Review Article

Selectfluor^{TM} F-TEDA-BF_4 as a Versatile Mediator or Catalyst in Organic Chemistry

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Abstract

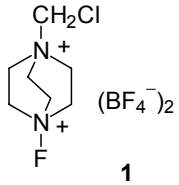
Selectfluor^{TM} *F-TEDA-*BF_4 **1** (1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetra-fluoroborate)) is not only one of the most valuable reagents for electrophilic fluorination but also a versatile mediator or catalyst for various other functionalisations of organic compounds. Its application for selective and effective iodination, bromination, chlorination, nitration and thiocyanation of a comprehensive range of organic compound is reviewed. Benzylic functionalisation of hexamethylbenzene mediated with F-TEDA-BF_4 in the presence of various sources of nucleophiles is described and a method for the synthesis of *para*-quinols or *para*-quinol ethers emphasised. F-TEDA-BF_4 is also useful for the promotion of allylstannation of aldehydes and imines, cleavage of *p*-methoxybenzylidene (PMP), tetrahydropyranyl (THP) or 1,3-dithiane protection, and rearrangements of bicyclic iodides, as well as for catalysis of the regioselective ring opening of epoxides or [4+2] cycloaddition reactions between imines and cyclic enol ethers.

Key words: Selectfluor™ F-TEDA-BF_4, iodination, bromination, hexametylbenzene, allylstannation, deprotection

Contents

Introduction

Selective fluorination of organic compounds under mild reaction conditions through an electrophilic reaction process is one of the most important strategies for accomlishing this task of wide interest to the basic and applied research community.[1–6] The group of chemicals enabling this type of fluorofunctionalisation are usually called electrophilic fluorinating reagents. Indicating the type of reactive bond through which an active fluorine atom is connected with the ligand part of a reagent, the group consists of three main families of reagents: *xenon fluorides*,[7] *fluoroxy reagents*,[8] and *N-F reagents*. One of the most important breakthroughs in modern organofluorine chemistry was accomplished in the late eighties of the last century by the scientific introduction and quickly following broad synthetic application of organic molecules incorporating a reactive N-F bond



1

1-Chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)
Selectfluor^{TM} F-TEDA-BF_4

as mild fluorinating reagents.[9–12] N-F reagents have practically revolutionised the common perception of selective synthesis of fluorinated organic compounds, which is no longer limited to specialised laboratories with sophisticated equipment and specially trained staff complying with strict safety precautions, but is an ordinary experimental protocol, convenient for routine work in any organic chemistry laboratory. These easily-handled "bench-top" materials, usually with optimal stability/reactivity characteristics and reasonable cost, are divided into three main groups: neutral N-fluoro amines (R^1R^2NF), N-fluoropyridinium and related salts, and quaternary N-F salts ($F\text{-}N^+R^1R^2R^3Y^-$). The most widely used members of the last group are N-fluoro derivatives of 1,4-diazabicyclo[2.2.2]octane and 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) **1**, known under the trade name *Selectfluor*^{TM} F-TEDA-BF_4 the most representative in the series.

Since its invention[13] and introduction in the scientific literature,[14] *Selectfluor*^{TM} F-TEDA-BF_4 quickly became one of the most popular reagents for electrophilic fluorofunctionalization of organic compounds,[15–18] used as an ordinary bench-top material in research laboratories, as well as a multi-ton scale produced chemical for several industrial applications.[19]

Some basic characteristics of F-TEDA-BF_4 are collected in Table 1. The material is a white solid decomposing at its melting point or lower, having complicated thermal behaviour. The compound is soluble, or at least moderately soluble, in acetonitrile, slightly soluble in methanol and acetone, insoluble in dichloromethane and very soluble in water. The stability of F-TEDA-BF_4 in water and some organic solvents has been studied.[20] It was established that its neutral or acidic water solutions are stable, while its fast decomposition takes place in alkaline water solutions. F-TEDA-BF_4 decomposes in DMSO (rapidly and exothermically) and DMF (slowly on heating), but is stable in acetonitrile or methanol solutions. Acetonitrile and methanol are thus accepted as the most convenient solvents for its reactions with organic compounds, while until very recently,[21] the corresponding chemistry in aqueous media was almost neglected.

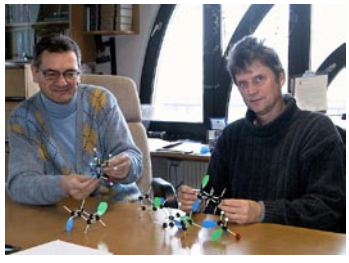
Table 1. Some characteristics of F-TEDA-BF_4 (**1**).

Characteristic	Data
Molecular formula	$C_7H_{14}B_2ClF_9N_2$
Molecular weight (g/mol)	354.26
Active fluorine (g/kg N-F)	53.6
(mmol /g N-F)	2.82
Melting point	170 °C (dec.)
NMR data (solvent):	D_2O;
^{19}F (δ in ppm from CCl_3F)	43.5, –152.0;
^1H (δ in ppm from TMS)	4.5, 5.0, 5.5
Solubility[a] :	
MeCN	s.
MeOH	s.s
Me_2CO	s.s.
CH_2Cl_2	is.
H_2O	s.
$E_{1/2}$ (V, SCE)	0.33
Commercial availability	Yes

[a] more than 0.05 g/L: soluble (s); 0.01g/L–0.05g/L: moderately soluble (m.s.); less than 0.01g/L: slightly soluble (s.s.); insoluble (is.).

A very important characteristic of F-TEDA-BF_4, which considerably affects its convenience as a reagent for various transformations of organic compounds, is its oxidative power. As evident from Table 1 its half-wave potential ($E_{1/2}$)[22] characterises it as strong oxidant, one of the strongest in the series of N-F reagents.[23] *Selec-*

Biographical Sketches



Marko Zupan *(left), born in Ljubljana in 1947, completed his PhD in organic chemistry (mentor Alfred Pollak) in 1974. Since 1970 he has been a member of University of Ljubljana and in 1987 has been nominated as Professor of Organic Chemistry at the Faculty of Chemistry and Chemical Technology. Since 1972 he has been an associate member of the Jožef Stefan Institute, and Scientific Adviser there since 1987.* ***Stojan Stavber*** *(right) was born in Maribor in 1951 and completed his PhD in 1987 (mentor Marko Zupan). As the undergraduate student he has joined Zupan's group at Jožef Stefan Institute in 1974, has been nominated as Scientific Adviser there in 2000 and actually as Head of Department for Physical and Organic Chemistry. The scientific work of Zupan and Stavber published in more than 200 original scientific articles is dealing mainly with organohalogene chemistry, especially organofluorine chemistry, the photochemistry of fluoro-organic molecules and polymer-supported reagents. The chemistry of Zupan-Stavber group has been awarded by the Republic of Slovenia with B. Kidrič Fund Award for Important Discoveries on Fluorination of Organic Molecules (1981), B.Kidrič Fund Awards for Patent and Innovations (1983, 1985, 1987), and Zois Award for research excellence in the field of Organic Chemistry (2000).*

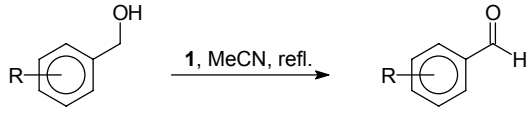
fluor^{TM} F-TEDA-BF_4 is thus one of the most powerful electrophilic fluorinating reagent from the N-F family and a potential multipurpose chemical suitable for mediation of other functionalisations or transformations of organic compounds. The literature data concerning its use as a fluorinating reagent have been comprehensively documented during the last decade,[9–12,15–18] while a review of its applications as a reagent or catalyst for "other-than-fluorine" functionalisation of organic compounds is the subject of the present account.

Functalisation of Organic Compounds in the Presence of F-TEDA-BF_4

Oxidation of primary alcohols

The hydroxy functional group is an oxidisable structural moiety ordinarily sensitive to the presence of chemicals having a certain oxidising power. Reactions of benzylic alcohols with F-TEDA-BF_4 were studied and their oxidation to benzaldehyde derivatives established.[24] Reactions in acetonitrile were found, at least for derivatives bearing a deactivated aromatic ring, to be relatively slow (Table 2) and have limited synthetic importance, but nevertheless the protection of this functional moiety is required when **1** is used for fluorination of organic molecules bearing a benzylic hydroxy group. Aliphatic primary alcohols are also readily oxidised to corresponding aldehydes by **1** in MeCN.[25]

Table 2. Reaction of benzylic alcohols **2** with *Selectfluor*^{TM} F-TEDA-BF_4 (**1**).



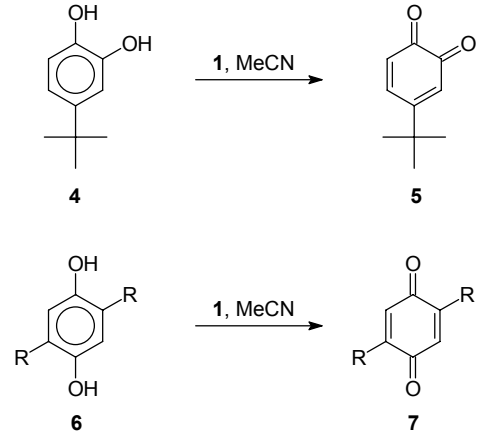
2 **3**

R	Time (h)	Yield (%)
H	18	43
4-NO_2	65	62
2-NO_2	435	56
2-Cl	45	42
4-Cl	15	37

Oxidation of some phenols

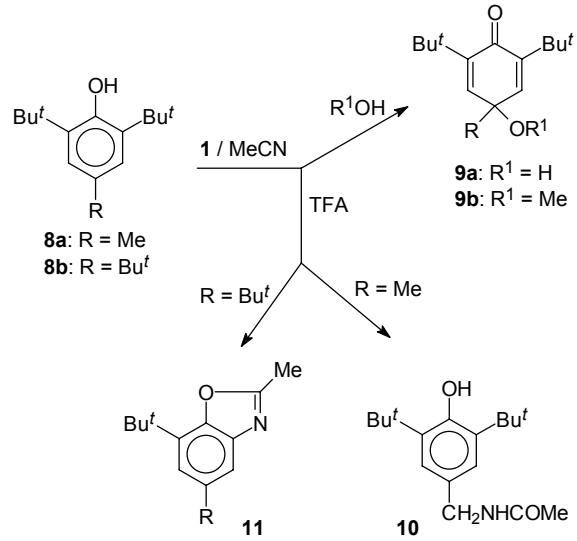
Reactions of phenols with F-TEDA-BF_4 were extensively studied. These derivatives, substituted by an additional hydroxy substituent on *ortho* **4** or *para* **6** position, were readily oxidized to the corresponding quinones **5** or **7** (Scheme 1) by **1** in MeCN.[25]

The course of reactions of 1,3,5-trialkyl substituted phenols **8** (Scheme 2) with **1** were found to be considerably dependent on the structure of the target substrates and the solvent used.[26] The reaction of **8** in pure acetonitrile gave fluorinated products while in the



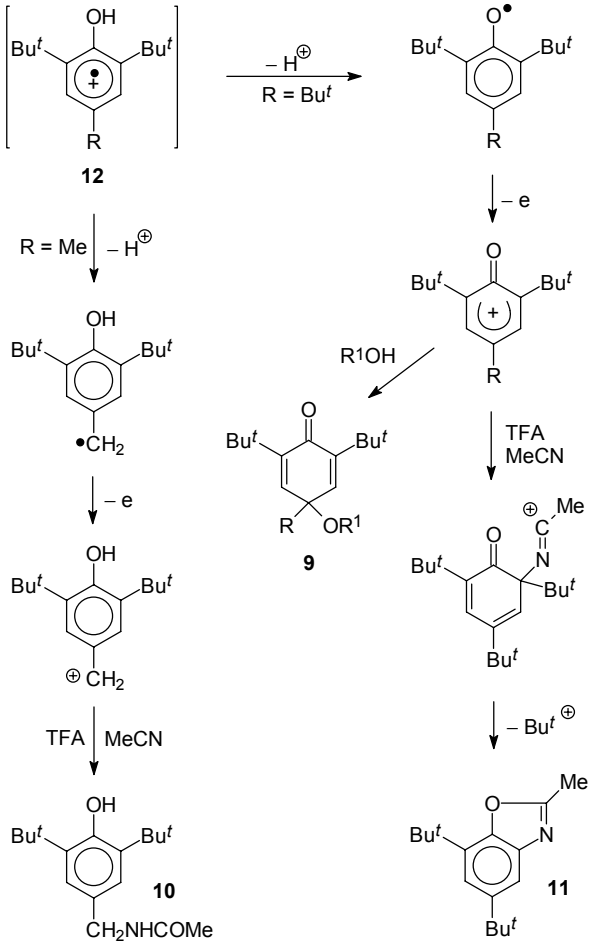
a: R = H
b: R = Bu^t
c: 1,4-naphthalenedione

Scheme 1



Scheme 2

presence of alcohols or water *para* quinols **9a** or *para* quinol ethers **9b** were formed. However, the presence of more acidic nucleophile-like trifluoroacetic acid (TFA) caused quite different transformations of the target phenols. The reaction of **8a** with **1** in MeCN/TFA 9:1 solvent mixture resulted in the formation of 2,6-di-tert-butyl-4-methylacetamidophenol **10** as the main product (70%), accompanied by small amounts of ring and side chain trifluoroacetoxy and/or acetamido substituted phenols. The similar reaction of 2,4,6-tri-tert-butylphenol **8b** gave 2-methyl-5,7-di-tert-butylbenzoxazole **11** as the main product (65%), accompanied by small amounts of 2- and 4-acetamido derivatives of di-tert-butylphenol, 2,6-di-tert-butylquinone, various isomers of trifluoroacetoxy-substituted derivatives and N-tert-butylacetamide. It is obvious that, under these conditions, the reaction intermediates reacted with MeCN



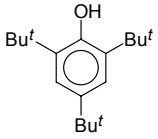
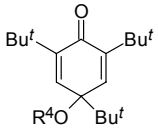
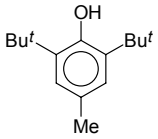
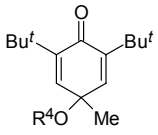
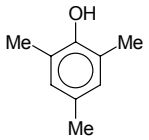
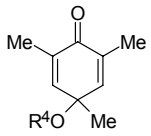
Scheme 3

following a Ritter-type reaction as the main process, instead of being quenched with TFA as an external nucleophile.

The reaction rates were shown to obey simple second-order kinetics and the values of the second-order rate constants (k_2) were found to be dependent on the structure of the target phenol and decreased with the bulkiness of the substrate.[26] Methanol slightly increased the rate, while water decreased it considerably. Activation enthalpies (between 72 and 78 kJmol^{-1}) and activation entropies (between –5 to –42 Jmol^{-1}K^{-1}) were obtained. Activation entropies were found to be higher for less hindered substrates, indicating that the rate-determining steps were mainly regulated by steric factors. An electron transfer-type process thus forming cation-radical species **12** as the key intermediates, which were further transformed to products **9**, **10** or **11**, was postulated as the reaction pathway (Scheme 3).

A method for efficient synthesis of various types of *para*-quinols or *para*-quinol ethers was developed[27] on the basis of the above mentioned investigations and the corresponding results are collected in Table 3.

Table 3. Synthesis of para-quinols and para-quinol ethers mediated by F-TEDA-BF$_4$ (**1**).[27]

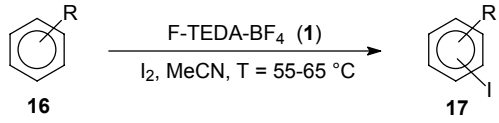
Phenol	R^4	Product	Yield (%)
	H		19
	Me		79
	Et		75
	Pr		77
	HOC_2H_4		79
	H		78
	Me		82
	Et		75
	HOC_2H_4		81
	$MeOC_2H_4$		78
	H		76
	Me		85
	Et		82
	CF_3CH_2		38
	HOC_2H_4		76
	$MeOC_2H_4$		79

Iodination of arenes

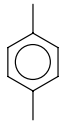
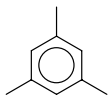
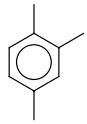
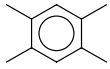
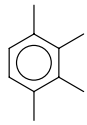
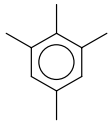
Iodo substituted aromatic molecules have been recognised for a long time as valuable synthetic tools, above all in carbon-carbon bond formation, mainly through metal catalysed coupling reactions. In addition, many iodinated aromatic derivatives are used in medicine as drugs or diagnostic aids, contrasting agents, and radioactively labelled markers. The chemistry dealing with selective iodination of arenes has thus attracted broad interest in the wider scientific community. Electrophilic iodination using a variety of electrophilic iodine species has been accepted as the most convenient general synthetic approach. Elemental iodine should be certainly the most convenient iodination reagent for this task but a certain activation in order to increase its weak electrophilicity is typically necessary. Hydrogen iodide, liberated during iodo the substitution process, ordinary interferes with the selectivity and efficiency of these reactions, while one iodine atom is lost in this case for iodofunctionalisation of the target compound. The activation of electrophilicity of elemental iodine could be achieved by polarisation of the I-I bond or by oxidative formation of I^+ species and it was first demonstrated in our laboratory that *Selectfluor*^{TM} F-TEDA-BF$_4$ is an appropriate mediator for this task.

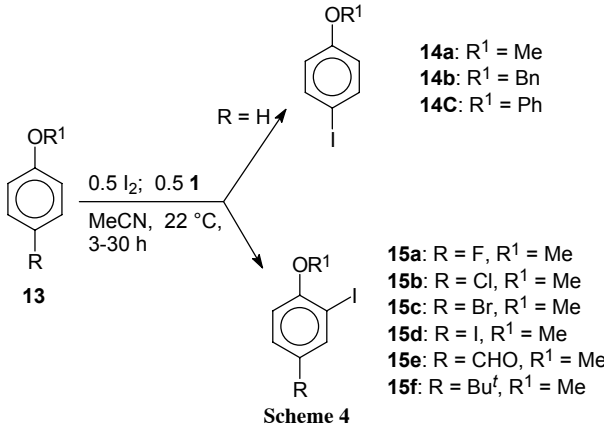
As shown in Scheme 4 room temperature regioselective iodination of aromatic ethers **13** could be efficiently performed using the I_2 / F-TEDA-BF$_4$ tandem.[28] Only a half-equivalent of I_2 and **1** was necessary for conversion of the starting material into the

Table 4. Iodination of methyl-substituted benzenes 16 mediated by F-TEDA – BF_4 (**1**).[29]



16 **17**

Methyl benzene **16**	Reaction conditions		Iodo methylbenzene (**17**)	Yield (%)
	16 : I_2 : **1**	Reaction time (h)		
	1 : 0.6 : 0.6	3	1-iodo-2,4-dimethylbenzene	85
	1 : 5 : 5	24	1,3,5-triiodo-2,4-dimethylbenzene	65
	1 : 1.5 : 1.5	5	1,4-diiodo-2,5-dimethylbenzene	81
	1 : 5 : 5	24	1,3,4-triiodo-2,5-dimethylbenzene	65
	1 : 0.6 : 0.6	1	2-iodo-1,3,5-trimethylbenzene	88
	1 : 1.1 : 1.1	3	2,4-diodo-1,3,5-trimethylbenzene	80
	1 : 3 : 3	24	1,3,5-triiodo-2,4,6-trimethylbenzene	83
	1 : 0.75 : 0.75	1.5	1-iodo-2,4,5-trimethylbenzene	88
	1 : 4 : 4	24	1,2,4-triiodo-3,5,6-trimethylbenzene	68
	1 : 0.6 : 0.6	1.5	1-iodo-2,3,4-trimethylbenzene	88
	1 : 4 : 4	24	1,2,3-triiodo-4,5,6-trimethylbenzene	69
	1 : 0.75 : 0.75	1.5	3-iodo-1,2,4,5-tetramethylbenzene	88
	1 : 2 : 2	2.5	1,4-diiodo-2,3,5,6-tetramethylbenzene	68
	1 : 0.75 : 0.75	1	1-iodo-2,3,4,5-tetramethylbenzene	85
	1 : 2 : 2	2.5	1,2-diiodo-3,4,5,6-tetramethylbenzene	67
	1 : 0.75 : 0.75	1	2-iodo-1,3,4,5-tetramethylbenzene	88
	1 : 2 : 2	2.5	1,3-diiodo-2,4,5,6-tetramethylbenzene	68



14a: R^1 = Me
14b: R^1 = Bn
14C: R^1 = Ph

15a: R = F, R^1 = Me
15b: R = Cl, R^1 = Me
15c: R = Br, R^1 = Me
15d: R = I, R^1 = Me
15e: R = CHO, R^1 = Me
15f: R = Bu^t, R^1 = Me

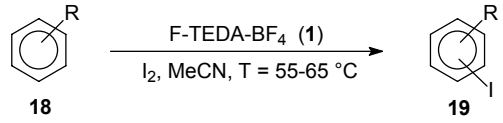
Scheme 4

4-iodo substituted derivatives **14a-c,** or the 2-iodo products **15a–f** when the *para* position in the substrate was already occupied.

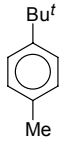
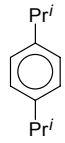
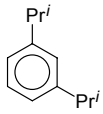
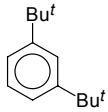
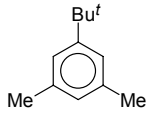
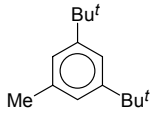
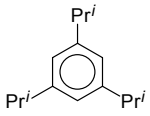
This very useful synthetic approach was further applied for the selective transformation of a series of methyl substituted benzene derivatives **16** to the corresponding mono-, di- and even tri-iodo substituted derivatives **17**, depending on the ratio between target substrate, iodine, and F-TEDA-BF_4.[29] The results are collected in Table 4.

As evident from the data in Table 5, the method was also efficient in the case of sterically hindered alkyl substituted benzene derivatives where selective progres-

Table 5. Iodination of sterically hindered alkyl-substituted arenes 18 mediated by F-TEDA–BF_4 (**1**).[30]



18 **19**

Alkyl benzene (**18**)	Reaction conditions		Iodo alkylbenzene **19**	Yield (%)
	18 : I_2 : **1**	Reaction time (h)		
	1 : 0.6 : 0.6	3	4-*tert*-butyl-2-iodo-1-methylbenzene	88
	1 : 2.5 : 2.5	5	5-*tert*-butyl-1,3-diiodo-2-methylbenzene	80
	1 : 0.75 : 0.75	4	2-iodo-1,4-diisopropylbenzene	77
	1 : 2.5 : 2.5	6	1,4-diiodo-2,5-diisopropylbenzene	81
	1 : 0.6 : 0.6	3	1-iodo-2,4-diisopropylbenzene	89
	1 : 2.2 : 2.2	6	1,5-diiodo-2,4-diisopropylbenzene	71
	1 : 0.6 : 0.6	4.5	1,3-di-*tert*-butyl-5-iodobenzene	83
	1 : 0.6 : 0.6	1.5	5-*tert*-butyl-2-iodo-1,3-dimethylbenzene	88
	1 : 0.75 : 0.75	5	1,5-di-*tert*-butyl-2-iodo-3-methylbenzene	58
	1 : 5 : 5	24	5-*tert*-butyl-1,2-diiodo-3-methylbenzene	77
	1 : 0.75 : 0.75	2	2-iodo-1,3,5-triisopropylbenzene	90

sive iodination could be achieved using the I_2 / F-TEDA-BF_4 tandem in acetonitrile reaction media.[30]

A variety of aromatic compounds was regioselectively iodinated with iodine and F-TEDA-BF_4 in imidazolium- and pyridinium-based ionic liquids, 1-butyl-3-methylimidazolium hexafluorophosphate ([bmim][PF_6]) and 1-butylpyrodinium tetrafluoroborate ([bpyr][BF_4]). Iodination was *para*- directed when possible, otherwise it occurred in the *ortho*-position.[31] The corresponding results of these **1** mediated iodinations under "eco-friendly" reaction conditions are shown in Table 6.

Iodination of ketones

An iodine atom bonded at the position α to the carbonyl group makes the molecule a convenient synthon for further functionalisation. For the preparation of α-iodinated ketones various indirect methods like halogen interchange reactions or electrophilic iodination of silyl enol ethers or enol acetates are common synthetic procedures, while direct methods of iodofunctionalisation are still scarce. Activation of elemental iodine by F-TEDA-BF_4 has been found to be an excellent synthetic procedure of direct iodofunctionalisation of ketones α to the carbonyl group. As shown

Table 6. Iodination of aromatic compounds with I_2 / F-TEDA-BF_4[a] in ionic liquids.[31]

Aromatic substrate	Solvent	Product distribution (mol %)	Yield[b] (%)
Toluene	[bmim][PF_6]	4-Iodotoluene (65); 2-iodotoluene(35)	40
1,4-Dimethylbenzene	[bpyr][BF_4]	2-Iodo-1,4-dimethylbenzene	90
	[bmim][PF_6]		90
1,3,5-Trimethylbenzene	[bpyr][BF_4]	2-Iodo-1,3,5-trimethylbenzene	90
	[bmim][PF_6]		95
1,2,4,5-Tetramethylbenzene	[bmim][PF_6]	3-Iodo-1,2,4,5-tetramethylbenzene	43
Anisole	[bpyr][BF_4]	4-Iodoanisole	57
	[bmim][PF_6]		56
4-Methylphenol	[bpyr][BF_4]	2-Iodo-4-methylphenol	48
	[bmim][PF_6]		66
Phenol	[bmim][PF_6]	4-Iodophenol(90); 2-iodophenol(10)	72
2,6-Di-iso-propylphenol	[bpyr][BF_4]	2,6-Di-iso-propyl-4-iodophenol	40
	[bmim][PF_6]		50
Aniline	[bpyr][BF_4]	4-Iodoaniline	25
	[bpyr][BF_4]		56[c]
	[bmim][PF_6]		40
4-Nitrophenol	[bpyr][BF_4]	2-Iodo-4-nitrophenol	13
3,4-Dimethoxyacetophenone	[bpyr][BF_4]	α-Iodo-3,4-dimethoxyacetophenone	81
	[bmim][PF_6]		27

[a] Reaction conditions: I_2 (0.9 mmol); F-TEDA-BF_4 (0.9 mmol); arene(1.8 mmol); solvent 3 mL; 24 h; 80 °C;
[b] Calcd. on the starting material; [c] Aniline/I_2/**1** 1.2 : 0.6 : 0.6.

in Scheme 5 reactions of aryl methyl ketones **20** in a methanol solution of I_2 / **1** resulted in the formation of the corresponding α-iodo substituted ketones[32] **21a–k** in high yield. In the case of compounds **22** bearing an activated aryl ring, the regioselectivity of iodination depended on the solvent used. In MeOH, iodination at the α-carbonyl was found to be exclusive (**23**, **25**, **27**, and **29**), while in MeCN selective ring iodination was achieved (**24**, **26, 28**, and **30**).

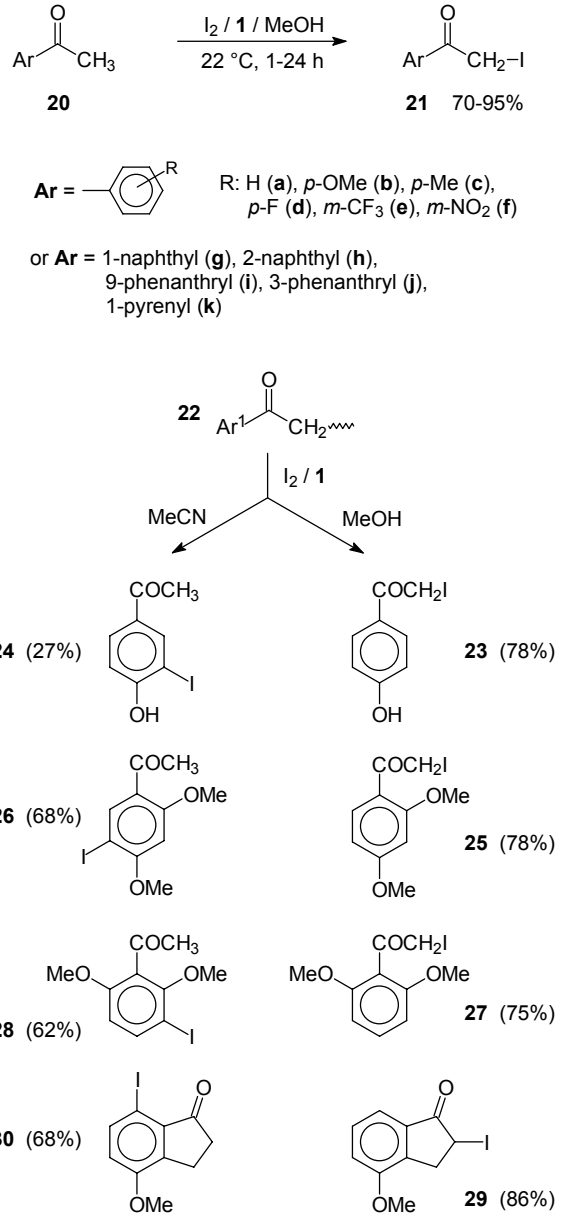
The synthetic importance of the method has been proven by its application for selective iodofunctionalization of different types of acetyl substituted aromatic and heteroaromatic derivatives[33] as shown in Table 7, as well as a variety of indanone and tetralone derivatives,[34] as becomes evident from the data collected in Table 8.

Bromination of unsaturated carbon-carbon bonds

Oxidative bromination of various alkenes using potassium bromide as the source of the electrophilic bromine species and F-TEDA-BF_4 as the oxidant was reported. The course of the reaction was found to depend crucially on the structure of the alkene substrate.[35]

Derivatives of styrene (**31a**,**b**, Scheme 6) were almost quantitatively transformed to vicinal bromohydrins or methyl ethers **32** using the **1** / KBr / MeCN system in the presence of water or methanol. The bromination of phenyacetylene **33** under F-TEDA-BF_4 mediation in water resulted in the formation of α,α-dibromoacetophenone **34** when a neutral aqueous solution of **1** and KBr was used; in the presence of a weak base (E)-1,2-dibromostyrene **35** was formed, while under acidic conditions (Z)-1,2-dibromostyrene **36** was the predominant product.[35]

For a system having a double bond conjugated with a carbonyl group (**37**, **39**, Scheme 7) α-bromo-conjugated products **38** or **40** were obtained. When a carbonyl was conjugated with a phenyl group on the β-position (**41**), oxidative bromination, using the **1** / KBr / aqueous MeCN system, gave stereoselectively *erythro*-dibromo products **42a–c**, while in the case of a chalcone target (**41**, R^3=Ph, R^4=H) using dry MeCN the bromoamidation process resulted in **43.** On the other hand, derivatives of *trans*-cinnamic acid underwent decarboxylic bromination, yielding β–bromostyrene



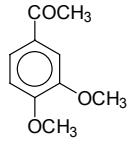
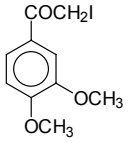
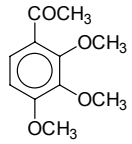
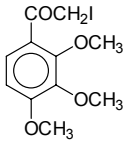
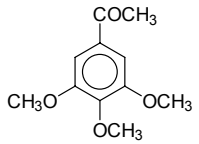
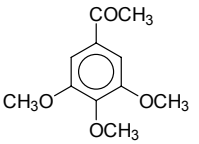
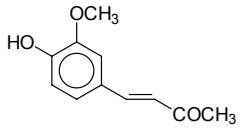
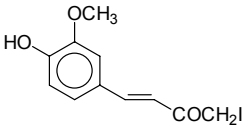
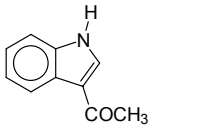
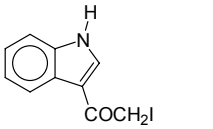
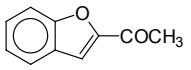
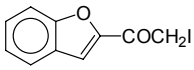
Scheme 5

derivatives **44a–c** with very high E/Z stereoselectivity. Bromination followed by intramolecular ring closure in the case of a target like **45** also proceeded smoothly but lacked diastereoselectivity, thus forming **46** in high yield.[35]

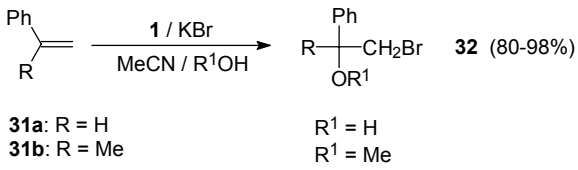
Other types of oxidative functionalisation of arenes

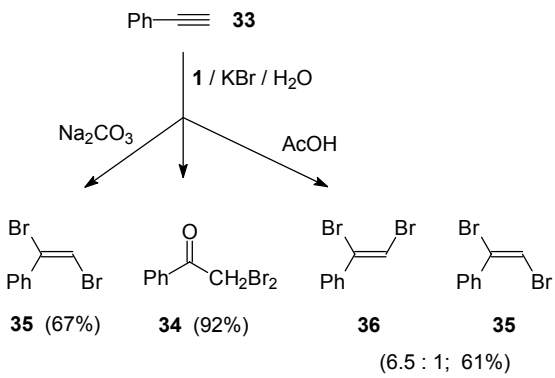
Electrophilic functionalization of benzene derivatives with various electrophilic species generated *in situ* from their anionic precursors by reaction of F-TEDA-BF_4 in MeCN solution at room temperature was reported and the results are collected in Table 9.[36] It was established that different anionic precursors could be

Table 7. Iodination of aryl ketones[a] by I_2 activated with F-TEDA-BF_4.[33]

Ketone	α-Iodo ketone	Yield[b] (%)
		85
		82
		83
		84
		75
		70

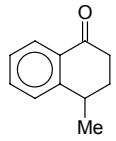
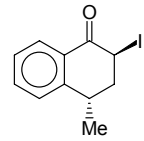
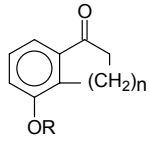
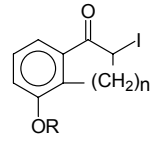
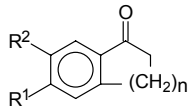
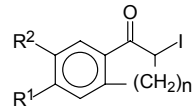
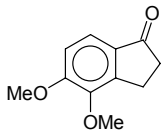
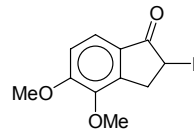
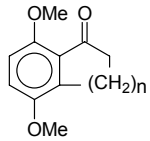
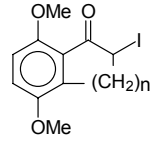
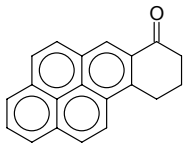
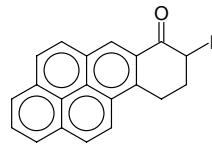
[a] Reaction conditions: ketone (2 mmol), F-TEDA-BF_4 (1.2 mmol), I_2 (1 mmol), methanol (20 mL), 22 °C, reaction time 20-48 hours; [b] Refers to the isolated pure products.





Scheme 6

Table 8. Iodination of substituted 1-indanones and 1-tetralones by I_2 activated with F-TEDA-BF_4.[34]

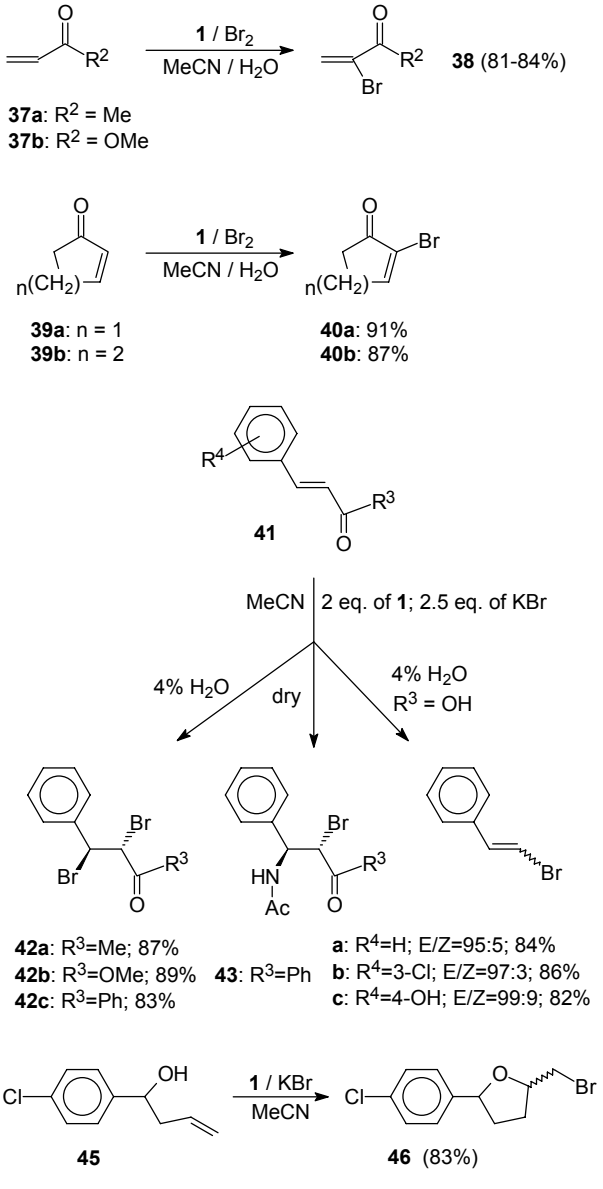
Ketone		Time (h)	α-Iodo ketone	Yield[b] (%)
		24		86
	**a**: n = 1; R^1 = H	20		64
	b: n = 2; R^1 = H	20		69
	c: n = 2; R^1 = Me	20		87
	**a**: n = 2; R^1 = OH, R^2 = H	20		73
	b: n = 1; R^1 = OMe, R^2 = H	20		86
	c: n = 1; R^1 = H, R^2 = OMe	5		85
	d: n = 2; R^1 = H, R^2 = OMe	6		86
	e: n = 1; R^1 = R^2 = OMe	6		84
	e: n = 2; R^1 = R^2 = OMe	6		85
		6		86
	**a**: n = 1	5		85
	b: n = 2	6		87
		24		63

[a] Reaction conditions: ketone (2 mmol), F-TEDA-BF_4 (1.1 mmol), I_2 (1 mmol), methanol (20 mL), 20 °C, reaction time 5-24 hours.
[b] Refers to the isolated pure products.

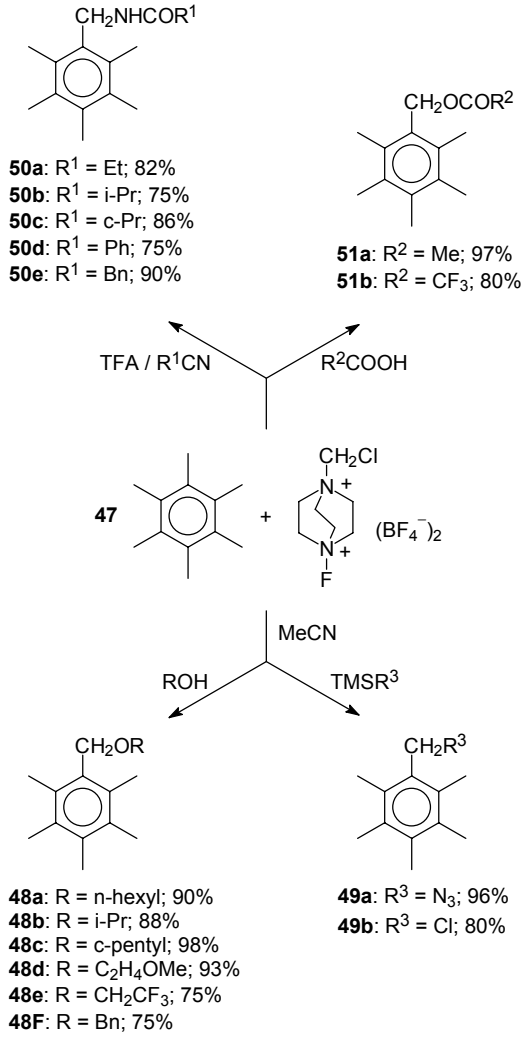
oxidised by **1** to active electrophilic species which readily functionalised the benzene ring. The reactivity in a group of easily oxidizable anions decreases in the order $Br^- > Cl^- > SCN^- > NO_2^-$, the second group includes anions like AcO^- and TfO^- which are difficult to oxidize to their cationic forms, while the third group which includes cyanide, cyanate, methoxide or thiomethoxide anions, could not be oxidized with **1** under the reaction conditions used. The reaction of sodium, potassium or ammonium salts of the anions from the first group with an activated benzene ring in the presence of equimolar or slightly excess amounts of **1** resulted in the formation of bromo, chloro, thiocyano or nitro-substituted benzene derivatives. From the comparative studies it was established that potassium salts gave the best results and that F-TEDA-BF_4 afforded the highest yields of substituted products in the shortest reaction time. The best choice of solvent for this valuable reaction was found to be MeCN, while reactions did not proceed in MeOH.[36]

Functionalisation at a benzylic carbon atom

In the functionalizations described in the sections 2.2. to 2.6., F-TEDA-BF_4 acted as an oxidant to produce electrophilic species from various sources (I^+ from I_2 or I^-, Br^+ from Br^- or NO_2^+ from NO_2^- etc.). In this section a few additional examples of functionalization are described when **1** acts mainly as an oxidant for a



Scheme 7



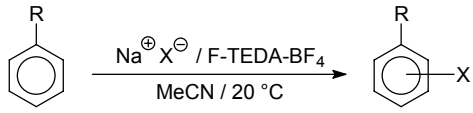
Scheme 8

chosen substrate, thus forming an electron deficient reactive intermediate which reacts with an external nucleophile.

An example of this kind is derivatisation of a benzylic carbon atom in hexamethylbenzene (HMB) **47** is shown in Scheme 8. Reactions of HMB with F-TEDA-BF_4 in MeCN solvent in the presence of alcohols resulted in the formation of pentamethylbenzylalkyl ethers **48a–f** in high to excellent yield, while in the presence of trimethylsilyl derivatives like TMS-azide or TMS-chloride, the corresponding pentamethylbenzyl-substituted derivatives **49a,b** were readily formed. Reactions in TFA or in acetic acid gave pentamethylbenzyl acetate **51a** or trifluoroacetate **51b**, while transformation in TFA in the presence of various nitriles resulted in Ritter-type benzylic amidation and the corresponding pentamethylbenzyl amides **50a–e** were isolated.[37]

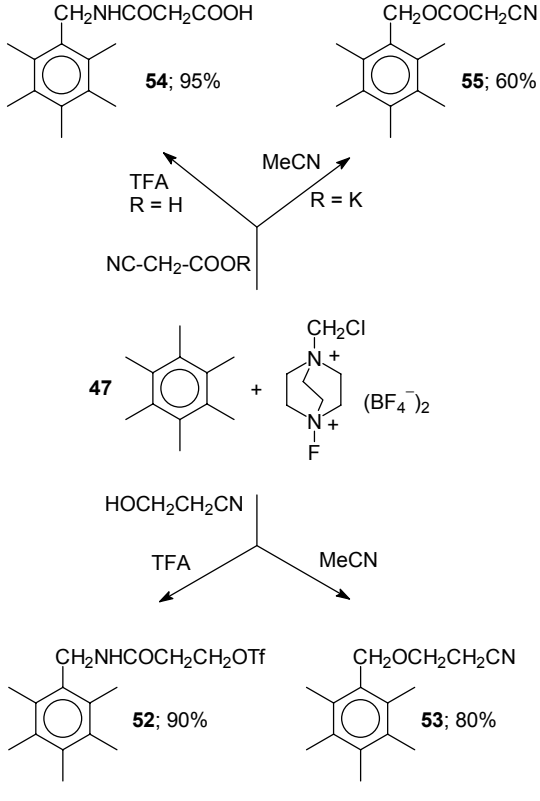
It was also established that by using appropriate reaction conditions and **1** as mediator, selective functionalisation of HMB can also be obtained in the presence of compounds bearing two different nucleophilic centres (Scheme 9). When TFA was used as the solvent, 2-cyanoethanol yielded selectively the benzyl amide derivative **52**, while in MeCN it gave benzylic ether **53**. On the other hand, cyanoacetic acid as a source of external nucleophile was activated at its cyanide moiety if TFA was used as solvent and the corresponding benzyl amide **54** was formed, while in MeCN, potassium cyanoacetate acted as a carboxy nucleophile and pentamethylbenzyl cyanoacetate **55** was formed.[37]

Table 9. Oxidative functionalization of benzene derivatives a mediated by F-TEDA-BF_4. [36]

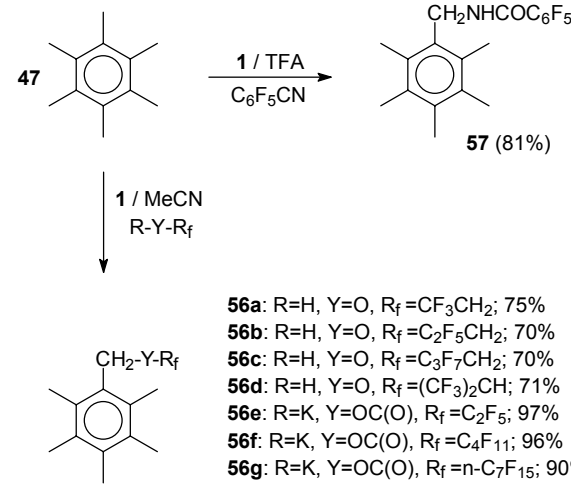


Aromatics	X^-	Time (h)	Conversion (%)	Product distribution (mol%)[a]
benzene	Br	72	100	bromobenzene (100)
	Cl	72	100	chlorobenzene(97), dichlorobenzenes(3)
	NO_2	72	100	nitrobenzene (100)
phenol	Br	3	90	bromophenols(87), 2,4-dibromophenol(12)
	Cl	42	42	chlorophenols (25), fluorophenols (67)
	NO_2	68	98	nitrophenol (81), fluoronitrophenol (16)
anisole	Br	21	100	4-bromoanisole (100)
	Cl	42	58	chloroanisoles (67), fluoroanisoles (31)
	SCN	21	67	SCN-anisoles (94)
	NO_2	97	43	nitroanisoles (13), fluoroanisoles (87)
acetanilide	Br	3	87	bromoacetanilide (99)
1,4-dimethoxybenzene	Br	113	100	2-bromo-1,4-dimethoxybenzene (100)
	Cl	113	100	2-chloro-1,4-dimethoxybenzene (100)
	SCN	160	60	2-SCN-1,4-dimethoxybenzene (100)
	NO_2	184	100	2-nitro-1,4-dimethoxybenzene (100)
4-nitrophenol	NO_2	45	95	2,4-dinitrophenol (100)

[a] In some cases regioselectivity not determined.



Scheme 9



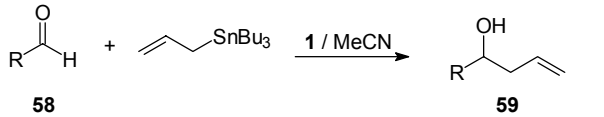
Scheme 10

A similar synthetic protocol was applied for direct introduction of a perfluoroalkyl moiety containing functional groups at the benzylic position in HMB (Scheme 10). The reaction of HMB with an acetonitrile solution of 1 in the presence of perfluoroalcohols or potassium salts of perfluoroalkanoic acids resulted in a high yield formation of the corresponding R_f benzylic ethers 56a–d or esters 56e–g, while benzylic amidation in TFA failed

except in the case of pentafluorobenzonitrile, where the corresponding perfluoro substituted benzyl benzamide 57 could be isolated in high yield.[38]

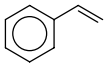
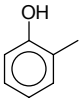
Allylation of aldehydes and imines

Allystannanes have been widely used for the conversion of aldehydes or ketones to homoallylic alcohols or of imines to homoallylic amines. Promotion of these transformations using strong Lewis acids or rare earth metals is necessary, and the processes are very sensitive to moisture and difficult to handle on a large-scale. It has been found that F-TEDA-BF_4 could be an efficient promotor for these functionalisations with excellent moisture and air tolerance.[39] Aryl and alkyl adehydes **58** were readily allylated to **59** with tributylallyltin in the presence of a stoichiometric amount of F-TEDA-BF_4 (Scheme 11).



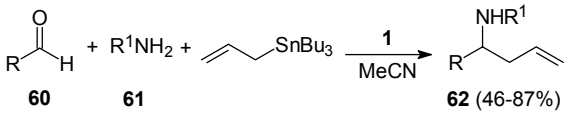
58 **59**

a: R = Ph (76%); **b**: R = 1-naphthyl (90%); **c**: R = n-heptyl (83%)

d: R =  (93%); **e**: R =  (86%)

Scheme 11

Using **1** as the promoter, one-pot allylation of imines with tributylallyltin thus forming homoallylic amines **62** was achieved in moderate to good yield (Scheme 12). Aldehyde **60** (0.8 mmol), amine **61** (1.2 mmol) and **1** (0.8 mmol), were stirred in MeCN solution at room temperature for a few minutes, the first portion of tributylallyltin was then added (1.2 mmol), stirred for 30 min and the second portions of **1** (0.4 mmol) and tributylallyltin (1.2 mmol) were added in order to carry the reaction to completition.[39]

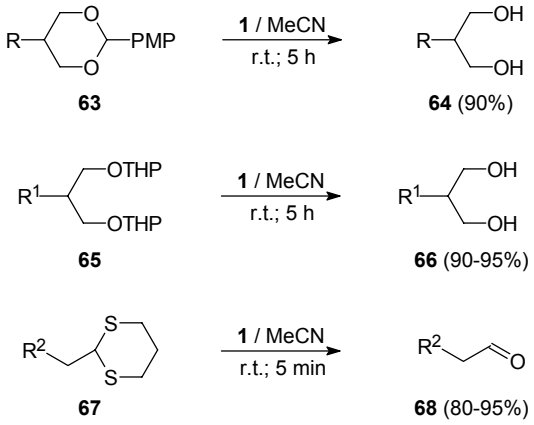


60 **61** **62** (46-87%)

Scheme 12

Cleavage of p-methoxybenzylidene (PMP), tetrahydropyranyl (THP) and 1,3-dithiane protecting groups

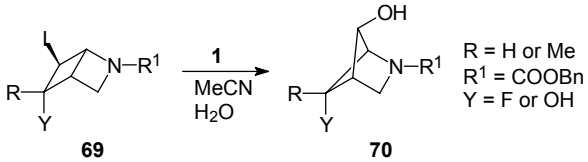
A new and efficient method for cleavage of PMP, THP and 1,3-dithiane protecting groups with F-TEDA-BF_4 has been discovered and developed.[40] PMP and THP are very useful protecting groups for diols. Their deprotection usually requires strong acidic or oxidative conditions, which could cause incovenience when multifunctional groups are present in target derivatives. It has been shown that 1 can smoothly and efficiently cleave PMP 63 and THP 65 protective groups under mild reaction conditions (Scheme 13). 1,3-Dithiane protection of carbonyl is often used in synthetic procedures, but its removal is relatively difficult and requires harsh conditions. It has been demonstrated that F-TEDA-BF_4 could easily cleavage 1,3-dithiane protection 67 in a few minutes reaction at room temperature.[40]



Scheme 13

Rearrangements of bicyclic iodides

Stereoselective synthesis of 5,6-difunctionalized-2-azabicyclo[2.1.1] hexanes containing 5-*anti*-fluoro or hydroxyl in one methano bridge (70, Scheme 13) was performed by rearrangement of the iodo-substituted precursors 69 induced by an aqueous MeCN solution of F-TEDA-BF_4.[41]

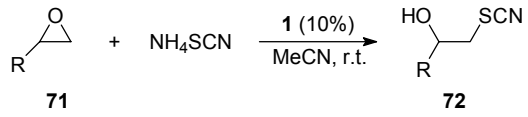


69 **70**

Scheme 14

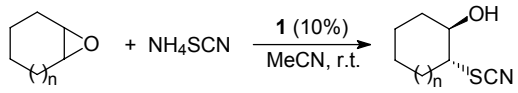
Regioselective ring opening of epoxides

A variety of epoxides **71**, Scheme 15 underwent rapid ring opening with ammonium thiocyanate in the presence of 10 mol% of F-TEDA-BF_4 in MeCN at room temperature, thus regioselectively affording the corresponding β-hydroxy thiocyanates **72** in excellent yields. Cycloakyl oxides **73** under similar reaction conditions gave β-hydroxy thiocyanates **74** with *anty*-stereoselectivity.[42]



71 **72**

a: R = Ph; 80%
b: R = n-Bu; 75%
c: R = CH_2OPh; 90%
d: R = CH_2COPh; 86%
e: R = CH_2ONaph; 90%
f: R = CH_2(*p*-OMe)Ph; 95%

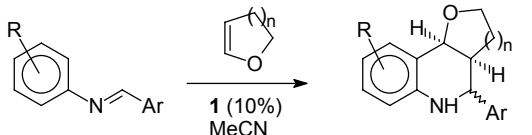


73 **74a**: n = 1; 89%
74b: n = 2; 85%

Scheme 15

Cycloaddition reactions

Aryl imines **75**, Scheme 16 underwent smooth [4+2] cycloaddition reactions with cyclic enol ethers like 3,4-dihydro-2H-pyran and 3,4-dihydrofuran in the presence of 10 mol% of **1** in MeCN at room temperature to afford pyrano- (**76**, n=2) or furanotetrahydroquinoline (**76**, n=1) derivatives in high yield and with *endo*-selectivity.[43]



75 **76**
endo/exo from 80:20 to 94:4;
yields 85-94%

Scheme 16

Conclusions and Perspectives

1-Chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate); *Selectfluor* F-TEDA-BF_4 is one of the most popular modern reagents for selective fluorination of organic compounds under mild reaction conditions. As evident from the present compilation of the corresponding literature reports, it also can act as a versatile mediator or catalyst for several other types of functionalization or transformations of organic derivatives, thus opening up new and interesting prospects.

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Povzetek

Selectfluor™ F-TEDA-BF_4 (1-klorometil-4-fluoro-1,4-diazoniabiciklo[2.2.2]oktan bis(tetrafluoroborat)) ni samo eden najbolj koristnih reagentov za elektrofilno fluoriranje ampak tudi vsestranski mediator ali katalizator za mnoge druge funkcionalizacije ali pretvorbe organskih spojin. Opisana je njegova uporaba pri številnih reakcijah jodiranja, bromiranja, kloriranja, nitriranja ali uvedbe tiocianatne skupine v različne vrste organskih spojin. Funkcionalizacijo heksametilbenzena na benzilno mesto je moč izvesti zelo uspešno z F-TEDA-BF_4 ob prisotnosti različnih nukleofilov. F-TEDA-BF_4 je odličen reagent za pripravo *para*-kinolov ali *para*-kinol etrov iz ustreznih fenolov, uporabili so ga za aliliranje aldehidov in iminov, za PMP ali THP deprotekcijo glikolov ali odstranitev 1,3-ditianske zaščite karbonilne skupine, pri nekaterih premestitvah v skupini bicikličnih jodidov, ugotovili pa so tudi, da katalizira regioselektivno odpiranje epoksidnih obročev in nekatere [4+2] cikloadicijske reakcije med imini in cikličnimi enolnimi etri.