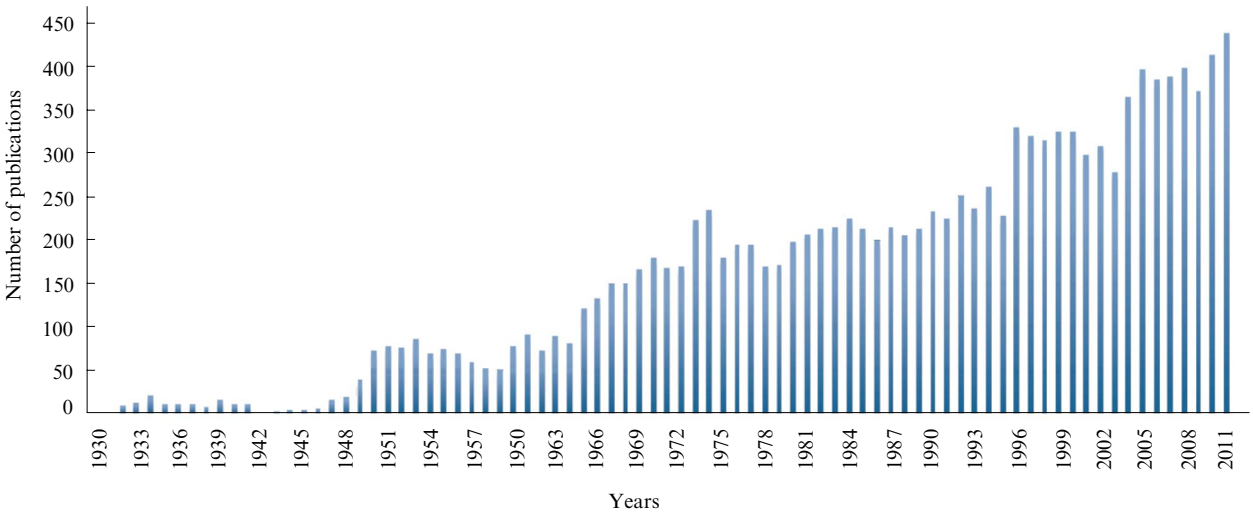


Figure 1. Growth of the number of publications in organofluorine chemistry.

were used as coolants. The subsequent development of this area was related to the exceptional role of the Manhattan Project (development of A-bomb and hydrogen bomb). Currently, the fluorine chemistry has turned into an extensive branch of science and technology which develops fluorine-containing biologically active compounds for pharmaceutics and agrochemistry, coolants, fuels, surfactants, textile chemicals, polymers, dyes and various materials. The increasing role of organofluorine compounds in various spheres has lately attracted a great number of scientists in this field. The development of new methods for selective introduction of fluorine atoms and fluorine-containing groups into organic molecules for the preparation of biologically active compounds and useful materials has become a 'hot' research area. Owing to the unique structure–reactivity relationship observed for organofluorine compounds, the fluorine chemistry is an area of broad interest of fundamental science. Therefore, most important scientific and technological achievements related to fluorine chemistry were made by joint efforts of fundamental and applied researchers.

The following events can be considered as milestones of the development of fluorine chemistry:[7,8]

— isolation of elemental fluorine by Henri Moissan (1886);

— F Swarts' discovery of the Cl/F exchange reaction under the action of SbF_3 (1892);

— preparation of Freons by Thomas Midgley (1928);

— the invention of Teflon by Roy J Plunkett; onset of the fluoropolymer chemistry (1938);

— synthesis of perfluorinated organic compounds by means of CoF_3 (1947);

— discovery of electrochemical fluorination by John Simons (1949);

— early experiments of J Fried in the medicinal fluorine chemistry (synthesis of fluorinated steroids) (1954);

— discovery of the noble gas chemistry by Neil Bartlett (preparation of $XePtF_6$) (1962);

— appearance of the theory of ozone layer depletion under the action of chlorofluorocarbons (Rowland–Molina hypothesis) (1974);

— direct fluorination by elemental fluorine performed by H Margrave (1979);

— isolation of the fluorinating enzyme (David O'Hagan) (2003);

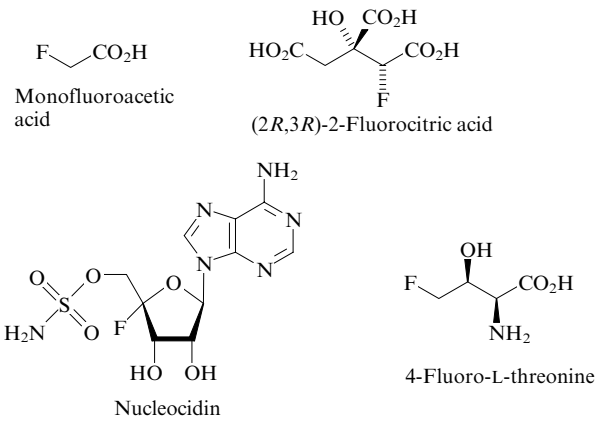
— synthesis of Fludelone (trifluoromethyl-substituted epothilone) by Samuel Danishefsky (2005).

Some of the above-listed achievements were rewarded by the highest award — the Nobel Prize in chemistry; however, many other may also be worthy of this honour. Pay attention to the gap between the events of 1979 and 2003. This does not mean that nothing special or significant was done between these dates. It is just because during this period (actually during the last 50 years), scientists performed such a large number of important works that it is almost impossible to choose between them. Russia has considerably contributed to the development of the chemistry of fluorine and fluorine compounds, and the names of Academicians I L Knunyants and A V Fokin and their followers went down into the history. The same is true for Professor L M Yagupolskii (Ukraine). This considerable and ever growing interest in the organofluorine chemistry is confirmed by the increasing number of publications in this area (Fig. 1).‡

The content of fluorine in the Earth crust is rather high (fluorine is the 13th most abundant element); it is present in the minerals fluorite, fluoroapatite and cryolite. However, only 12 organic compounds containing a fluorine atom have been found in nature to date (Fig. 2).[9] (Note that of these, eight ω-fluorinated fatty acids occur in one and the same plant.[9])

Compounds containing a fluorine atom acquire specific properties determined by fluorine. First, fluorine is the most electronegative element (Table 1).[8] Fluorine is able to form chemical bonds almost with all elements, the bond energies being very high in many cases. The C–F bond is the strongest single bond involving carbon. One more specific

‡ The search of scientific documents in the field of fluorine chemistry (the key word in the search string is 'fluorine' in the document titles throughout 1930–2011). The electronic scientific search system Scopus (URL: www.scopus.com, access date: March 11, 2012).



$FCH_2(CH_2)_8CO_2H$
ω-Fluorocapric acid

$FCH_2(CH_2)_{16}CO_2H$
ω-Fluorostearic acid

$FCH_2(CH_2)_{12}CO_2H$
ω-Fluoromyristic acid

$FCH_2(CH_2)_{18}CO_2H$
ω-Fluoroarachidic acid

$FCH_2(CH_2)_{14}CO_2H$
ω-Fluoropalmitic acid

$FCH_2(CH_2)_5CH{=}CH(CH_2)_7CO_2H$
ω-Fluoropalmitoleic acid

$FCH_2(CH_2)_7CH{=}CH(CH_2)_9CO_2H$
ω-Fluoroeicosenoic acid

$FCH_2(CH_2)_4CH{=}CHCH_2CH{=}CH(CH_2)_7CO_2H$
ω-Fluorolinoleic acid

Figure 2. Naturally occurring organofluorine compounds.

Table 1. Comparative characteristics of H, C, F and Cl atoms.

Parameter	Elements			
	H	C	F	Cl
Pauling electronegativity	2.2	2.55	3.98	3.16
van der Waals radius /Å	1.20	1.7	1.47	1.75
Length of the H_3C-X bond /Å	1.087	1.535	1.382	1.785
Energy of the H_3C-X bond /kcal mol^{-1}	103.1	88.0	108.1	81.1

feature of the fluorine is the small atomic size: this is the second smallest substituent after hydrogen (the van der Waals radius of fluorine is only ~20% greater than that of hydrogen). Fluorine is the only element that can be substituted for any number of hydrogen atoms in organic compounds. Since the C–F bond energy is greater than the C–H bond energy, organic compounds of fluorine are, most often, chemically and thermally more stable than the corresponding hydrocarbons. Moreover, for perfluorinated compounds, low level of intermolecular interactions accounts for easy evaporation (in the case of liquids) or sublimation (for solids). Due to weak intermolecular interactions, liquid perfluorinated compounds have low surface tension and solid perfluorinated compounds have poor wettability and low adhesion.[10] Finally, the introduction of a fluorine atom or trifluoromethyl group increases the lipophilicity of the molecule and, hence, the intake of biologically active molecules through biomembranes is enhanced.[10] All these features resulted in the extensive use of organofluorine compounds in various fields of medicine, in the development of new materials and in agriculture.

In the early 1930s, Thomas Midgley presented a report dealing with organofluorine compounds as new coolants at a conference of the American Chemical Society. As a demonstration of the properties of dichlorodifluoromethane (Freon 12, CCl_2F_2), Midgley inhaled this compound and then breathed it out onto a candle flame, which was extinguished. This amazing, for that time, event initiated the research and the subsequent use of Freons. In 1931, the company Kinetic Chemicals launched the industrial manufacture of Freon 12 and Freon 11 (CCl_3 F) and in 1933, they started to produce tetrafluorodichloroethane (Freon 114, $CClF_2CClF_2$). The production of trifluorotrichloroethane (Freon 113, CCl_2FCCl_2F) was started in 1934 and the production of difluorochloromethane (Freon 22) began in 1936.

Soon after that, it was found that pyrolysis of $CHClF_2$ affords tetrafluoroethylene, which polymerizes on keeping in an autoclave at room temperature to give polytetrafluorethylene (Teflon) (Scheme 1).

Scheme 1

$$CHClF_2 \xrightarrow[-HCl]{600\ ^\circ C} [:CF_2] \longrightarrow CF_2{=}CF_2 \longrightarrow \underset{\text{Teflon}}{\left(CF_2{-}CF_2\right)_n}$$

Subsequently fluoropolymers have found extensive use as elastomers, thermally stable plastics, coatings, membranes and so on owing to their unique properties such as high thermal and chemical stability, low combustibility, low surface energy, excellent biocompatibility, *etc.*

Modern fluorinated polymers are widely used as a variety of materials; amorphous fluoropolymers are essential for the manufacture of microchips and optical fibre. Ion exchange polymers such as Nafion (**1**) are widely used as conducting membranes in fuel cells.[2]

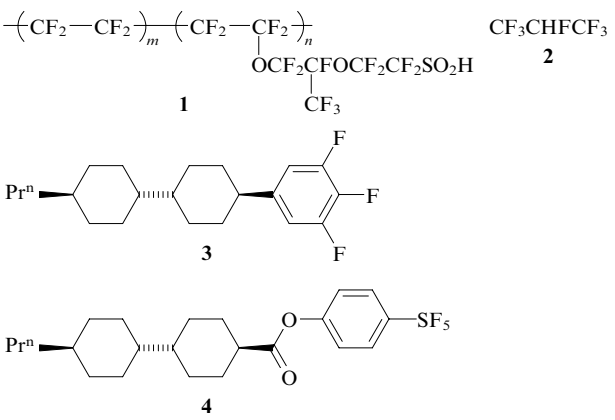
Bromotrifluoromethane and bromochlorodifluoromethane are employed as efficient fire extinguishing agents, as they do not conduct electricity, readily decompose and are not hazardous for humans.[2] However, in 2003, the use of these agents was prohibited (as they are greenhouse gases, which destroy the ozone layer) and they were replaced by other fluorinated materials such as heptafluoropropane **2**.

Organofluorine compounds are indispensable in the production of modern TV sets and displays. The presence of fluorine atoms in liquid crystals, on the one hand, strongly affects the dielectric permittivity due to the strong electron-withdrawing ability of fluorine and, on the other hand, it causes only minor changes in the molecular structure due to the small size of the fluorine atom, which makes these compounds (*e.g.*, compounds **3** and **4**) highly valuable for the manufacture of liquid crystals.[2, 8]

This section of the review gives selected examples of using organofluorine compounds in industry and as functional materials. However, there is no other field that would

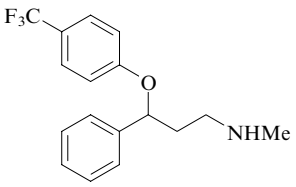
employ orgnofluorine compounds as extensively as medicine or pharmaceutics.

Structures **1**–**4**

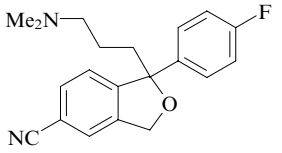


Among numerous pharmaceutical drugs existing in the world, about 150 drugs are fluorine-containing compounds.[11] However, although this number is small, these drugs are highly important and often irreplaceable. High electronegativity and small size of the fluorine atom and low polarizability of the C–F bond are largely responsible for the molecule's biological activity, binding to enzymes and receptors and participation in the compound metabolism. Fluorine-containing drugs are used for various purposes. For example, compounds **5**–**7** are antidepressant drugs belonging to the class of serotonin neurotransmitters.[5] Compound **5** called Fluoxetine (Prozac) is the key medicine for treating mental depression.

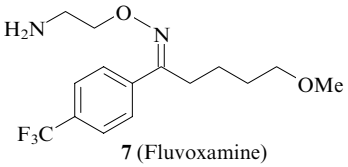
Structures **5**–**7**



5 (Fluoxetine)



6 (Citalopram)

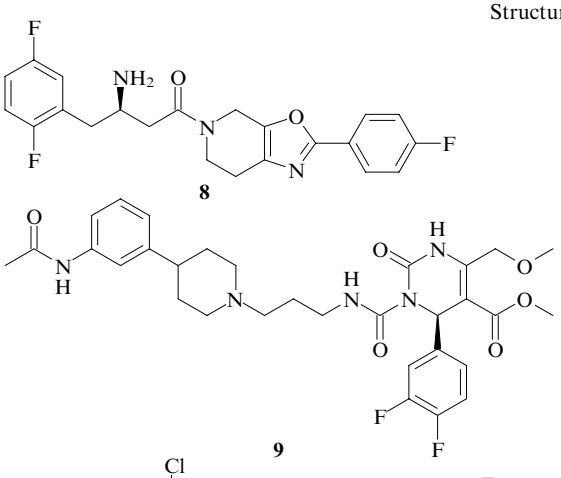


7 (Fluvoxamine)

Yet another class of compounds are pharmaceutical agents used to treat cardiovascular diseases and metabolic diseases (diabetes, hypertension, adiposity). Thiazole (**8**) is used for preventing diabetes, and compound **9** is a remedy against adiposity. Disubstituted 3,3,3-trifluoro-2-hydroxypropylamine **10** and fluorinated derivative of pyridine **11** are cholesteryl ester transfer inhibitors; hence, they are used to prevent cardiovascular diseases.[5]

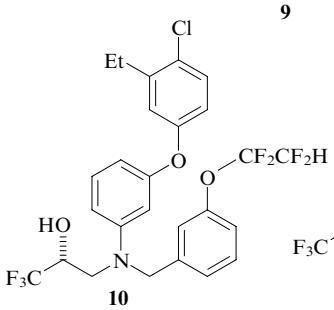
Finally, perhaps the most important area of application of fluorinated compounds in medicine pertains to anticancer agents. 5-Fluoruracil (**12**), 5-fluoro-2′-deoxyuridine (**13**) and their derivatives were among the first agents to be widely used for preventing and treating various tumours.[12]

Structures **8**–**11**

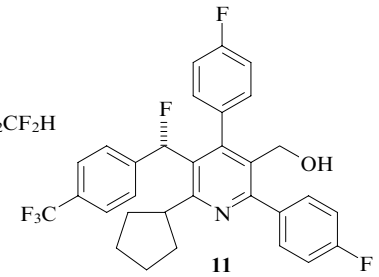


8

9

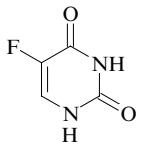


10

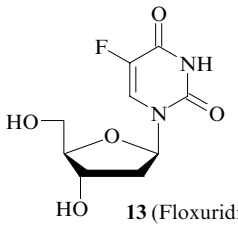


11

Structures **12**, **13**



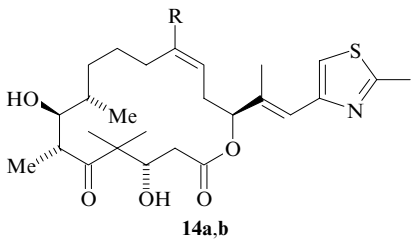
12 (5-Fluorouracil)



13 (Floxuridine)

Rather recently, a series of second-generation epothilones exhibiting extremely high antitumour activities were synthesized.[13] It was found that replacement of the methyl group in the deoxyepothilone B molecule (dEpoB, **14a**) by a trifluoromethyl group enhances the activity of the drug (Fludelone, **14b**) against some tumour cells (Table 2).

Structures **14**



14a,**b**

R = Me (**a**, dEpoB), CF_3 (**b**, Fludelone)

Here, examples are given of only some pharmaceutical agents containing fluorine atoms. In recent years, the number of such agents has constantly increased. For example, whereas in the 1970s, only 2% of all new pharmaceuticals contained fluorine atoms or fluorinated groups, now this percentage is 30%–40%. Hence, a topical task of

Table 2. Inhibition of the tumour cell growth by deoxyepothilone B and Fludelone.[13]

Histology	Tumour cell line	IC_{50}/nmol litre^{-1} (see [a])	
		dEpoB	Fludelone
Lung cancer	A549	3.9 ± 0.4	3.7 ± 2.4
Colon cancer	HT-29	7.2 ± 2.2	4 ± 1.7
	HCT-116	7.5 ± 3.1	3.6 ± 1.3
Breast cancer	MDA-MB-435	7.8 ± 4.2	5.8 ± 2.8
Ovarian cancer	IGROV	15 ± 3.8	2 ± 1.2
	SK-OV-3	13 ± 4.7	1.6 ± 0.5
	OVCAR-3	14 ± 3.6	1.1 ± 0.4
	OVCAR-4	16 ± 2.5	1.8 ± 0.7
Myeloma	RPMI-8226	36.7 ± 2.0	7.6 ± 1.2
	CAG	61.3 ± 4.2	12.0 ± 1.8
	OPM-2	38.9 ± 3.3	8.2 ± 2.2
	NCI-H929	42.7 ± 4.5	9.2 ± 1.9
	MOLP-5	68.6 ± 5.5	14.4 ± 2.6
Marrow stroma	HS-27a	100 ± 10	102 ± 8
	HS-5	100 ± 8	96 ± 7

[a] IC_{50} is the 50% inhibition concentration.

modern chemistry is to devise methods for introduction of fluorine atoms and organofluorine groups into substrates.

Despite the growing demand for fluorinated structures, there is still a large gap between laboratory results and their commercialization. Most of the large-scale syntheses of organofluorine compounds are performed by companies that specialize in processes conducted under severe conditions, which are normally required for fluorination. Therefore, a chemist should think in advance over incorporation of fluorinated building blocks into the structure during the synthesis of pharmaceutical agents. This has a number of undesirable consequences, including the restriction of all conditions of synthesis at the subsequent stages due to the fluorinated group and a decrease in the product yield due to side reactions with fluorine. New methods for introduction of fluorine at late stages of the synthesis are highly demanded.

III. Methods for introduction of fluoroalkyl substituents into various substrates

The introduction of available fluoroalkyl substituents into intricate structures at final stages of the synthesis is an important challenge of synthetic chemistry. The growing interest in this issue resulted in significant achievements in the last 20 years. Perfluoroalkylation reactions are customarily classified, according to the nature of organofluorine species involved, into radical ($R_F^{\bullet}$), nucleophilic (R_F^-) and electrophilic (R_F^+). Note that the introduction of trifluoromethyl groups has been studied in more detail, because this group is used most often to modify biologically active compounds (first of all, pharmaceuticals).[1,2] Methods for the introduction of fluoroalkyl substituents were considered in numerous publications, in particular, in monographs and reviews,[8,14–16] which, however, pay little attention, if any, to the preparation of compounds with phosphorus–fluoroalkyl or metal–fluoroalkyl bonds and to electrochemical fluoroalkylation, C–H fluoroalkylation and many other important processes. In this review we specially emphasize the latest achievements in these fields and summarize recent results that develop traditional approaches to fluoroalkylation. The fundamental reactions and reactions that are of historical value for the chemistry of fluorine and fluoroalkyl derivatives will be mentioned to demonstrate the fundamentals of this field of chemical science.

1. Radical perfluoroalkylation

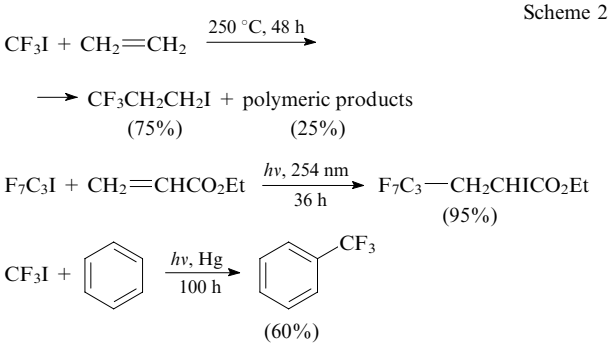
Perfluoroalkyl radicals are to be generated by methods that do not affect other functional groups present in the substrates. Due to their initially electrophilic nature, either highly polarizable σ-electronic systems (*e.g.*, thiolates, selenides or phosphites) or, more preferably, electron-enriched π-systems (*e.g.*, alkenes and aromatic compounds) are convenient substrates for these radicals.

Perfluoroalkyl halides serve as the most available source of perfluoroalkyl radicals. The corresponding fluoroalkyl radicals can be generated by treatment with radical initiators or by photochemical or electrochemical action. The first two methods have found wide use,[17] whereas the last one has been little used so far. Other possible ways for radical generation include thermal or photochemical fragmentation of perfluoroacyl peroxides[18] or perfluoroalkylsulfonyl bromides.[19]

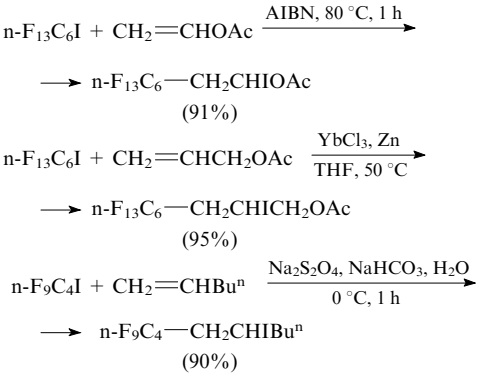
In the 1940s, the addition reaction of perfluoroalkyl radicals to alkenes was discovered.[20] Radical chain reactions can be initiated not only photochemically but also thermally (Scheme 2). Obvious drawbacks of this method were the severe conditions and the formation of polymeric products.[21,22] Nevertheless, this method was also suitable for preparing perfluorinated aromatic compounds.[23]

By analogy with the radical addition of CCl_4 to alkenes,[24] it was found that the addition of fluoroalkyl halides to alkenes in the presence of radical initiators occurs at lower temperatures.[17,25] As initiators, salts of metals in low oxidation states are used in heterogeneous reactions and dithionites are employed in homogeneous processes (Scheme 3).[26]

Scheme 2



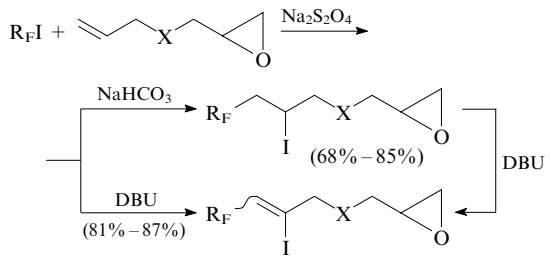
Scheme 3



AIBN is azobisisobutyronitrile

Saloutin and co-workers [27] proposed a one-step method for preparing (perfluoroalkyl)epoxyalkenes in high yields under mild conditions by the reaction of perfluoroalkyl iodides with alkenes (allyl glycidyl ether, 1,2-epoxydec-9-ene) in the presence of sodium dithionite and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as a radical initiator (Scheme 4). In the absence of DBU, the epoxyalkane is formed, which can be completely converted to epoxyalkene in the presence of DBU.

Scheme 4

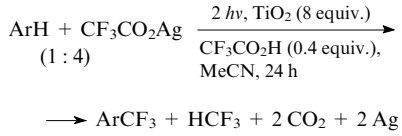


$R_F = CF_3$, C_4F_9, $C_3F_7OCF(CF_3)CF_2OCF(CF_3)$; X = O, $(CH_2)_4$

Similar ideas were employed in the studies of Církva *et al.*[28, 29] to prepare polyfluoroacetates from perfluoroalkyl iodide and allyl acetate.

One more approach to photochemical fluoroalkylation is based on the use of CF_3CO_2Ag as a source of the CF_3 radical and titanium dioxide as a photocatalyst.[30] This method was used to obtain trifluoromethyl aromatic derivatives; however, the product yields were moderate (Scheme 5). A variety of trifluoromethyl-substituted fullerenes were prepared by using silver trifluoroacetate at 300 °C.[31]

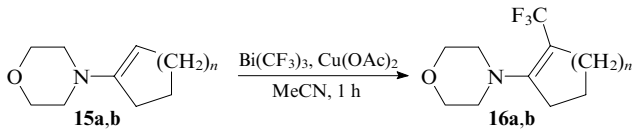
Scheme 5



ArH	$ArCF_3$	Yield (%)
PhH	$PhCF_3$	50
1,4-$Cl_2C_6H_4$	2,5-$Cl_2C_6H_3CF_3$	45
PhBr	$BrC_6H_4CF_3$ ($p:o:m$ = 2 : 1 : 1)	46
$PhCO_2Et$	$CF_3C_6H_4CO_2Et$ ($m:o:p$ = 3 : 2 : 3)	26

Naumann and co-workers [32] successfully used the $Bi(CF_3)_3-Cu(OAc)_2$ system for radical trifluoromethylation, the copper salt being necessary for this reaction. According to this method, reactions with enamines **15a**,**b** afforded (trifluoromethyl)enamines **16a**,**b** (Scheme 6). In the case of 1-morpholino-2-trifluoromethylcyclopentene (**16a**), the yield was 83% and in the case of 1-morpholino-2-trifluoromethylcyclohexene (**16b**), the yield was almost twice lower, namely, 41%. When *N*,*N*-diethylaniline was introduced in this reaction, a 2-trifluoromethyl- and 4-trifluoromethyl-*N*,*N*-diethylaniline mixture in 1 : 1.7 ratio was formed, the overall yield being 48%.

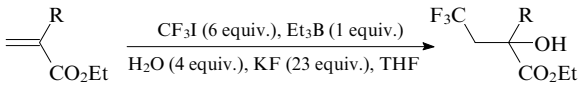
Scheme 6



n = 1 (**a**), 2 (**b**)

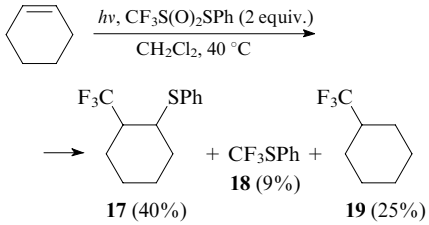
The radical hydroxytrifluoromethylation of α,β-unsaturated esters can be performed by means of trifluoromethyl iodide and triethylborane in the presence of potassium fluoride and water (Scheme 7).[33]

Scheme 7



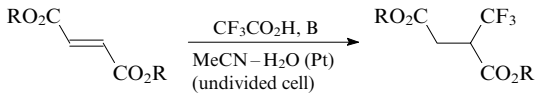
It was found that aliphatic thiols can be perfluoroalkylated by perfluoroalkyl iodides and bromides in the presence of NaO_2SCH_2OH in a DMF–water mixture;[34] aromatic amines are trifluoromethylated by the $CF_3I-Zn-SO_2$ system.[35] By photolysis of trifluoromethanethiosulfonates $CF_3S(O)_2SR$ or trifluorothioacetates $CF_3C(O)SR$ in the presence of alkenes,[36] it is possible to obtain, for example, (trifluoromethyl)thio derivatives **17** and **18** and trifluoromethylcyclohexane (**19**) (Scheme 8).

Scheme 8



Recent publications deal with electrochemical trifluoromethylation of butyl acrylate,[37] dialkyl fumarate (Scheme 9),[38] unsaturated nitriles [39] and aromatic compounds [40] in which trifluoroacetic acid serves as a source of the trifluoromethyl radical.

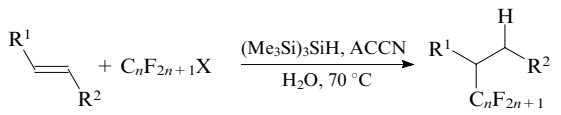
Scheme 9



R = Et (45% yield), Pr^i (19%), Bu^n (52%); B is base

One more approach was demonstrated by Postigo and co-workers.[41, 42] They took as the base the radical reaction involving $(Me_3Si)_3SiH$ as the mediator and 1,1′-azobis(cyclohexanecarbonitrile) (ACCN) in water as the radical initiator. The appropriate bromides and iodides were used as the sources of perfluoroalkyl groups (Scheme 10).

Scheme 10



R^1 = CHO, R^2 = Me; R^2 = H: R^1 = Bu^n, Ph, CN, *etc.*; X = Br, I

The reaction involves the initiated generation of the $R_3Si^{\bullet}$ radicals, which react with perfluoroalkyl halide to yield perfluoroalkyl radicals, which then add to the double bond. This approach was investigated in relation to non-fluorinated analogues.[42–44] The use of this reaction is faced by certain limitations. First, it is necessary that the $R_3Si^{\bullet}$ radicals react faster with R_FX than with alkene, while the resulting $R_F^{\bullet}$ radicals react with alkene rather than with R_3SiH. By using perfluorohexyl iodides, good product yields were attained; however, bromides provided only moderate yields. Furthermore, water to be used in the reaction had to be completely degassed. Despite the limitations, the reaction has a great practical potential.

Radical perfluoroalkylation can involve simultaneously photocatalysis and organocatalysis,[45] and also use titanium oxide as a photocatalyst.[46] Radical perfluoroalkylation of polycyclic aromatic compounds is non-selective.[47] A recent publication[48] describes the light-induced iodoperfluoroalkylation of multiple bonds in water.

Cascade radical addition–cyclization–trapping reaction follows the addition route that is unfavourable from the standpoint of polarity, namely, addition of electrophilic perfluoroalkyl radicals to electron-deficient acceptors.[49]

Not long ago, radical perfluoroalkylation reactions, where fullerene derivatives served as substrates, were implemented,[50] but they are also generally non-selective.

Thus, during the last two decades, radical perfluoroalkylation methods have been considerably advanced. Unfortunately, many of them require drastic conditions. Nevertheless, approaches that imply reactions in aqueous media under mild conditions and give products in high yields are also being developed.

2. Electrophilic perfluoroalkylation

Perfluoroalkyl halides do not function as effective perfluoroalkylating electrophilic reagents, as might be expected by analogy with alkyl halides. The stability of

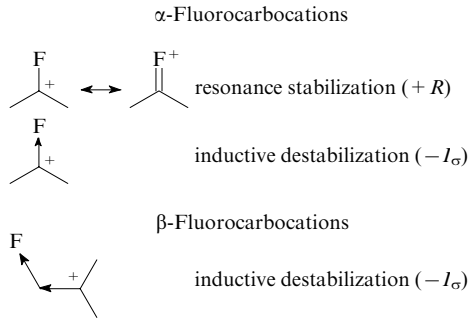


Figure 3. Stabilizing and destabilizing effects for fluorinated carbocations.

fluorinated carbocations[51] is determined by the subtle interplay between the inductive destabilization and mesomeric stabilization of the positive charge. Fluorine atoms in the α-position stabilize the positively charged carbon atom owing to the π-donor effect (+ *R*) of free electron pairs. On the other hand, the positive charge is destabilized by the negative inductive ($-I_\sigma$) effect of fluorine. Fluorine atoms in the β-position relative to the positively charged carbon atom exert only a strong destabilizing inductive effect (Fig. 3).

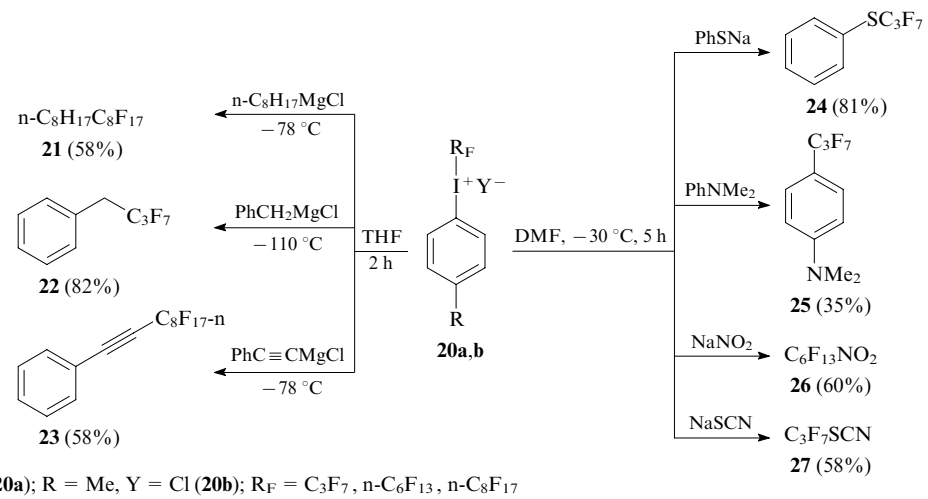
Due to the strong destabilizing inductive effect, only few salts of α- and β-fluorocarbocations have been described. Despite numerous attempts to isolate salts of F_3C^+, this simplest perfluorinated carbocation is still only the subject of numerous theoretical investigations.[52, 53]

a. Perfluoroalkyliodonium salts

Perfluoroalkyl groups do not react with non-oxidizable nucleophiles by the true electrophilic mechanism due to their high electronegativity (*e.g.*, the electronegativity of the CF_3 group is 3.45, whereas that of the Cl atom is only 3.0). On the other hand, if the electronegativity of the leaving group X of the potential perfluoroalkylating reagent R_FX is increased to a value equal to or higher than the R_F electronegativity, then electrophilic perfluoroalkylation formally becomes feasible.[54]

This concept was implemented by L M Yagupolskii's research team,[55] who were the first to perform electrophilic

Scheme 11



R = H, Y = OTf (**20a**); R = Me, Y = Cl (**20b**); R_F = C_3F_7, n-C_6F_{13}, n-C_8F_{17}

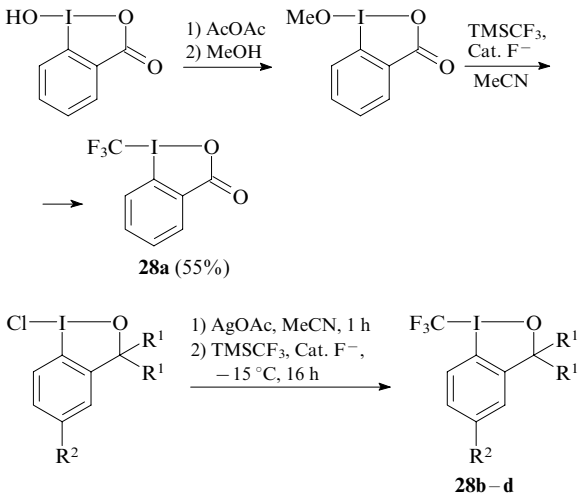
perfluoroalkylation of various nucleophiles using perfluoroalkyliodonium chlorides. Later it was shown that tetrafluoroborates are more reactive.[56] A similar reactivity was found for triflates (so-called FITS reagents — perfluoroalkyl phenyl iodonium trifluoromethanesulfonates) developed by Umemoto's team [54] (Scheme 11). Iodonium salts **20a** (R = H, Y = OTf) were used to synthesize compounds **21**–**23**, while salts **20b** (R = Me, Y = Cl) were used to obtain derivatives **24**–**27**. Fluoroalkyliodonium salts showed themselves as versatile reagents for functionalization of a variety of substrates and introduction of various fluoroalkyl groups; however, these reactions have to be performed at low temperatures, which makes the method less convenient.

In order to prepare salts **20,** perfluoroalkyl iodides are successively oxidized to iodine(III) bis(trifluoroacetates) or difluorides, which react with arenes according to the electrophilic substitution pattern. The intermediates thus formed are converted to chlorides (**20b**) or tetrafluoroborates **20c** (Yagupolskii reagents), or triflates (**20a**,**d**), or hydrosulfates (**20e**) (Umemoto reagents) (Scheme 12). Either covalent or ionic character of a particular iodonium salt is mainly determined by the electronegativity of the counter-ion Y. The ionicity of the I—Y bond increases in the series Y: Cl < OSO_2Me < OSO_3H < OTf, in accordance with the ^{19}F NMR chemical shifts of the CF_2 group. Even for the most electronegative trifluoromethanesulfonate group, the I—Otf bond, although highly polarized, is not completely ionic.[54]

The use of FITS reagents is associated with additional difficulties faced by their synthesis, particularly, great losses upon successive recrystallizations from the reaction mixture and the use of expensive trifluoromethanesulfonic acid the excess of which is very difficult to recover.

In 2006, Togni and co-workers [57, 58] synthesized new, more stable perfluoroalkyliodonium derivatives **28a**–**d** (Scheme 13).

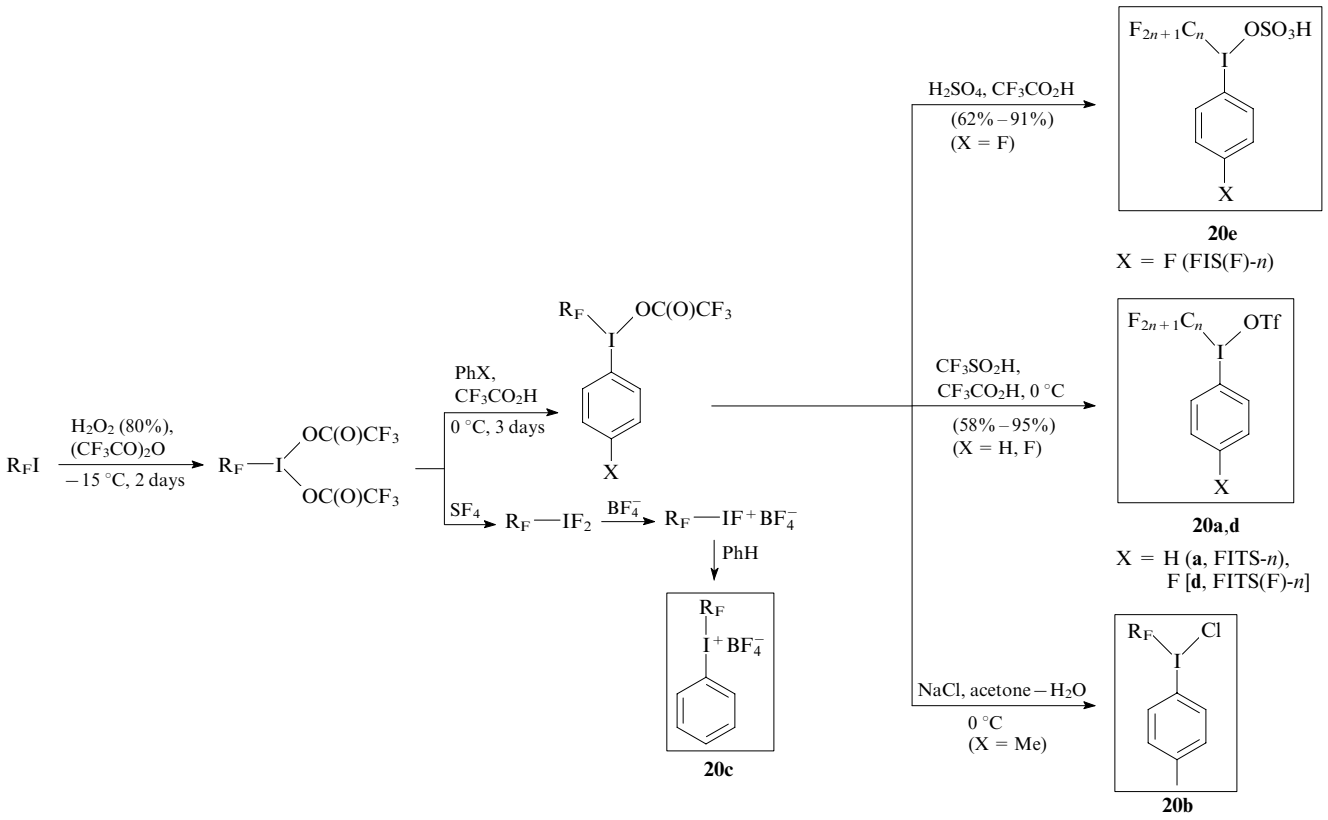
Scheme 13



TMS = $SiMe_3$; R^2 = H: R^1 = Me (**b**, 46% yield), CF_3 (**c**, 50%); R^1 = CF_3, R^2 = Me (**d**, 39%)

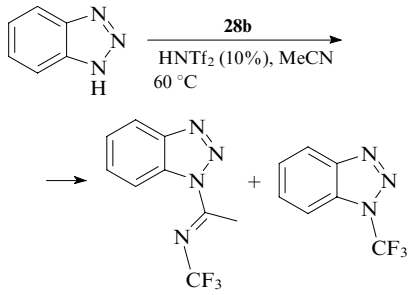
Compound **28b** was used to trifluoromethylate β-keto esters and α-nitro esters and to prepare trifluoromethyl derivatives of sulfur, phosphorus and oxygen compounds.[58] Compounds **28a**,**b** successfully served for trifluoromethylation of aromatic and aliphatic primary and secondary phosphines.[59, 60] Moreover, in the case of derivative **28a**, trifluoromethylation of aromatic and aliphatic alcohols was accomplished.[61, 62]

Scheme 12



Recently, Togni and co-workers[63] reported on the discovery of a reaction resembling the Ritter reaction, giving N-trifluoromethylated imines upon acid-catalyzed electrophilic trifluoromethylation of nitriles in the presence of azoles such as benzotriazole, indazole and pyrazoles. The trifluoromethyl group is transferred from hypervalent iodine under rather facile conditions (Scheme 14).

Scheme 14



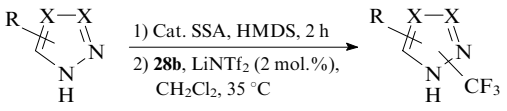
The same fluoroalkylating agent was used by Togni's team to fluoroalkylate a variety of substrates;[64–75] it was also used by many other research teams.[76–84]

The formation of *N*-trifluoromethylbenzotriazole as a by-product in this reaction (see Scheme 14) indicates that direct N-trifluoromethylation of azoles with trifluoromethylating agents of this type is indeed possible. This reaction is potentially useful and desirable.

Here it is pertinent to note that in 2000, Yagupolskii *et al.*[85] reported one of the first syntheses of *N*-trifluoromethylazoles *via* successive interconversions of functional groups but an efficient procedure appeared only in the most recent works by Togni's team.[86]

These researchers were able to select conditions for effective direct N-trifluoromethylation of azoles in high yields. The optimization of the reaction conditions for benzotriazole resulted in the desired compounds being formed as the major products. The optimized conditions imply *in situ* silylation of the substrate with 1,1,1,3,3,3-hexamethyldisilazane (HMDS) in the presence of catalytic amounts of sulfuric acid on silica (SSA) followed by trifluoromethylation in a concentrated solution in CH_2Cl_2 at 35 °C in the presence of a catalytic amount of $HNTf_2$ and $LiNTf_2$ (Scheme 15). These conditions were applied with success to different azoles (indazoles, pyrazoles, triazoles and tetrazoles).[86]

Scheme 15

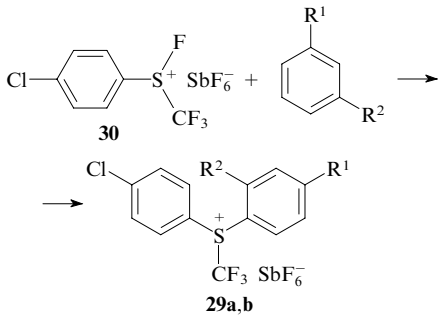


X = N, CR′

b. Fluoroalkylaed onium salts of chalcogens (S, Se, Te, O)

In 1984, L M Yagupolskii published data on the synthesis and reactivity of trifluoro-substituted sulfonium salts. Today he is deservedly called the pioneer of the electrophilic perfluoroalkylation chemistry.[87] Salts **29a**,**b** were synthesized by the reactions of compound **30** with *m*-xylene and anisole, respectively (Scheme 16).[88] These salts reacted with sodium *p*-nitrothiophenolate to give trifluoromethyl *p*-nitrophenyl sulfide but did not react with *N*,*N*-dimethylaniline. This publication remained unnoticed for some period due to low reactivity of sulfonium salts.

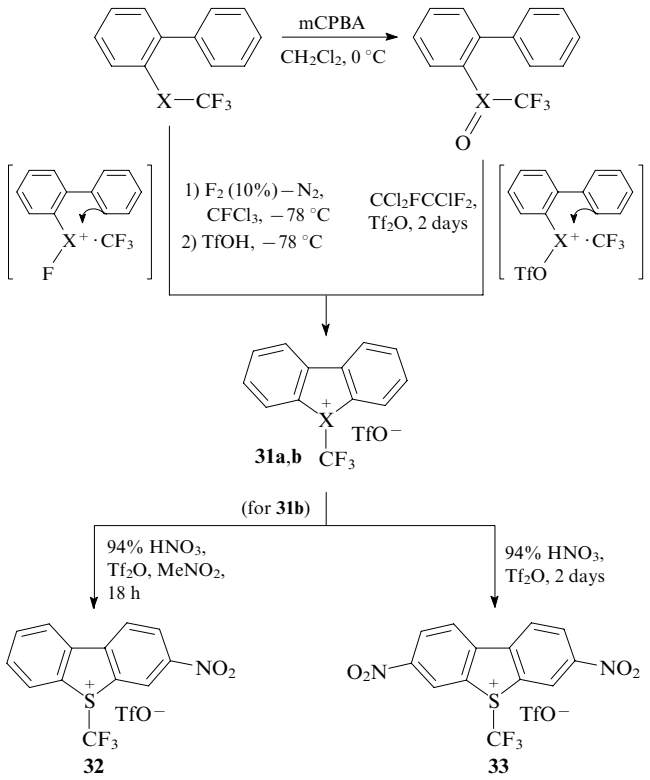
Scheme 16



$R^1 = R^2 = Me$ (**a**); $R^1 = OMe$, $R^2 = H$ (**b**)

In 1990, Umemoto's reasearch team developed a new perfluoroalkylation system based on fluoroalkyl derivatives of dibenzothiophene, dibenzoselenophene and dibenzotellurophene salts.[54, 89] Salts **31a**,**b** were synthesized either by oxidation of the initial sulfides (selenides) followed by cyclization or by direct fluorination by a $F_2(10\%)-N_2$ mixture (Scheme 17). Salt **31b** was then converted to nitro derivatives **32** and **33**. Trifluoromethyl-substituted dibenzotellurophene salts were prepared in good yields by the reaction of 2-(trifluoromethyltelluro)biphenyl with DMSO and Tf_2O. Nitro-substituted tellurium-containing salts were prepared by a similar reaction with HNO_3 and Tf_2O.[89]

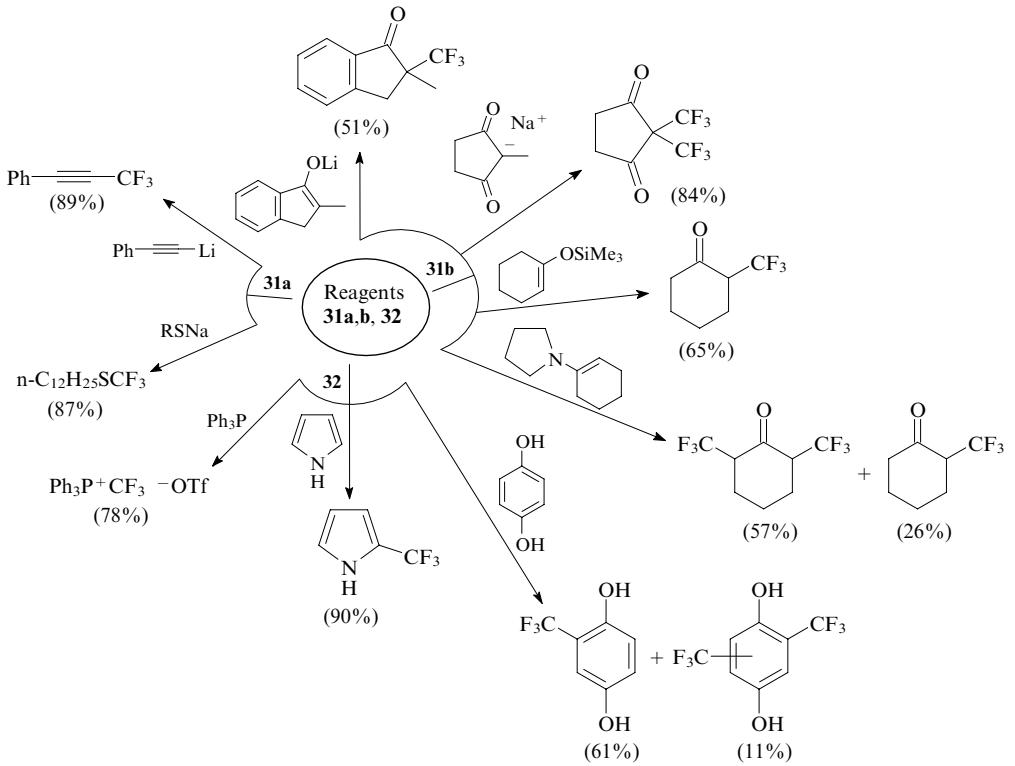
Scheme 17



*m*CPBA is *m*-chloroperoxybenzoic acid; X = Se (**31a**), S (**31b**)

The reactivity of these compounds increases in the sequence of chalcogens Te < Se < S and the sequence of substituents in the rings Alk < H < NO_2. More potent

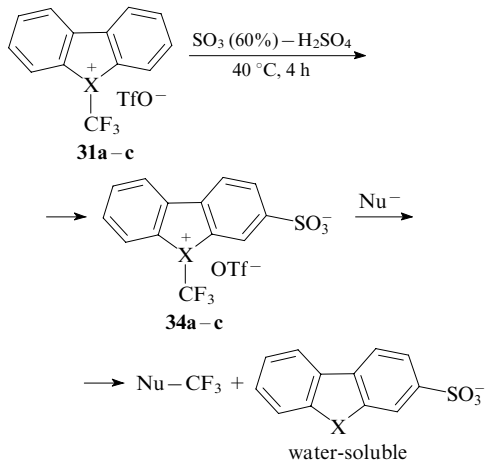
Scheme 18



perfluoroalkylating agents react with less reactive nucleophiles to give good yields of products, weaker reagents react with strong nucleophiles with good yields of products. Finally, medium-strength trifluoromethylating agents react with moderate nucleophiles giving high yields of products. Salts **31a**,**b** and **32** were chosen as useful trifluoromethylating agents with different reactivities. The reactivity towards trifluoromethylation increases in the sequence **31a** < **31b** < **32**. Taking advantage of the above-noted regularities and using these trifluoromethylation agents, it was possible to functionalize a broad range of nucleophiles (carbanions, phenols, anilines, phosphines, thiolates and halides) (Scheme 18).

Trifluoromethylated onium salts of chalcogens are soluble and do not decompose in a multitude of polar solvents such as DMSO, DMF, acetonitrile, THF and dichloromethane. Dibenzothiophene (or the corresponding derivatives of other chalcogens) are formed as by-products of trifluoromethylation of any nucleophile, which causes additional difficulties for the isolation of the major reaction products. In order to facilitate the isolation of the reaction products, zwitter-ion sulfonic derivatives **34a**–**c** were synthesized. In this case, the by-product is formed as dibenzothiophenesulfonic acid, which can be conveniently removed from the reaction mixture *via* extraction into aqueous solutions of bases [54] (Scheme 19).

Scheme 19



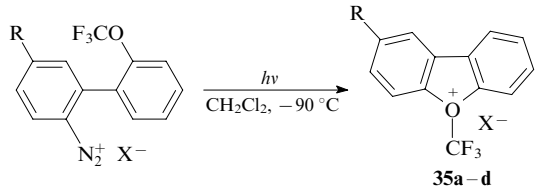
X = Se (**a**), S (**b**), Te (**c**)

Trifluoromethyl derivatives of various porphyrins were isolated using the most potent trifluoromethylating reagent **32**.[90] Trifluoromethylation of β-keto esters and alkenyloxysilanes was accomplished under mild conditions by using trifluoromethyldibenzothiophenium tetrafluoroborate (**31d**).[91] β-Keto esters reacted with tetrafluoroborate **31d** in the presence of excess potassium carbonate and a catalytic amount of tetrabutylammonium iodide in DMF for 3 h giving rise to α-trifluoromethyl-β-keto esters in moderate yields. In the reaction with (−)-menthyl-β-keto ester, the diastereomeric excess (*de*) was 4% (the overall product yield was 97%). In the reaction of **31b** with alkenyloxysilanes in DMF in the presence of $Bu^n_4N^+[Ph_3SnF_2]^-$, α-trifluoromethyl ketones were obtained in good yields.[3,91,92]

Thermally unstable trifluoromethylated oxonium cations were synthesized for the first time by photolysis of diazonium salts at very low temperatures (Scheme 20).[54,93] The low-temperature NMR data confirmed the formation of the O–CF_3 bond in salts **35a**–**d**. As the temperature is raised, the salts start to decompose at −70 °C and are completely destroyed at −30 °C. The decomposition gives tetrafluoromethane, which confirms the ease of generation of F_3C^+ from trifluoromethyloxonium salts. The stability of these compounds increases in the following sequences of substituents in the ring F < H < Alk and counter-ions $BF_4^- < PF_6^- < SbF_6^- < Sb_2F_{12}^-$. More potent electron-

donating groups in the ring and less electrophilic counterions increase the stability of trifluoromethyloxonium salts.

Scheme 20



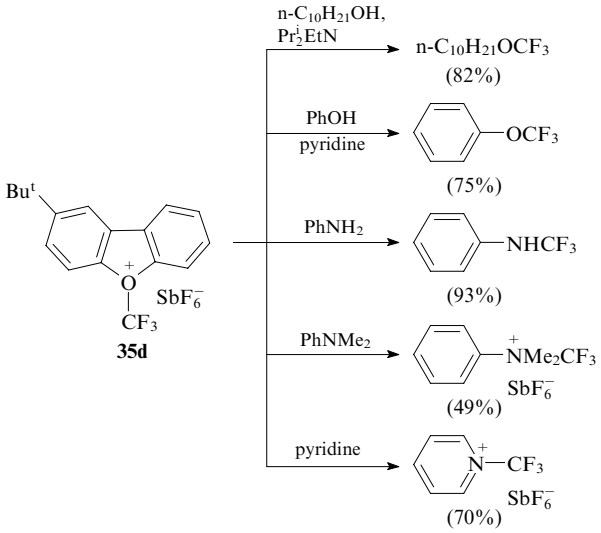
35a–d

R = F, X = BF_4 (**a**); R = H: X = PF_6 (**b**), SbF_6 (**c**);
R = Bu^t, X = SbF_6 (**d**)

The use of trifluoromethyloxonium salts made it possible to perform direct trifluoromethylation at the oxygen and nitrogen atoms (Scheme 21).[16] Alcohols and phenols reacted with compound **35d** in the presence of pyridine or trialkylamine in dichloromethane at low temperature to give trifluoromethyl ethers in good yields. The reactions of **35d** with primary and secondary amines yielded *N*-trifluoromethylamines. Ammonium and pyridinium salts were formed in the reactions with tertiary amines and pyridine (see Scheme 21).

Obviously, trifluoromethylated oxygen and sulfur onium salts have considerable differences. Aniline reacts with trifluoromethyloxonium salt **35d** to give *N*-trifluoromethylaniline, whereas salt **32** with aniline gives a mixture of *ortho*- and *para*-trifluoromethylated aniline isomers.

Scheme 21



35d

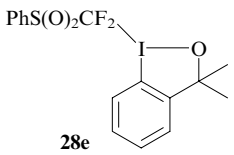
When made to react with alkylamines, salts **35a–d** give *N*-trifluoromethylamines, whereas salts **31a**,**b**, **32** and **33** decompose to afford CF_3H. These differences are attributable to the difference in the reaction mechanisms for these compounds. Trifluoromethyloxonium salts are expected to react by the S_N1 or S_N2 mechanism, which implies the formation of F_3C^+ or $F_3C^{\delta+}$ species. In turn, in the case of trifluoromethyl derivatives of dibenzothiophene, charge transfer complexes are formed,[54] their geometry being

Table 3. Electrophilic fluoroalkylation reagents and nucleophiles.[87]

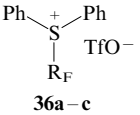
Reagent	Nucleophiles											
	keto derivatives [a]	sulfides	aromatics	phosphines	alcohols [b]	phenols [b]	amines	sulfonic acids	acetic acid	enol silyl ether	dicyanoalkylidenes	alkynes
36a [c]	+	+	+									
31b,**c**	+	+	+	+						+	+	+
37	+										+	
38a				+			+	+				
36b,**c**	+											+
38b	+	+		+	+	+	+	+	+			
35d					+	+	+					
28a			+	+	+	+		+		+		
28b	+	+	+	+			+	+		+		
28e		+										
39a,**b**	+										+	+
39c		+		+	+		+					
40a		+					+					+
39d	+ (see [b])				+	+		+	+			
40b,**c**												+

[a] Ketones, diketones, aldehydes, enamines, esters, β-keto esters; [b] O-alkylation; [c] commercially available.

Structures **28e**, **36–40**

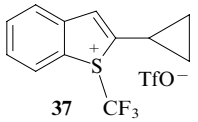


28e

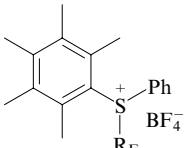


36a–c

R_F = CF_3 (**a**), CF_2Br (**b**), CF_2CF_3 (**c**)

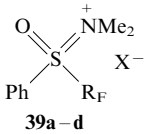


37



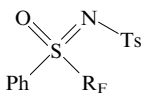
38a,**b**

R_F = CF_2H (**a**), CH_2F (**b**)



39a–d

R_F = CF_3: X = BF_4 (**a**), TfO (**b**); R_F = CF_2H: X = BF_4 (**c**), PF_6 (**d**)



40a–c

R_F = CF_2H (**a**), CF_2Br (**b**), $CFCl_2$ (**c**)

responsible for the reaction selectivity (formation of *ortho*- and *para*-isomers). The oxygen atom in trifluoromethyloxonium salts has a more pronounced electron-withdrawing effect, which is sufficient to generate F_3C^+, whereas the electron-withdrawing properties of sulfur do not suffice for the formation of the true trifluoromethyl carbocation.

Recent years have seen revived interest in reactions involving electrophilic perfluoroalkylating reagents. Both the pioneering works and numerous recent advances provide the possibility to easily add perfluoroalkyl groups (mainly trifluoromethyl group) to miscellaneous nucleophiles. The review of Macé and Magnier,[87] dedicated to the memory of Professor Lev Yagupolskii, surveys the achievements along this line (Table 3). Most reactions occur under mild conditions and are selective and tolerant with respect to other functional groups. Obviously, the range of nucleophiles will be extended. Those nucleophiles that are still missing from the table or are under research and reactant selection (primary and secondary amines, phenols and tertiary and secondary alcohols) will form subjects of investigation for the near future.

Thus, electrophilic perfluoroalkylation methods open up new opportunities for the synthesis of diversified products. However, one cannot but mention the drawbacks of these methods. Often it is necessary to use thermally or chemically unstable compounds, which restricts the conditions of applicability of many of the above procedures. Also, as in the case of radical perfluoroalkylation, the approach is mainly valid for trifluoromethylation reactions.

3. Nucleophilic perfluoroalkylation

Nucleophilic fluoroalkylation implies the formation of the R_F^- anion as the reactive species. All perfluoroalkyl carbanions are stabilized by the negative inductive ($-I_\sigma$) effect of fluorine atoms. On the other hand, organic α-fluorocarbanions are destabilized due to the p–π repulsion between the lone electron pairs of fluorine and the anionic centre ($+I_\pi$) (Fig. 4). This is reflected in the rather weak acidity of CHF_3 as compared with other halomethanes (the pK_a values for trihalomethanes and methane are as follows: CHF_3 30.5, $CHCl_3$ 22.4, $CHBr_3$ 22.7, CH_4 48.2).[94–97]

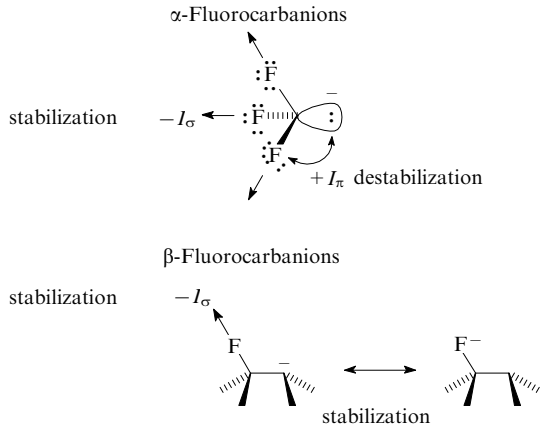


Figure 4. Stabilizing and destabilizing effects for fluorinated carbanions.

Conversely, for β-fluorocarbanions, the presence of negative hyperconjugtion[95] has a stabilizing effect (see Fig. 4). For example, in the perfluoro-*tert*-butyl anion, the negative charge is not fully concentrated on the carbon atom but relatively high partial charges occur on all β-fluorine atoms.[96]

The presence of fluorine atoms at the carbanion centre considerably affects the nucleophilic alkylation reactions. It was noted that F substituents at the anionic carbon atom have a negative effect on many nucleophilic fluoroalkylation reactions; this was called the 'negative fluorine effect' (Fig. 5).[97] Presumably, this is due to two factors:

— thermal instability of fluorinated carbanions against α-elimination (self-decomposition);

— nucleophilicity inherent in fluorinated carbanions due to the effect of fluorine atoms (*e.g.*, the hard–soft nature of fluorinated carbanions).

To overcome this negative fluorine effect , attempts were made to develop nucleophilic fluoroalkylation reactions with fluorinated sulfones and related reagents. These results can be summarized as four approaches: (i) a change in the

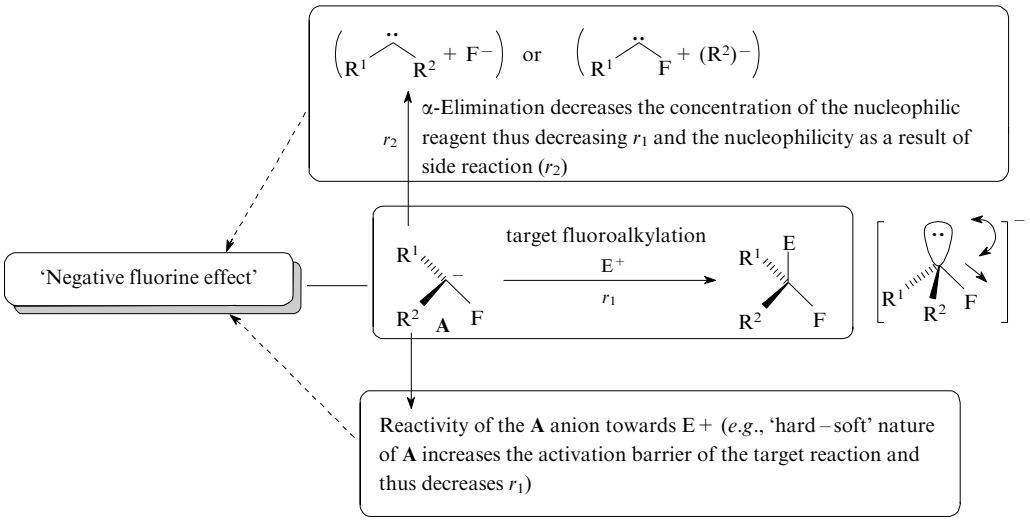


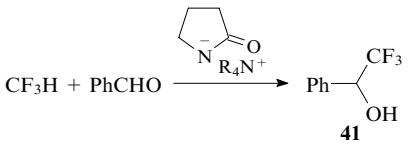
Figure 5. Schematic illustrating the 'negative fluorine effect'.

number of fluorine atoms, (ii) minor changes of neighbouring groups, (iii) change in the counter-ion metal, in particular, using the carbon–metal covalent bond for variation of reactivity, (iv) creation of more favourable conditions for generation of carbene species. These approaches are considered in every detail in a review.[97]

Generally, the perfluorinated organic anions can be generated by the same methods as usual alkyl or aryl anions, in particular, either by deprotonation of CH bonds on treatment with strong bases or by exchange of a halogen atom with a metal atom (the halogen is most often iodine or bromine).

Deprotonation of R_FH is an effective way of generation of fluoroalkyl carbanions from the atom economy standpoint and in view of the low cost of R_FH.[98] The first example of reactions based on trifluoromethane deprotonation was reported by Shono *et al.*[99] in 1991 (Scheme 22).

Scheme 22

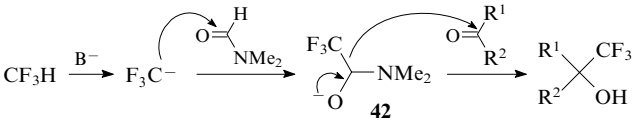


41

R	Yield (%)
Et	34
Bu^n	74
n-C_8H_{17}	80

The conduction of this reaction was methodically complicated by several factors: first, the boiling point of trifluoromethane is −82.2 °C; second, despite the good yields of product **41**, compounds used as bases were generated electrochemically *in situ*. The reaction was also carried out in the presence of some bases (LiH, NaH and Bu^tOK) but the yields were 0%, 28% and 40%, respectively. Finally, the third issue that limits the applicability of this method is the necessity to trap and stabilize the trifluoromethanide anion immediately after the formation in order to avoid its fragmentation. The last mentioned issue is likely to be the major obstacle to further development of this method. However, the persistent effort of researchers [100, 101] has met with success. It was found that when DMF serves as the solvent in the presence of a strong base [Bu^tOK, $(SiMe_3)_2NK$, DMSO–KH], adduct **42** formed by the trifluoromethanide anion and DMF acts as the trifluoromethylating reagent (Scheme 23).

Scheme 23

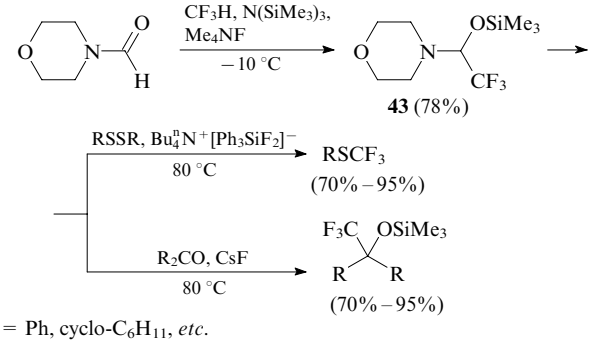


42

B^- is base

Adduct **42** proved to be a convenient trifluoromethylating reagent for various carbonyl compounds.[102] Subsequently, convenient and stable reagents were obtained based on the CF_3H–DMF adduct, for example, compound **43**, which was used to trifluoromethylate a variety of organic compounds (Scheme 24).[103–105]

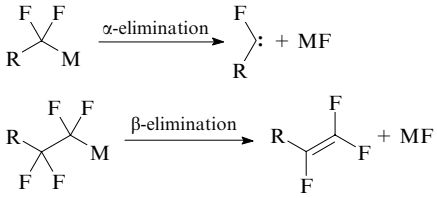
Scheme 24



R = Ph, cyclo-C_6H_{11}, *etc.*

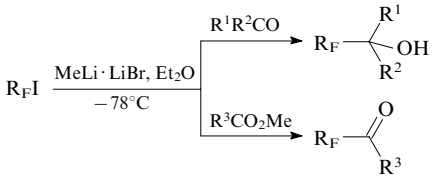
If the carbanion is bonded to metal, for example, lithium or magnesium, the possibility of liberation of high crystal lattice energy upon the formation of poorly soluble fluoride (*e.g.*, 245 kcal mol^{-1} for LiF) contributes to fragmentation of organometallic perfluoroalkyl compounds. If there are α-fluorine atoms such as in CF_3Li (the existence of which was not unambiguously proven), elimination of one of these atoms gives rise to a carbene. If the molecule also contains β-fluorine atoms, β-elimination produces a terminal perfluoroalkene (Scheme 25).

Scheme 25



These specific features of perfluoroalkyl organometallic compounds should be taken into acount when working with them. Perfluoroalkyl lithium compounds are generated *in situ* at very low temperatures (−78 °C and below) and immediately react with an appropriate electrophile, which is represented most often by carbonyl compounds — aldehydes, ketones [106, 107] or esters § (Scheme 26).

Scheme 26



R^1 = Me, R^2 = n-C_5H_{11}; R^1 = n-C_7H_{15}, R^2 = H; R^1–R^2 = $(CH_2)_5$, *etc.*; R^3 = Ph, $Ph(CH_2)_2$, CH_2=CH, Pr^i, Bu^t, *etc.*

Despite the inconvenience of handling, perfluoroalkyl lithium compounds were employed a short while ago in flow microreactors immersed into a bath maintained in a thermostat.[108] In the first stage, perfluoroalkyl halide reacted with methyllithium and, after that, an electrophile was added to the reaction mixture.

Fluoroalkyl Grignard reagents are known but they are thermally very unstable. Smith *et al.*,[109] while studying

§ See H Uno, Y Shiraishi, H Suzuki *Bull. Chem. Soc. Jpn.* **62** 2636 (1989).

organofluorine Grignard reagents, found that they rapidly decompose at temperatures of about −70 °C or higher. Moreover, the compounds described as R_FX (X = Br, I) do not react directly with magnesium metal; hence, the metal–halogen exchange is more convenient (Scheme 27).[109, 110] A drawback of this method is that product **44** is highly contaminated by halide **45**, which may complicate the further synthesis.

Scheme 27

$$R_FX + RMgX \longrightarrow \underset{\mathbf{44}}{R_FMgX} + \underset{\mathbf{45}}{RX}$$

Fluoroalkyl zinc reagents, which are more stable than Mg compounds, are also rather difficult to prepare and isolate. Insoluble fluoroalkyl zinc derivatives are known to decompose above −40 °C.[111] Soluble reagents are thermally more stable [112] but have some other drawbacks. For example, trifluoromethylzinc bromide exists in acetonitrile as two forms occurring in equilibrium (Scheme 28).[113] Therefore, $(MeCN)_2Zn(CF_3)Br$ acts as a difluoromethylating agent and a nucleophilic fluorinating agent rather than as a trifluoromethylating agent.

Scheme 28

$$MeCN{-}\underset{\displaystyle CF_3}{\overset{\displaystyle Br}{Zn}}{-}NCMe \rightleftharpoons [CF_2ZnBr(MeCN)_2]^+F^-$$

However, in DMF or THF, trifluoromethyl zinc derivatives can serve as sources of nucleophilic trifluoromethyl fragments generated *in situ* upon sonication. Perfluorinated organic zinc compounds are used in the Barbier reaction, in palladium-catalyzed cross-coupling and in hydroperfluoroalkylation of alkynes and alkenes.[114, 115]

Zinc and copper compounds with perfluoroalkyl groups are stabilized owing to more covalent nature of the metal–carbon bond. As has already been noted, copper(I) compounds are prepared and isolated rather easily and react over a broad temperature range. Trifluoromethylcopper(I) can be obtained by decarboxylation of trifluoroacetates in the presence of copper(I) salts at 150 °C or by the reaction of copper powder with fluoroalkyl iodides. However, even for CF_3Cu, which appears stable at the first glance, an equilibrium between trifluoromethylcopper(I) and the difluorocarbene copper(I) complex was proved to exist, the equilibrium being dependent on the temperature and the solvent.[116] This equilibrium can be used to increase the chain length of perfluoroalkylcopper(I) *via* insertion of a difluorocarbene (Scheme 29). The addition of a stoichiometric amount of hexamethylphosphoramide (HMPA) into the reaction mixture stabilizes trifluoromethylcopper and this terminates the chain growth.

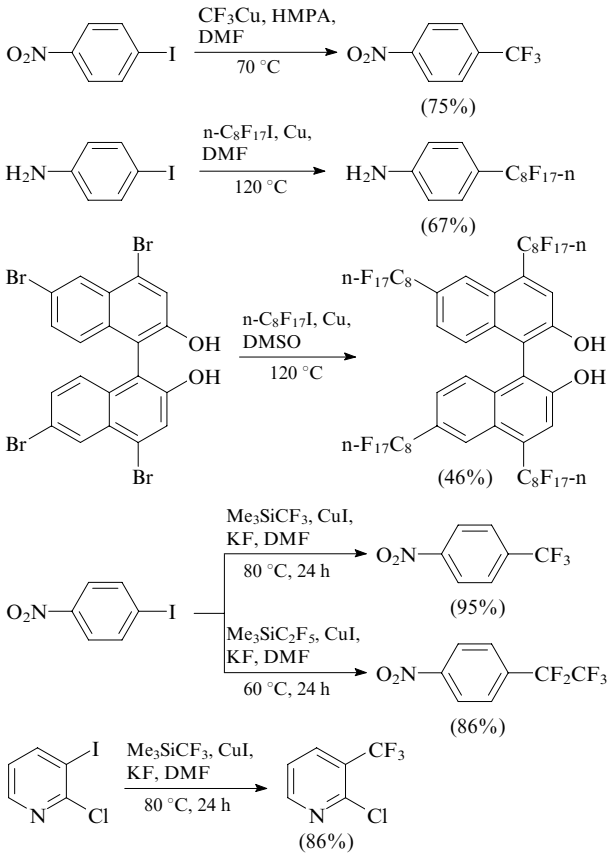
Scheme 29

$$CF_3Cu \rightleftharpoons [CF_2Cu]^+F^- \xrightarrow{CF_3Cu} CF_3CF_2Cu + CuF$$

$$CF_3CF_2Cu \rightleftharpoons [CF_3CFCu]^+F^- \xrightarrow{\text{further chain elongation}} \cdots$$

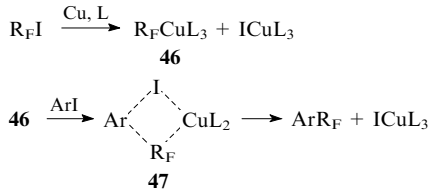
The perfluoroalkylcopper reagents are used most often in the cross-coupling reactions with aryl bromides and iodides to give perfluoroalkyl-substituted aromatic compounds (Scheme 30).[116] The key difficulty associated with trifluoromethylation reactions involving copper is in the formation of perfluoroethyl derivatives, which resist separation during workup of the reaction mixture and purification. These impurities appear as a result of the above-mentioned insertion of difluorocarbenes, which can, however, be suppressed by optimization of the reaction conditions (selection of the appropriate solvent and low temperature). The reaction is carried out under mild conditions if Me_3SiCF_3 is used as the primary source of nucleophilic trifluoromethyl group, together with potassium fluoride and copper iodide in a DMF–HMPA solvent mixture. In this case, trifluoromethylcopper(I) is formed *in situ*.[117] The same method (although involving $Me_3SiC_2F_5$) is utilized for pentafluoroethylation of aryl iodides (see Scheme 30).[118, 119]

Scheme 30



The mechanism of copper-involving cross-coupling of aryl and perfluoroalkyl iodides is supposed to be similar to the mechanism of reaction of aryl halides and copper(I) salts with organic nucleophilic anions (*e.g.*, CuCN)[121] (Scheme 31).[120] First, a solvent complex of perfluoroalkylcopper(I) **46** is formed. Then the complex is coordinated to aryl iodide to give complex **47**, and this is followed by ligand exchange.[121] This process probably involves several electron transfers. The efficiency of the reaction depends to a large extent on the solvating power of the solvent towards the copper(I) complex. The highest yields were achieved by using DMF, pyridine and DMSO. The complex formed is rather stable; therefore, the synthesis can proceed in the presence of free carboxy, amino and hydroxy groups.

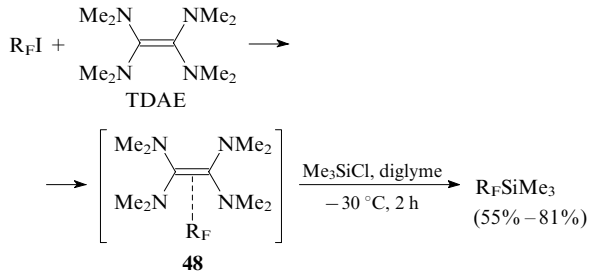
Scheme 31



L is solvent

An alternative way of generation of nucleophiles from perfluorohexyl iodides without the participation of metals was described in 1989;[122] however, it was further developed only in the 21st century.[123] It was found that the reaction of perfluoroalkyl iodides with the organic reducing agent, tetrakis(dimethylamino)ethylene (TDAE), at low temperature affords convenient perfluoroalkyl nucleophilic reagents (the formation of charge transfer complex **48** is suggested). V Petrov,[123] an employee of DuPont, proposed using this system for generating the Ruppert–Prakash reagent, Me_3SiCF_3 (Scheme 32).

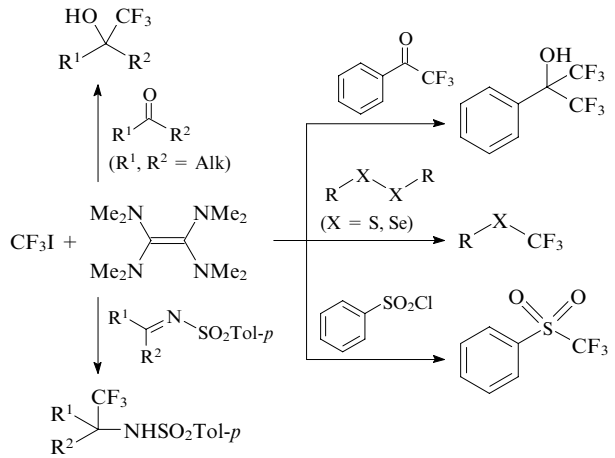
Scheme 32



R_F = C_2F_5, n-C_3F_7, iso-C_3F_7, n-C_4F_9

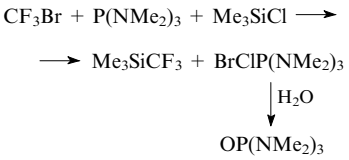
Dolbier and co-workers [124–126] used the same approach; however, they extended the range of substrates. Successive trifluoromethylation was accomplished for aldehydes and ketones, sulfates, disulfides, diselenides and imines (Scheme 33). However, when perfluoroalkyl halides with longer chains were employed in the reaction, the product yields substantially decreased.[127]

Scheme 33



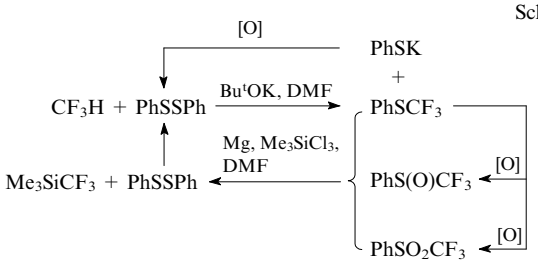
In recent years, numerous publications appeared dealing with nucleophilic perfluoroalkylation involving the Ruppert–Prakash reagent, Me_3SiCF_3, and its higher perfluoroalkylated homologues.[128, 129] Initially, Me_2SiCF_3 was synthesized by Ruppet's research team.[130] However, its remarkable properties as a nucleophilic trifluoromethylating agent were noticed and systematically investigated by another research team headed by Prakash.[131] Trimethylperfluoroalkylsilanes have become popular in organic synthesis owing to their stability, convenience of handling (the boiling point of Me_3SiCF_3 is 54–55 °C) and the diversity of the methods of synthesis. Trifluoromethyl(trimethyl)silane is formed upon the reaction of CF_3I or CF_3Br with (chloro)-trimethylsilane in the presence of various reducing agents, for example $P(NMe_2)_3$ (initial method of synthesis), TDAE [123] or aluminium.[132] According to the initial Ruppert procedure, treatment of the reaction mixture with water furnishes a stoichiometric amount of carcinogenic HMPA [$OP(NMe_2)_3$]. Moreover, the method implied the use of bromotrifluoromethane, which destroys the ozone layer and is banned in some countries (Scheme 34).

Scheme 34



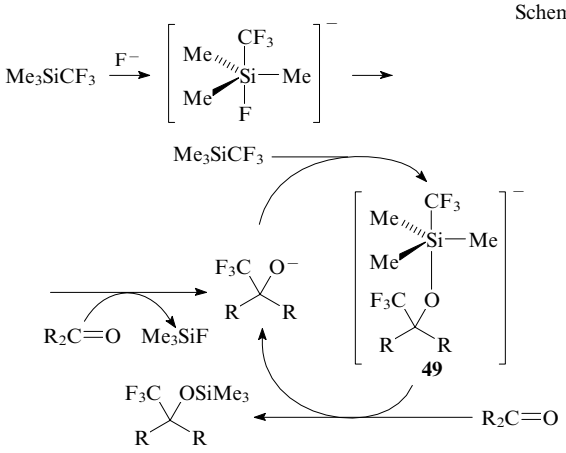
A new convenient procedure implies the use of trifluoromethane in a diphenyl disulfide-catalyzed cycle (Scheme 35).[133–135]

Scheme 35



In the case of catalysis by Lewis bases (the fluoride or *tert*-butoxide anion is often used), trimethyl(trifluoromethyl)silane can transfer the CF_3 group to various electrophilic substrates. The mechanism of this transfer (Scheme 36) comprises the formation of alkoxy(trimethyl)-trifluoromethyl silicon derivative **49** (resembling a carbanion). This species adds the trifluoromethyl group to a carbonyl group according to a self-activating chain reaction, which is initiated by a small amount (5%–10%) of the

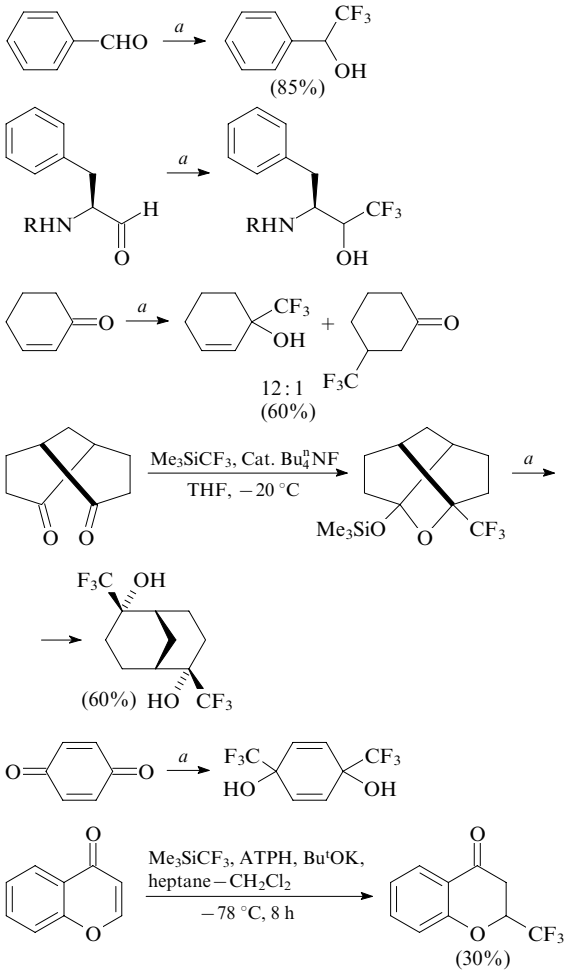
Scheme 36



fluoride anion.[131] Some silicon intermediates of this type were even isolated and characterized by NMR or X-ray diffraction.[136] It is of interest that the addition reaction is not initiated by Lewis acids, unlike reactions of most organosilicon compounds.

The nucleophilic addition of a trifluoromethyl group to aldehydes, ketones and other carbonyl compounds gives rise to the corresponding trimethylsilyl ether, which is subsequently hydrolyzed to alcohol. Owing to the standard mild conditions, this method is widely used even for unstable compounds. Unlike most other methods, fluoride-induced perfluoroalkylation by means of organosilicon compounds is applicable to carbonyl derivatives that are able to enolyze. In the reactions with α,β-unsaturated compounds, 1,2-addition to the carbonyl group is preferred.[129] If the oxygen atom is coordinated to a sterically crowded Lewis acid [for example, aluminium(III) tris(2,6-diphenylphenoxide) (ATPH)], the reaction selectively gives 1,4-addition products (Scheme 37).[137]

Scheme 37



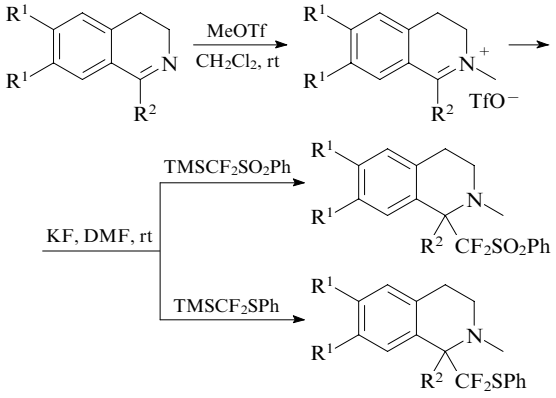
(*a*) 1) Me_3SiCF_3, Cat. Bu^n_4NF, THF, −20 °C; 2) HCl

The use of chiral catalysts, for example, tris[(*S*,*S*)-3,4-diphenylpyrrolidino]sulfonium triphenyldifluorostannate, opens up the way to enantioselective nucleophilic trifluoromethylation with prochiral carbonyl compounds.[138] However, the enantiomeric excesses of compounds obtained by this method are moderate.

Since the first mention of the synthetic application of Me_3SiCF_3 in 1989, this generalized approach has been used to prepare diverse compounds in many areas of modern chemistry: for the synthesis of analogues of natural products (carbohydrates, nucleotides and steroids),[139] in pharmaceutical chemistry (*e.g.*, preparation of trifluoromethylated analogues of the antimalarial drug artemizin),[140] for the production of liquid crystals and other functional materials (*e.g.*, in nucleophilic substitution reactions of aliphatic trifluoromethylsulfonates).[141]

An effective and facile method of nucleophilic difluoromethylation of the C=N bond in heterocycles under the action of alkylating agents was developed quite recently.[142] Cyclic iminium salts obtained from dihydroisoquinolines (or quinolines, or pyridines) were successfully difluoromethylated by sulfur-containing fluoroalkylsilanes to give a number of new difluoromethylated N-heterocyclic compounds in 34%–94% yields (Scheme 38).

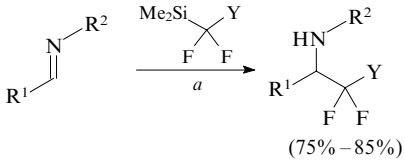
Scheme 38



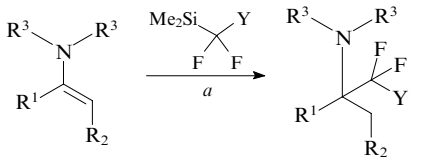
R^1 = MeO: R^2 = H, Me; R^1 = H: R^2 = Ph, Me

Nucleophilic fluoroalkylation of imines and enamines on treatment with α-phenylsulfanyl-, α-phenylsulfonyl- and α-diethylphosphoryl-substituted fluorinated silanes was

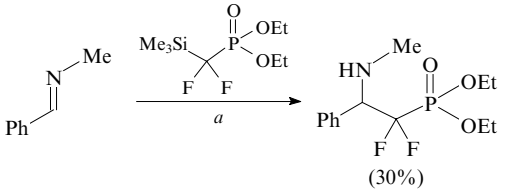
Scheme 39



R^1 is 2-furyl, R^2 = cyclo-C_6H_{11}; R^1 = Ph, R^2 = Me;
R^1 = Bu^t, R^2 = Bn; R^1 is 1-naphthyl: R^2 = Me, cyclo-C_3H_5, *etc.*



R^1–R^2 = $(CH_2)_4$: R^3–R^3 = $(CH_2)_2O(CH_2)_2$, $(CH_2)_4$;
R^1 = Me, R^2 = CO_2Me, R^3–R^3 = $(CH_2)_4$, *etc.*

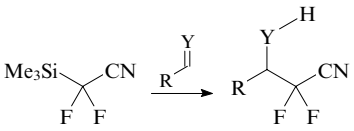


(*a*) KHF_2, CF_3CO_2H, MeCN; Y = SPh, SO_2Ph, $P(O)(OEt)_2$

investigated by Dilman's research team.[143] The reaction is facilitated by hydrofluoric acid, which is generated *in situ* from KHF_2 and trifluoroacetic acid. It is of interest that sulfur reagents are suited for both imines and enamines, whereas the phosphorus reagent binds efficiently only to enamines (Scheme 39).

The same research team synthesized a new silicon reagent, (trimethylsilyl)difluoroacetonitrile, by inserting difluorocarbene into silyl cyanide.[144] The obtained silane proved to be a good reagent for difluoromethylation of aldehydes, *N*-toluenesulfonylimines, *N*-alkylimines and enamines in basic or acidic media (Scheme 40).

Scheme 40



Y = O, NTs, NAlk; R = Ph, 4-$O_2NC_6H_4$, 1-napthyl, 2-pyridyl, *etc*.

It can be stated with confidence that nucleophilic perfluoroalkylation methods are used most widely in the synthetic chemistry of organofluorine compounds.

IV. Metal derivatives in perfluoroalkylation reactions

1. Perfluoroalkyl metal derivatives: synthesis, binding and reactivity

Organometallic compounds MR_F containing trifluoromethyl or perfluoroalkyl groups are key intermediates in most important and interesting perfluoroalkylation reactions of various substrates and have lately aroused particular interest.[3, 6, 15, 145–148]

The van der Waals radius and the bulk of the CF_3 group are much greater than those of CH_3: 2.7 Å, 42.5 Å^3 and 2.0 Å, 16.8 Å^3, respectively.[149] The trifluoromethyl group is highly lipophilic, as follows from its hydrophobicity parameter (1.07), which is much higher than that of CH_3 (0.51) but lower compared with Bu^t (1.68).

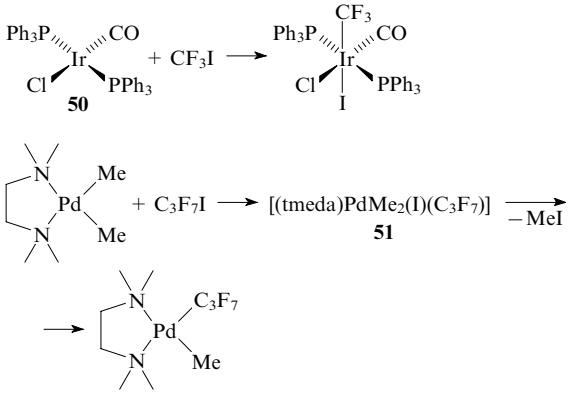
Perfluoroalkyl groups, including CF_3, form strong and usually relatively inert bonds with carbon atoms in organic molecules.[2, 8, 10] On the other hand, stability of the metal–perfluoroalkyl bonds depends appreciably on the natures of both R_F and the metal. This issue is discussed in detail in some reviews on perfluoroalkyl derivatives of main group and transition elements.[149–153] In general, the $M-R_F$ bonds are much stronger and much less reactive than the M–R bonds in non-fluorinated metal alkyls. Most often (but not always), the metal–carbon bond is shorter for $M-CF_3$ than for $M-CH_3$. The C–F bonds in the trifluoromethyl group at the metal are, as a rule, longer and weaker than those in organic CF_3 derivatives.[153]

A number of methods exist for the synthesis of metal perfluoroalkyls. The most widely used methods include oxidative addition of polyfluorohaloalkanes to metals and their complexes, transmetallation, decarboxylation or decarbonylation of metal perfluoroalkylcarboxylates.

The reactions of perfluoroalkyl halides with metals (formally, oxidative addition) are widely used to prepare R_FM. This method was used by Emeléus and Haszeldine[154, 155] more than 60 years ago to synthesize the first trifluoromethyl metal derivatives, in particular, $(CF_3)_2Hg$ and CF_3HgI from CF_3I and Hg (or Cd, Zn, Ag, Cu and Mg amalgam).

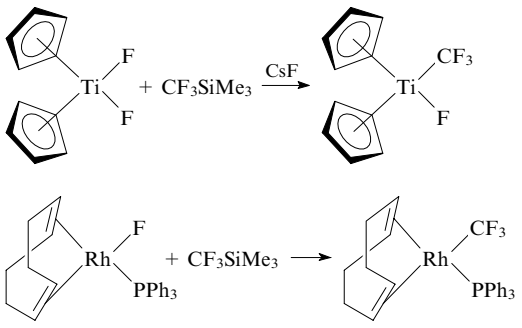
The reactions of perfluoroalkyl halides with metal powders have found wide use for generation of R_FCu species [121] and trifluoromethylzinc (and Cd) from CF_2X_2 (X = Br, Cl).[116] Two types of oxidative addition of R_FX to coordinatively unsaturated metal complexes are presented in Scheme 41.[156, 157] The reaction of the Vaska's complex (**50**) with CF_3I affords an Ir^{III} adduct, which is stable and can be isolated; the proof was reported for the *trans*-adduct. In the R_FX oxidative addition of the other type, the intermediate complex of the metal in a high oxidation state is unstable and undergoes reductive elimination, which does not involve the $M-R_F$ bond formed. Indeed, the very unstable intermediate Pd^{IV} complex **51** immediately reductively eliminates methyl iodide (see Scheme 41).

Scheme 41



Transmetallation, *i.e.*, the transfer of R_F from one metal (element) atom to another is apparently used most often as a laboratory method for the preparation of perfluoroalkyl metal derivatives. Several approaches to the compounds MCF_3 as sources of CF_3 groups were developed and these compounds were proved to be convenient reagents for the synthesis of trifluoromethyl derivatives of other elements. These include the transfer of CF_3 from $(CF_3)_2Cd \cdot DME$ (DME is 1,2-dimethoxyethane) to various metals [158] and the synthesis of trifluoromethylcopper using CF_3 derivatives of Hg, Cd and Zn.[159] However, currently the commercially available Ruppert reagent is the most widely used source of CF_3 in the synthesis of trifluoromethyl metal complexes. This method is universal, as indicated by two reactions involving transition metals of the beginning [160] and the end [161] of the row (Scheme 42).

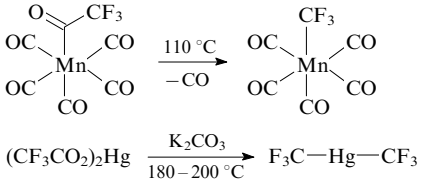
Scheme 42



Decarbonylation of perfluoroacyl derivatives illustrates a different approach that is used to prepare CF_3 complexes

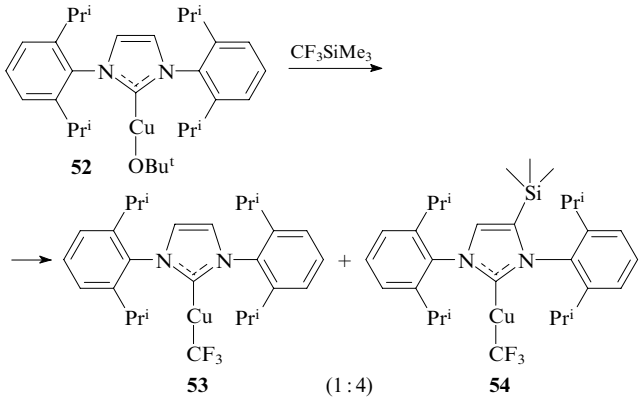
of d metals (Scheme 43). Decarboxylation of $(CF_3CO_2)_2Hg$ is an excellent route giving $(CF_3)_2Hg$ in a high yield (see Scheme 43).[162]

Scheme 43



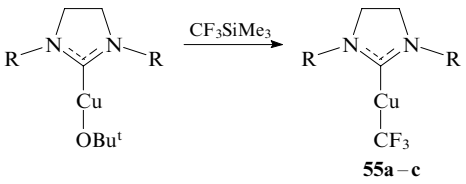
The synthesis and reactivity of perfluoroalkyl cuprates were considered in detail in Section III.3. However, it is noteworthy that perfluoroalkyl copper derivatives are fairly stable and can be easily isolated. Taking advantage of these properties, Vicic and co-workers[163] synthesized a number of copper(I) complexes with the trifluoromethyl group. Note that the reaction of complex **52** with the Ruppert–Prakash reagent afforded target product **53** and unexpectedly gave also silylated complex **54** (Scheme 44).

Scheme 44



To avoid the formation of silylated products, complexes **55a–c** were synthesized (Scheme 45). All of the obtained compounds were fully characterized; moreover, complexes **54** and **55a** were examined by X-ray crystallography.

Scheme 45

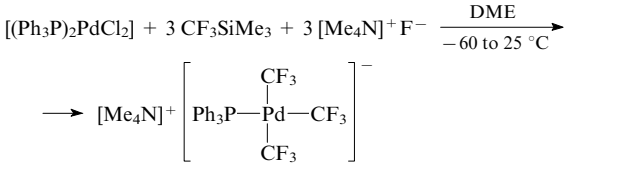


R = Pr^i (**a**), 2,4,6-$Me_3C_6H_2$ (**b**), 2,6-$Pr^iC_6H_3$ (**c**)

The first perfluoroalkyl palladium complexes were synthesized in the early 1960s.[164] The complexes [(bpy)PdMe(n-C_3F_7)], [(bpy)Pd(n-$C_3F_7)_2$], [$(Ph_3P)_2$Pd.(.CF_3)(I)] and [(dppe)Pd(CF_3)(I)] [bpy is bipyridine, dppe is 1,2-bis(diphenylphosphino)ethane] were prepared by oxidative addition of the corresponding perfluoroalkyl halides. Thus, passing gaseous CF_3I through a solution of [$(Ph_3P)_4$Pd] resulted in [$(Ph_3$ $P)_2$Pd(CF_3)(I)] in a 78% yield.

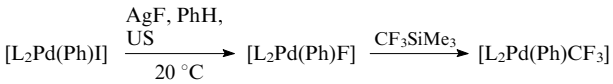
Subsequently it was shown that in the synthesis of palladium complexes by using the Ruppert–Prakash reagents, the trifluoromethyl carbanion can replace not only chloride ligands but also phosphine ligands at the palladium atom (Scheme 46).[165]

Scheme 46

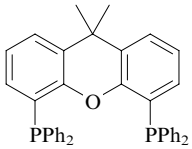


A problem faced by the replacement of a weakly bound phosphine ligand is the uncontrolled formation of excess trifluoromethyl carbanion from the $CF_3SiMe_3-F^-$ system. This problem can be eliminated by conducting the desired trifluoromethylation by the reaction of Pd fluoride complex with the Ruppert–Prakash reagent without an external activating source such is F^-. This approach was used to prepare the complexes [$(Ph_3P)_2$Pd(Ph)(CF_3)] and [(Xantphos)Pd(Ph)(CF_3)] in high yields (Scheme 47). The structures of the complexes were fully characterized by X-ray crystallography.[166]

Scheme 47



US is ultrasound; L = PPh_3 (82% yield), Xantphos (88%)



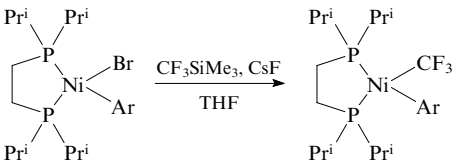
Xantphos

The first perfluoroalkyl nickel complexes were synthesized by the Stone research team[167–169] in the 1960s by oxidative addition of perfluoroalkyl halides to nickel complexes.[167–172] For example, the complexes [LNi(R_F)L′] (where L = dppe, L′ = I: $R_F = C_2F_5$, n-C_3F_7; L = Cp, L′ = CO: $R_F = CF_3$, C_2F_5, n-C_3F_7; Cp is cyclopentadienyl)[167,168] were prepared by the reaction of [(dppe)Ni($CO)_2$] or [CpNiCO]$_2$ with the corresponding R_FI. Nickel perfluoroalkyls were supposed[173] as the products of the reaction of [Ni$(CO)_4$] with R_FI in electron-donating solvents.

The first structure of the perfluoroalkyl nickel derivative [CpNi(PPh_3)CF_3] was published in 1970.[174]

A series of trifluoromethyl aryl nickel complexes [(dippe)Ni(Ar)(CF_3)] [dippe is 1,2-bis(diisopropylphosphino)ethane] were obtained recently by Vicic and co-workers[175] (Scheme 48), who used the method developed previously for the synthesis of palladium complexes.[176] With a twofold excess of CF_3SiMe_3–CsF, the complex [(dippe)Ni$(I)_2$] was converted to [(dippe)Ni$(CF_3)_2$] in a 26% yield. The complexes [(dippe)Ni(2-Naph)(CF_3)] (Naph is naphthyl) and [(dippe)Ni$(CF_3)_2$] were studied by X-ray crystallography. It was shown that in comparison with the non-fluorinated [(dippe)NiMe_2], the Ni–C_F and Ni–C bonds are similar in length, and the Ni–P bond is longer in the R_F derivative.

Scheme 48



Ar	Yield (%)	Ar	Yield (%)
Ph	75	2-Naph	70
3-MeC_6H_4	54	4-$MeOC_6H_4$	75

Most of stoichiometric perfluoroalkylation reactions involving organometallic reagents are conducted with the participation of perfluoroalkyl cuprates (see Section III.3). Several examples of catalytic formation of $ArCF_3$ were reported; however, this type of reactions is still uncommon. In 1989, a publication appeared [177] that reported trifluoromethylation of aryl and alkyl halides with $FSO_2CF_2CO_2Me$ in the presence of a catalytic amount (12%) of CuI, the yield of the target products being 61%–92%. Recently, a series of trifluoromethylation reactions by the Ruppert–Prakash reagent catalyzed by copper iodide with 2-(dimethylaminomethyl)pyridine as the ligand was reported.[178] When the catalytic system was used, all other factors being the same, the yield was lower. Yet another similar catalytic method [178] implies the use of the more accessible CuI–1,10-phenanthroline system; however, much more expensive CF_3SiEt_3 served as the source of the trifluoromethyl group.

Detailed investigations [6] of the electronic effects of the CF_3 groups (whether this group is an electron acceptor or donor) demonstrated that the view of R_F as hard ligands with substantial electron-withdrawing capacity are somewhat contrived and can cause fallacy. It was found that the CF_3 ligand stabilizes the derivatives of some metals in high oxidation states and hampers both the oxidative addition and reductive elimination.[179]

The CF_3 group makes the metal more negatively charged with the energies of all its d orbitals being lowered, which accounts for its lower proneness to oxidative addition.[179] Strange as it may seem at the first glance, the increase in the negative charge on an atom with simultaneous stabilization of the HOMO of this atom is rather often encountered in chemistry.

The task of development of perfluoroalkylation methods that would involve intermediate metal σ-complexes $M-C_F$ characterized by relatively high rates of oxidative addition and reductive elimination, which is necessary for an effective catalytic cycle, still remains topical.

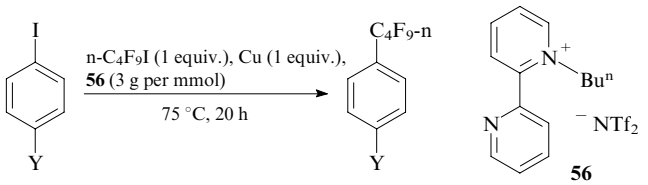
Thus, despite the development of perfluoroalkylation techniques in the last decades, there are virtually no convenient, facile, and mild catalytic perfluoroalkylation procedures. Further progress along this line may be largely promoted by metal complex catalysis, which is indispensable in many up-to-date synthetic processes.

2. Perfluoroalkylation involving metals and higher R_F

The major application of trifluoromethylated molecules is in the synthesis of biologically active compounds such as agricultural chemicals and pharmaceuticals. Compounds with longer perfluoroalkyl chains are used more widely as building blocks for various materials, polymers, elastomers or surfactants.[180] Many of the above-described trifluoromethylation reactions can also be useful for the introduction of longer R_F chains. Like trifluoromethylation, these reactions are often performed using perfluoroalkyl copper(I) derivatives,[116, 120, 121, 181–184] fluoroalkyl zinc reagents [114, 115] or some fluoroalkyl modifications of the Ruppert–Prakash reagent. Stoichiometric reactions with these reagents were surveyed in Section III.3.

Recently it was shown that a new ionic liquid, 1-n-butyl-2-(2-pyridyl)pyridinium bis(trifluoromethanesulfonyl)-amide (**56**), can serve as a recoverable medium for the cross-coupling of aryl iodides with perfluoroalkyl iodides in the presence of Cu. This reaction gave excellent preparative yields (85%–91%) under mild conditions (75 °C) (Scheme 49).[185]

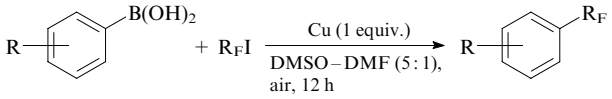
Scheme 49



Y = Me (86% yield), NO_2 (87% yield)

Aerobic fluoroalkylation of arylboronic acids in the presence of a ligand-free copper catalyst occurs under mild conditions (Scheme 50).[186]

Scheme 50



R = 4-MeO, 3-MeO, 4-BnO, 4-Cl, 4-CHO, 4-MeO_2C, 4-I, 4-Br, 3-Br, 3-NO_2, 3-Ph, 3,5-Me_2, *etc.*; R_F = C_2F_5, n-C_4F_9, n-C_6F_{13}, $(CF_2)_4Cl$, $CF_2C(O)R'$ (R′ = OEt, NEt_2)

The reaction tolerates a broad range of functional groups in the benzene ring, which makes the products suitable for further transformations.

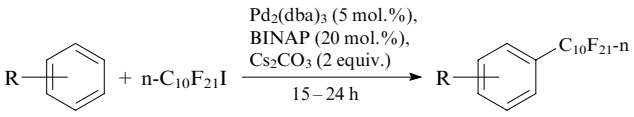
Mechanistic studies show that [R_FCu] are reactive Cu-containing species which form the desired perfluoroalkylarenes and that [R_FCu] is generated from [PhCu] by either the oxidative addition–reductive elimination mechanism or nucleophilic substitution mechanism *via* a halogen-eliminating intermediate.

Some examples of catalytic perfluoroalkylation of various substrates were published in recent years. The reactions of $ClCF_2CO_2Me$ or $BrCF_2CO_2Me$ with PhX (X = I, Br) in the presence of KF and a catalytic amount of CuI afford a mixture of perfluoroalkylbenzenes $CF_3(CF_2)_nC_6H_4X$ ($n = 0–2$).[149, 187] Nevertheless, benzotrifluoride ($n = 0$) becomes the major product if a stoichiometric amount of CuI is used under similar conditions.

A recent publication [188] deals with perfluoroalkylation of benzene and substituted arenes with perfluoroalkyl halides catalyzed by a Pd^0 complex with phosphine ligands in the presence of a base (Scheme 51).

The best yields (81%) were achieved by using 20 mol.% BINAP and caesium carbonate as the base. The use of other phosphines and potassium carbonate resulted in a maximum yield of 47%. By using twofold (or higher) excess of the phosphine ligand, the total yield was increased to 90%.

Scheme 51



dba is dibenzylideneacetone, BINAP is 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl

3. The prospects of using metal-promoted perfluoroalkylation of substrates

Since the publication [121] concerned with trifluoro- and perfluoroalkylation of various substrates promoted by metals or metal complexes, a considerable progress has been made. During the last 5 years, a number of promising results were obtained, including the first examples of the previously inconceivable Pd^{II}-catalyzed formation of the $Ar-CF_3$ bond,[166, 176] which was followed by the development of the first Pd-catalyzed trifluoromethylation of aryl chlorides.[189] Considerable advances are observed in the development of Cu-catalyzed trifluoromethylation techniques,[138, 178] which involved, in particular, thoroughly characterized Cu^{I} complexes [163, 175] that promote the formation of $Ar-CF_3$ bonds. However, many problems in this field are still to be solved. Trifluoro- or perfluoroalkylation of alkenes under mild catalytic conditions has not yet been accomplished. It is believed that further research should be aimed at the search for inexpensive recoverable solvents for various perfluoroalkylation reactions.[6] Copper is relatively cheap; hence, its use in stoichiometric amounts is admissible. However, certainly, it is more desirable to use catalytic amounts of copper or other available metals.

As regards the use of copper and its compounds, a key challenge is to develop promoters and conditions that would provide high yields of trifluoromethylation. As a rule, reactions proceed smoothly only for iodo derivatives; they are less successful for bromo derivatives and seldom occur for chloro derivatives. Palladium is incomparably more expensive than copper. Therefore, a Pd-based nucleophilic aromatic trifluoromethylation process that could be recognized as applicable on a larger scale should use minor, catalytic amounts of this precious metal. Furthermore, many ligands involved in Pd-catalyzed reactions are even more expensive than the metal. This is the case for BrettPhos [2,4,6-triisopropyl-3′,6′-dimethoxy-2′-(dicyclohexylphosphino)-1,1′-biphenyl], which is used in the only Pd-catalyzed nucleophilic aromatic trifluoromethylation reaction available to date.[189] This process is by itself a remarkable achievement, which is already used and will be used in medicinal chemistry and agrochemistry. Nevertheless, according to the modern Aldrich and Strem catalogues, BrettPhos may be too expensive for scaling-up: on March, 2012, the Aldrich price of BrettPhos was \$42.80 per 0.1 g or about \$230 000 per mole (537 g). Of course, the retail prices of chemicals are much higher than wholesale prices. Nevertheless, the basic price of BrettPhos should be almost 100 times lower than the current retail price to become comparable with the current price of palladium, which is \$2234.8 per mole (\$654 per troy ounce, according to the Johnson-Matthey data). Thus, a Pd-catalyzed trifluoromethylation reaction that could be scaled-up requires some other, cheaper ligands. The search for these ligands is challenging. These ligands should not only promote the reductive elimination of $ArCF_3$, the most difficult step of the catalytic cycle, but they also should be compatible with other steps within the same cycle. It is clear that BrettPhos satisfies both requirements but the ligand Xantphos does not. While allowing for the Pd-catalyzed formation of the $Ar-CF_3$ bond,[182] Xantphos is readily replaced by 'CF_3^-', which induces fast and irreversible deactivation of the catalyst. Yet another problem associated with the development of new ligands for Pd-catalyzed trifluoromethylation is easy transmetallation occurring between the complexes [$LPd(CF_3)Ar$] and [$LPd(Ar)X$] (X is the halide present in the substrate ArX), which are formed at different steps of the catalytic cycle. This transmetallation proceeds easily to give [$LPd(Ar)_2$], which undergoes reductive elimination of $Ar-Ar$ yielding the stable and catalytically inert complex [$LPd(CF_3)X$].[176] Publications devoted to Ni-catalyzed trifluoromethylation are still few in number.

It is pertinent to make some remarks concerning sources of CF_3 in trifluoromethylation reactions. Currently, the most popular reagents (such as the Ruppert reagent) are effective, safe and easily handled but expensive. Some cheaper potential sources of CF_3 are included in the Montreal protocol list of chemicals, which restricts their use for research in some countries. Trifluoromethane and alkali metal trifluoroacetates could be better sources of CF_3. However, trifluoromethane is notoriously known for the fact that it rapidly decomposes to give difluorocarbene upon deprotonation, and alkali metal trifluoroacetates are hygroscopic and poorly soluble in solvents that are suitable for trifluoromethylation. It is also noteworthy that the formation of $CuCF_3$ species from trifluoroacetates is accompanied by evolution of an equimolar amount of CO_2. In order to achieve good yields, trifluoroacetic acid is usually taken in a large excess (up to 10-fold). Thus, it is necessary to develop an efficient trifluoro- or perfluoroalkylation process that would employ a stoichiometric amount or a small excess of the reagent.

It is beyond doubt that studies in the field of trifluoromethylation and perfluoroalkylation involving metallic promoters and catalysts will be continued and become more intense.

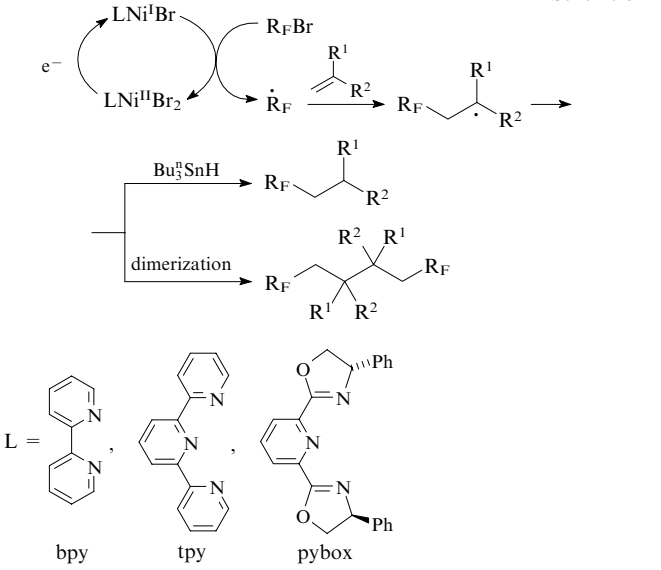
V. Electrochemical metal complex catalysis in perfluoroalkylation reactions

Complexes of transition metals such as Ni, Pd or Co in low oxidation states can react with many functional groups and thus catalyze the formation of the C–C, C–P, C–Si and other bonds. Electrochemical approaches can play an important role in this field. For example, electrochemical methods are suitable for preparing many organometallic compounds, for studying the reactivity of coordination compounds and for establishing the possible reaction mechanisms. The use of electrochemically generated catalysts in organic reactions has acquired increasing significance in recent years as regards both the new opportunities for organic synthesis and more in-depth studies of electron transfer, bond cleavage, substitution, addition and other reactions. As regards the industrial implementation, electrochemical reactions have several advantages: the conversion and the rate are easily controllable and the selectivity is controllable to a certain extent by variation of parameters

such as the current density and the potential.[190–192] The indirect reduction and oxidation of organic compounds where the redox reagents are formed and regenerated at an electrode is currently acquiring increasing significance among the up-to-date methods of organic synthesis. This is due to extensive, in some cases unique, opportunities for diverse transformations of organic compounds and development of economic and environmentally safe processes.[193] Electrons do not pollute the environment and the control over electrochemical processes can be easily automated. As a result, higher process selectivity with a simultaneous decrease in the energy expenditures and an increase in the current density can be achieved. Also, the interest in such reactions is caused by a number of other reasons: mild conditions (moderate temperature, ambient pressure), the possibility of conducting reactions in an almost closed system with a minor amount of the catalyst reactant, which is repeatedly recycled. The synthesis is highly environmentally friendly, especially as compared with traditional methods of organic chemistry. The electrochemical metal complex catalysis is being vigorously developed; a number of reviews on this topic were published.[194–196] Data on the electrochemical and chemical behaviours of most interesting transition metal complexes can be found in reviews [194–201] and numerous original papers cited therein.

According to a large number of recent publications, nickel complexes with various ligands are effective catalysts for electrochemical and chemical reactions such as cross-coupling and functionalization of alkenes. Recently it was found that nickel and platinum complexes in low oxidation states serve as efficient catalysts for the introduction of R_F groups. A simple and versatile one-step electrocatalytic method for addition of fluoroalkyl groups (straight- or branched-chain) to alkenes containing various substituents (Me, Ph, Py, AcO, Naph, 4-MeC_6H_4 and so on) was developed. The method is suitable for the preparation of both monomeric and dimeric products with one or two chiral carbon atoms (Scheme 52).[202–206] The reaction follows an unusual addition–dimerization pathway, it occurs under mild conditions and is accompanied by catalytic recycling of the accessible nickel complexes with N-heterocycles [2,2′-bipyridine, 2,2′:6′,2″-terpyridine, (*S*,*S*)-2,6-bis(4-phenyloxazolin-2-yl)pyridine].

Scheme 52



The stereoselective formation of the *meso*-form of the dimeric product is facilitated by a straight-chain structure of the perfluoroalkyl group, while the dl-form tends to form in the case of the iso structure of this group.

A scheme of electrocatalytic perfluoroalkylation of alkenes was proposed in which Ni^{I}L is the active form of the catalyst that is generated and recycled at the electrode. The complex (tpy)NiBr was isolated and characterized for the first time (Fig. 6); its metal-centred electronic structure was proved.

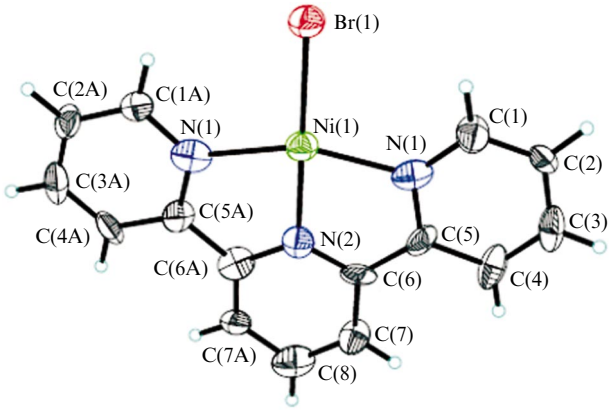


Figure 6. Structure of the complex (tpy)Ni^{I}Br involved in the electrocatalytic fluoroalkylation cycle.

The formation of LNi^{I} complexes with chosen ligands was confirmed by cyclic voltammetry (CV) and EPR spectroscopy. It was found that the EPR-monitored reduction of complexes is accompanied by appearance of a signal with a *g*-factor typical of LNi^{I} [2.1391, 2.1403 and 2.1845 for (bpy)Ni^{I}, (tpy)Ni^{I} and (pybox)Ni^{I} , respectively].

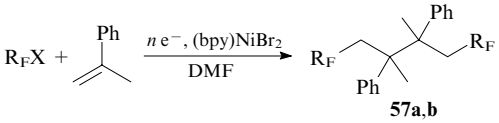
In recent years, the catalytic properties of platinum complexes have been compared with nickel complexes in similar reactions, and the latter are not always inferior. It was found that the platinum(II) complex with 4,4′,4″-tris(*tert*-butyl)-2,2′:6′,2″-terpyridine (tpy′) is also reduced to LPt^{I}, which is regenerated at the electrode and gives rise to the same products as nickel complexes in the catalytic perfluoroalkylation of alkenes.

Mechanistic studies of perfluoroalkylation disclosed the properties of nickel-based catalytic systems, which can also shed light on the reaction pathways of other substrates in electrochemical syntheses. Whereas for the nickel complex with bpy, the CV curves do not show separated reduction peaks, but show the overall two-electron reversible Ni^{II}/Ni^{0} transfer, in the case of nickel and platinum complexes with tridentate ligands (tpy, pybox), stepwise reversible M^{II}/M^{I}/M^{0} single-electron transfers take place. In the presence of increasing amount of perfluoroalkyl halides, the CV of the complexes show a substantial increase in the current of the first reduction peak for complexes with tridentate ligands. The active catalytic species is LM^{I}. The redox properties of the complexes with respect to perfluoroalkyl halides suggest that they may be potentially catalytically active in the perfluoroalkylation of substrates, for

example, alkenes, which are to be added to the reaction mixture to this end.

It was found that with the catalyst content of 10 mol.%, good yields of reaction products are achieved with both perfluorohexyl iodide and 6H-perfluorohexyl bromide (products **57a** and **57b**, respectively) (Scheme 53).

Scheme 53



57a,**b**

R_F = n-C_6F_{13} (**a**, 70% yield), $(CF_2)_6H$ (**b**, 49% yield)

It is especially peculiar that the final reaction product is a dimer containing two alkene and two perfluorinated residues, which has not been previously described in the literature.[207–210]

The structures of 2,3-dimethyl-2,3-diphenyl-1,4-bis(perfluorohexyl)butane (**57a**) and 2,3-dimethyl-2,3-diphenyl-1,4-bis(6H-perfluorohexyl)butane (**57b**) were determined by X-ray crystallography. Both molecules are located at centres of symmetry in the unit cell. Each of the two molecular fragments has chiral centres and the whole molecule is the *meso*-form (Fig. 7).

The structures of compounds **57a**,**b** were independently determined by the set of 1D and 2D NMR techniques. In particular, for compound **57b**, the combination of 1D (^{1}H, ^{1}H{^{19}F}, ^{13}C, ^{19}F) and 2D NMR (^{1}H–^{1}H COSY, ^{1}H–^{13}C HSQC/HMBC) methods[211,212] allows for unambiguous determination of the chain structure up to the C(3) carbon atom. Unfortunately, the large number of vicinal fluorine atoms with large spin–spin coupling constants for more remote carbon atoms [C(4)–C(6)] resulted in almost complete decline of the intensity and no signals for these atoms were observed in the ^{13}C NMR spectra. In this case, fluorine–fluorine and proton–fluorine correlation NMR experiments were of special value. In particular, the ^{1}H–^{19}F 2D HETCOR/HOESY technique allowed for structure determination up to the C(3) atom and then COSY ^{19}F–^{19}F 2D correlations were used for step-by-step determination of atoms of the perfluorinated chain; finally, using the ^{1}H–^{19}F 2D HETCOR method it was possible to move up to the terminal H atom, and thus the whole structure was established.[206]

It was noted that the spatial structure of substituents affects the formation of various diastereomeric forms (Table 4).

By screening various reaction conditions and reactants, the complex (bpy)$NiBr_2$ in DMF was found to be the catalyst of choice for these reactions. The complexes (tpy)$NiBr_2$ and (pybox)$NiBr_2$ catalyzed the addition–dimerization reactions (runs 5 and 6) but the product yields remained moderate; therefore, subsequently they were no longer used. In the case of the platinum complex (run 7), a good product yield was achieved and the single *meso*-isomer was obtained with high stereoselectivity. However, nickel complexes were more readily available and ensured higher yields. Note that nickel dibromide in a DMF–pyridine mixture (9 : 1) as a catalyst also gives the desired product but in a very low yield. It can be seen from Table 4 that the best overall yield of the product was obtained in run 12 where branched perfluoroisopentyl iodide was used.

The effect of various factors on the formation of different diastereomeric forms of dimers was considered. All experiments were carried out in a divided electrolytic cell with platinum cathode and anode. Table 4 does not include the results obtained in an undivided cell with sacrificial anodes made of Zn, Mg and Cu. The reason is that, first, the yields of products **57a**,**b** were moderate (37%, 28% and 45% for Zn, Mg and Cu anodes, respectively) and, second, reactions with sacrificial anodes were non-stereoselective, especially in the case of copper where the *meso* : dl ratio was 1 : 0.3).

In most instances, the synthesis was stereoselective and gave the *meso*-forms. The lowest stereoselectivity was observed in run 12 with branched perfluoroisopentyl iodide. However, this experiment served as the good foundation for further research aimed at the synthesis of the optically active stereoisomer. In particular, it was proposed to utilize alkenes containing bulky substituents. The electrocatalytic perfluoroalkylation of 2-vinylnaphthalene (run 13) furnished only the *meso*-isomer of 2,3-dinaphthyl-1,4-bis(6H-perfluorohexyl)butane **57g**. As the next alkene, α-methyl(4-methyl)styrene was made to react with 6H-perfluorohexyl iodide and the complex (bpy)$NiBr_2$ in DMF (run 14). As a result, (*S*,*S*)-2,3-dimethyl-2,3-bis(4-methylphenyl)-1,4-bis(6H-perfluorohexyl)butane (**57h**) was obtained in good yield and characterized as the only diastereomer.

The developed fluoroalkylation method was found to be applicable for functionalization of more intricate substrates containing unsaturated C–C bonds. The electrocatalytic

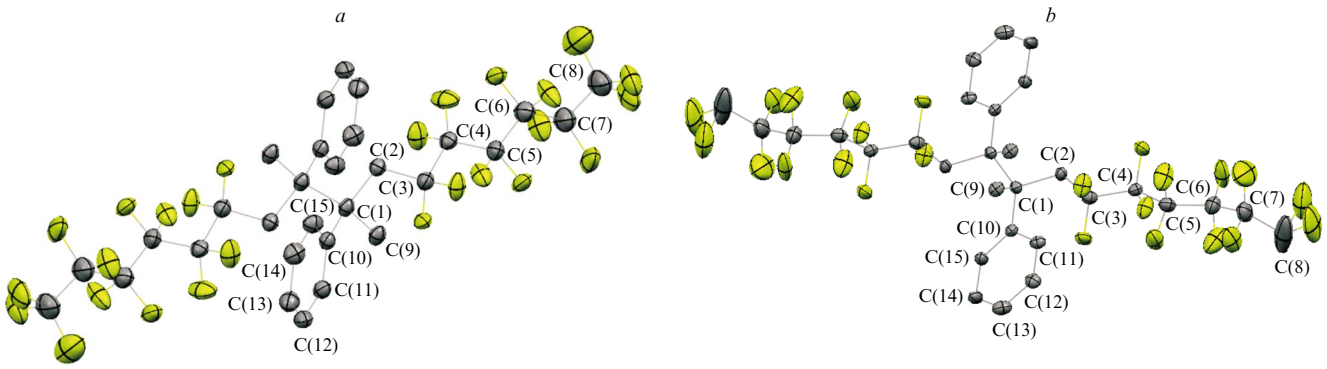
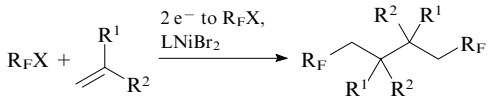


Figure 7. Molecular structure of compounds **57a** (*a*) and **57b** (*b*).[208]

Table 4. Perfluoroalkylation of alkenes under various conditions.



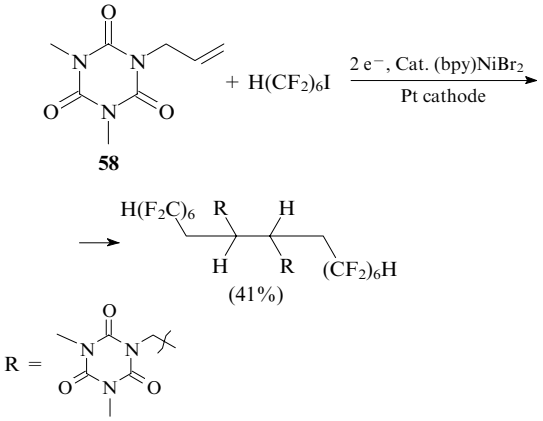
57a–h

Run No.	R_FX	R^1	R^2	Product [a]	Catalyst (10%)	Solvent	Yield (%)
1	$C_6F_{13}I$	Me	Ph	**57a**	(bpy)$NiBr_2$	DMF	70
2	$H(CF_2)_6Br$	Me	Ph	**57b**	(bpy)$NiBr_2$	DMF	49
3	$C_6F_{13}I$	Me	Ph	**57a** (1 : 0.15)	(bpy)$NiBr_2$	MeCN	53
4	$H(CF_2)_6I$	Me	Ph	**57b** (1 : 0.12)	(bpy)$NiBr_2$	MeCN	39
5	$C_6F_{13}I$	Me	Ph	**57a**	(pybox)$NiBr_2$	DMF	34
6	$C_6F_{13}I$	Me	Ph	**57a**	(tpy)$NiBr_2$	DMF	46
7	$H(CF_2)_6I$	Me	Ph	**57b**	(tpy′)$PtCl_2$	DMF	58
8	$C_6F_{13}I$	Me	Ph	**57a**	$NiBr_2$	DMF–pyridine (9 : 1)	14
9	$H(CF_2)_6Br$	H	AcO	**57c** (1 : 0.4)	(bpy)$NiBr_2$	DMF	51
10	$H(CF_2)_6I$	H	Py	**57d**	(tpy)$NiBr_2$	DMF	48
11	$C_6F_{13}I$	H	Py	**57e**	(bpy)$NiBr_2$	DMF	61
12	$(CF_3)_2CF(CF_2)_2I$	Me	Ph	**57f** (1 : 0.8)	(bpy)$NiBr_2$	DMF	72
13	$H(CF_2)_6I$	H	2-Naph	**57g**	(bpy)$NiBr_2$	DMF	68
14	$H(CF_2)_6I$	Me	4-MeC_6H_4	**57h** (0.23 : 1)	(bpy)$NiBr_2$	DMF	65

[a] The values in parentheses are the diastereomer ratios (*meso* : dl).

perfluoroalkylation of compound **58** was found to give the dimeric addition product (Scheme 54) similarly to reactions considered above.

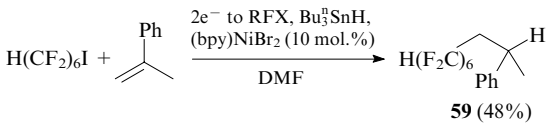
Scheme 54



Derivatives of isocyanuric acid possessing biological activity and containing fluoroalkyl substituents may be of practical value.

The use of proton-donor solvents, which are sometimes able to serve as sources of hydrogen atoms instead of ammonium perchlorate, did not prevent dimerization in this case. Tributyltin hydride was efficient as a source of hydrogen atoms, giving rise to selective formation of monomer **59** (Scheme 55),[206] which, however, was difficult to isolate in a pure state from the reaction mixture and, hence, the isolated product yield was rather low.

Scheme 55



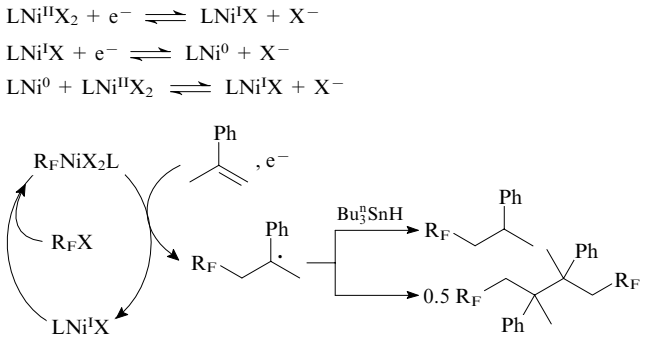
59 (48%)

Thus, relying on the obtained data on the catalytic activity of the selected nickel complexes in the electroreduction of perfluoroalkyl halides, an electrocatalytic method for fluoroalkylation of alkenes was elaborated and practically implemented. The addition–dimerization products, as distinct from the known cases of alkene functionalization reported in the literature, were obtained for the first time. The effects of various factors on the product yields and reaction stereoselectivity were assessed, the complex (bpy)$NiBr_2$ having proved to be the most efficient catalyst for this synthesis when carried out in a divided electrolytic cell with platinum cathode and anode. Using a set of physicochemical methods, it was found that the formation of particular stereoisomers can be affected by varying the structures of the initial substrates — perfluoroalkyl halides and alkenes. Controlled addition of perfluoroalkyl groups to alkenes to give either a dimeric or monomeric product was accomplished for the first time.

The σ-complexes R_FNiBrL (L is 4,4′-di(*tert*-butyl)-2,2′-bipyridine, 2,2′:6′,2″-terpyridine; $R_F = C_6F_{12}H$, C_5F_{11}) were isolated for the first time as key intermediates of the catalytic cycle, and it was found that their reduction is accompanied by electron transfer to the ligand, *i.e.*, the product is a ligand-centred radical. This accounts for the character of alkene perfluoroalkylation.

Considering the data from CV experiments, preparative electrolysis, EPR spectroscopy and other data, a scheme was proposed for the catalytic process (Scheme 56),[206] which comprised the oxidative addition and reductive elimination steps in which the complex LNi^I functions as the active catalytic species that is generated and recycled at the electrode and the σ-complex $LNiR_F$, which behaves as a ligand-centred radical, functions as the key perfluoroalkylating agent.

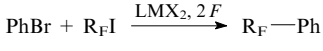
Scheme 56



Thus, a combination of preparative electrosynthesis, EPR and cyclic voltammetry provided evidence for the formation of fundamentally important intermediates of the catalytic cycle and revealed the separate steps that yield the desired perfluoroalkylation products. These data were employed to propose a scheme of the catalytic cycle.

Recently a one-step method was reported for catalytic aromatic perfluoroalkylation involving metal complexes that are reduced and recycled electrochemically under mild conditions where the metal ion of the sacrificial anode plays a crucial role.[213] Cross-coupling occurs successfully with bromo(iodo)benzene and perfluoroalkyl iodide under the action of some complexes of cobalt and nickel in low oxidation states (Scheme 57).

Scheme 57



Anode: Cu, Zn, Mg; M = Ni, Co; L is bpy, tpy, 2,9-dimethyl-1,10-phenanthroline, 4,4′-bis(*tert*-butyl)-2,2′-bipyridine, dppe

VI. Synthesis of fluoroalkylphosphines and fluoroalkylphosphine oxides

Organophosphorus compounds containing perfluoroalkyl groups attract particular attention of synthetic chemists, first of all, owing to the potential use as ligands in organometallic chemistry[214, 215] and especially in phase transfer catalysis involving organofluorine derivatives.[180] Phosphines functionalized by perfluoroalkyl groups show thermomorphic behaviour, which means a substantial enhancement of solubility upon temperature rise.[180] Finally, the introduction of fluorine atoms or fluoroalkyl groups into phosphorus compounds increases the bioabsorption and metabolic stability of biologically significant compounds.

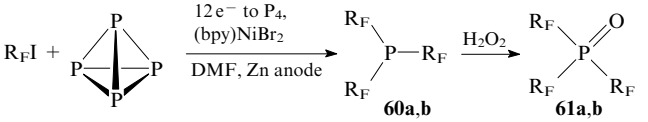
Recent years have seen growing interest in tertiary fluoroalkylphosphines; therefore, development of convenient one-step methods for their synthesis is a demanded line of research. The first synthesis of the phosphine $P[CH_2CH_2(CF_2)_5CF_3]_3$ was reported in 1985; it was based on the reaction of PCl_3 with $IZnCH_2CH_2(CF_2)_5CF_3$.[216]

Some advances in this area were made using Grignard reagents derived from fluoroalkyl halides.[217] One more option of catalytic formation of perfluorinated phosphines and phosphine oxides required *in situ* the preparation of organophosphorus stannanes and their subsequent reaction with perfluoroalkyl halides catalyzed by palladium complexes.[218] An alternative route to these compounds implied the addition of gaseous phosphine at the double bonds of fluorinated alkenes induced by radical initiators, which proceeds under drastic conditions (in steel reactors at high pressure).[219]

A convenient method for the electrochemical synthesis of triarylphosphines from white phosphorus was proposed;[199, 201, 220–222] however, this method is of low utility for alkylphosphines.

Recently, it was demonstrated that compounds with P–C bonds can be prepared directly from white phosphorus and fluoroorganic halides under the action of electrochemically generated complexes of nickel in low oxidation state. By joint electrolysis of fluoroorganic halides and an emulsion of white phosphorus in DMF in the presence of $(bpy)NiBr_2$ (Scheme 58), white phosphorus was activated and largely converted to products with the $P-R_F$ bonds.[223]

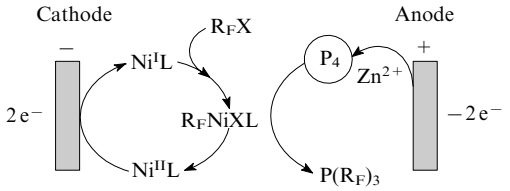
Scheme 58



$R_F = CH_2CH_2(CF_2)_3CF_3$ (**a**), n-C_6F_{13} (**b**)

The electrolysis was carried out in an undivided electrochemical cell with a platinum cathode and a sacrificial zinc anode without a supporting electrolyte. In all cases, tertiary phosphines **60a**,**b** were the major reaction products, and the formation of some phosphine oxides **61a**,**b** was proven by ^{31}P NMR spectra. However, since most tertiary phosphines are unstable, it was decided to perform further oxidation of phosphines to phosphine oxides **61**, which are stable and convenient for isolation. Yet another important aspect is that all electrosyntheses were conducted without supporting electrolytes, which simplifies the procedures of product isolation and thus extends the scope of applicability of this method. White phosphorus participates in the reaction with the perfluoroorganic halide where the metal complex catalyst is generated at the electrode. By analogy with functionalization of white phosphorus by Grignard reagents, it was suggested that the reaction of the organonickel intermediate $[R_FNi^{II}XL_n]$ with a white phosphorus molecule is the key step of the process (Scheme 59).

Scheme 59

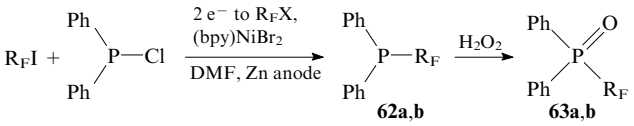


Successful one-step procedures for electrochemical coupling of chlorodiphenylphosphine and perfluoroalkyl halides catalyzed by nickel complexes were described (Scheme 60).[223]

Compounds **62b** and **63b** were obtained earlier by Rossi and co-workers[224] by the reaction of Ph_2P^- and R_FI ions in carcinogenic HMPA or liquid ammonia under photochemical treatment. However, the yields of diphenyl(perfluorohexyl)phosphine (**62b**) were relatively low and the authors were even unable to record the ^{31}P NMR spectra of this compound. Interestingly, the reactions using a sacrificial Mg anode gave mainly phosphine oxide, while the syntheses

with a Zn yielded phosphine with a minor amount of impurity.

Scheme 60



R_F = $(CH_2)_5CF_2H$ (**a**), n-C_6F_{13} (**b**)

Thus, it was demonstrated that various compounds with P—C bonds (phosphines and phosphine oxides) can be prepared directly from white phosphorus or from chlorodiphenylphosphine, the syntheses being accompanied by electrochemical generation of nickel complexes. High selectivity of electrosynthesis and mild reaction conditions ensure a high degree of conversion of white phosphorus to the desired products even in the absence of supporting electrolytes. Moreover, this method is advantageous over other known approaches as regards the atomic economy. The use of hazardous phosphine and unstable organometallic derivatives was avoided.

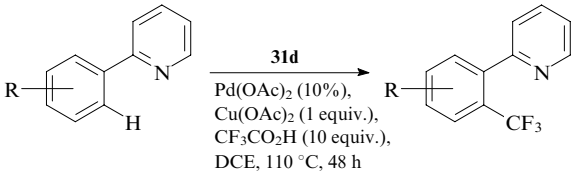
VII. Fluoroalkylation of the C—H bond

A new one-step catalytic method for *ortho*-fluoroalkylation of the C—H bond was developed in relation of 2-phenylpyridine based on palladium and nickel compounds in higher oxidation states rarely used in catalysis, which were formed upon electrooxidation of M^{II} precursors.[225]

A major problem associated with the use of the Pd^{II}/Pd^{IV} redox pair is that the co-oxidants used are either expensive (silver or other metal salts are often used) or they are difficult to separate from the reaction mixture (high-molecular-mass organic oxidants). In addition, every time where a new ligand or a new substrate is used or the reaction conditions are changed, a screening for selecting the optimal oxidant needs to be carried out. An objective of investigations into the C—H bond activation is to find a cheaper, environmentally clean and more controllable alternative to these processes by means of electrochemical oxidation. The advantages of the electrochemical process are in the much cheaper and recoverable redox co-catalysts (instead of silver or organic oxidants, there is an electrode for which the desired potential can be chosen).

Examples of catalytic functionalization of C—H bonds on nickel are relatively rare. One of the trends in the direct functionalization of these bonds that calls for new approaches is perfluoroalkylation. The first example of direct trifluoromethylation (Scheme 61) was reported by Wang *et al.*[83] Although functionalization is successful, this reaction employs stoichiometric amounts of expensive trifluoromethyldibenzothiophenium and copper(II) salts in the presence of 10 equiv. of trifluoroacetic acid.

Scheme 61



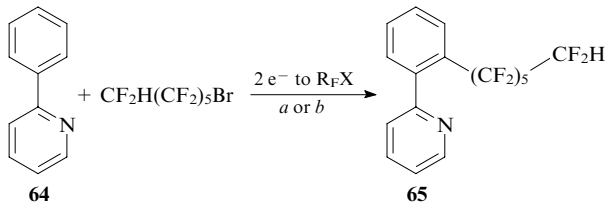
DCE is 1,2-dichloroethane

The $Cu(OAc)_2$ and CF_3CO_2H additives serve as the source of AcOH, which is needed for oxidation of the initially formed cyclopalladium dimer to the key mononuclear intermediate CF_3Pd^{IV} and can also improve the yield by removing the impurities of active Pd species generated at the step of the C—CF_3 coupling.

Recently, an electrochemical procedure for perfluoroalkylation of the C—H bond was proposed,[225] which moreover occurs with not only palladium but also with a nickel catalyst.

It was found that joint electrochemical oxidation of 2-phenylpyridine (**64**) and 6H-perfluorohexyl bromide catalyzed by $Pd_2(OAc)_2$(**64**)$_2$ at a 0.82 V potential *vs.* $Ag/AgNO_3$ results in selective *ortho*-fluoroalkylation (Scheme 62, conditions *a*). Palladium(II) is oxidized at the anode. It is notable that the dimeric palladium complex $Pd_2(OAc)_2$(**64**)$_2$ catalyzed this process more efficiently (the yield of product **65** was 30%) than palladium acetate, which provided the yield of only 10%.

Scheme 62



(*a*) $Pd_2(OAc)_2$(**64**)$_2$ or $Pd(OAc)_2$; (*b*) $[Ni(bpy)_3]^{2+}$

The reactivity of the complex $[Ni(bpy)_3]^{2+}$ towards electrocatalytic perfluoroalkylation was also studied (see Scheme 62, conditions *b*), the Ni^{II}/Ni^{III} oxidation of the catalyst in the presence of 6H-perfluorohexyl bromide and 2-phenylpyridine resulting in 2-[2-(6H-perfluorohexylphenyl]pyridine (**65**) in a higher yield (62%) than with the palladium catalyst.

Perfluoroalkanecarboxylic acids were tested for the ability to react with nickel and palladium catalysts because these acids are considered to be very convenient sources of perfluoroalkyl functional groups.[226] Joint electrochemical oxidation of 2-phenylpyridine (**64**) and perfluoroheptanoic acid (1 : 1) in the presence of various catalysts induced direct perfluoroalkylation *via* decarboxylation step of compound **66** (Scheme 63). Good yields of product **67** were obtained {81% and 85% for the catalysts $Pd_2(OAc)_2$(**64**)$_2$ and $[Ni(bpy)_3]^{2+}$, respectively}, thus being indicative of higher activity of perfluoroalkanecarboxylic acids compared with perfluoroalkyl bromides as substrates for direct perfluoroalkylation.

Scheme 63

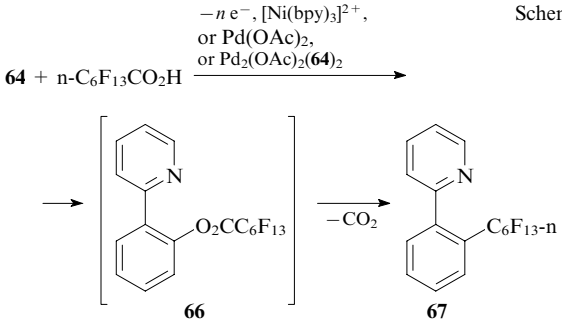


Table 5. Results of *ortho*-fluoroalkylation of 2-phenylpyridine on various catalysts (see Schemes 62 and 63).

Catalyst	Yield (%)	
	65	**67**
$Pd_2(OAc)_2$(**64**)$_2$	30	81
$Pd(OAc)_2$	10	$\leqslant 18$ [a]
$[Ni(bpy)_3]^{2+}$	62	85

[a] Compound **66** is formed in parallel (0% – 15%).

The results of *ortho*-fluoroalkylation induced by the $M^{II}/M^{III(IV)}$ catalysts are summarized in Table 5.

The electrocatalytic synthesis of fluoroalkyl-substituted 2-phenylpyridine is conducted under mild conditions at potentials that allow for generation of high oxidation states of complexed nickel and palladium. Only the electrocatalyst and the substrate are needed for this reaction to occur. The mechanisms of such redox processes continue to be studied in more detail, the synthesis conditions and the range of possible substrates being optimized in these studies.

* * *

The ever extending role of organofluorine compounds in various fields of science and practice has been lately recruiting new research teams into this area. Elaboration of new methods for selective introduction of fluorine atoms or fluorinated groups into organic molecules for the preparation of biologically active compounds and design of diverse useful materials have become vigorously developing lines of chemical research. A multitude of reviews, chapters of books and original publications dealing with this subject matter appeared during the last decade. Evidently, we witness a 'fluorine boom' and considerable progress in the fluoroalkylation, first of all, catalyzed by metals and metal complexes. Electrochemical approaches open up new prospects by ensuring mild conditions of synthesis, high rates and selectivity and the convenient control over the processes by varying parameters such as the current density and the potential.

The studies into perfluoroalkylation are in progress, the number of publications increasing in the avalanche-like fashion, which is due to both the scientific interest and the high demand of the results in a variety of spheres of science and technology. It is quite probable that in the near future we will witness impressive advances in this field of chemistry.

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