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Generation of heteroarylium-*N*-difluoromethylides and heteroaryl-*N*-difluoromethyl anions and their reactions with electrophiles: heteroaryl- and heteroarylium-*N*-difluoromethyl trimethylsilanes and a new heteroaryl-*N*-trifluoromethane

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Abstract

Reductive debromination of *N*-bromodifluoromethyl-4-dimethylaminopyridinium bromide, 1-bromodifluoromethyl-imidazole, 1-methyl-3-bromodifluoromethyl-imidazolium bromide and 1-bromodifluoromethyl-2-methyl-benzimidazole using tetrakis(dimethylamino)ethylene (TDAE) or tris(diethylamido)phosphite leads to new fluorinated carbanionic species, namely heteroarylium-*N*-difluoromethylides and heteroaryl-*N*-difluoromethyl anions. In the presence of electrophiles such as benzaldehyde, chlorodiphenylphosphine and chlorotrimethylsilane, the corresponding heteroarylium- and heteroaryl-*N*-difluoromethylated derivatives, imidazole-*N*-difluoromethyl-phosphines and -silanes, 2-methyl-benzimidazole-*N*-difluoromethyltrimethyl-carbinols-phosphines and -silanes were obtained. Similar 4-dimethylaminopyridinium derivatives were synthesized.

Keywords: Imidazole-*N*-difluoromethyltrimethyl-silane; 1-Difluoromethyltrimethylsilyl-pyridinium triflate; *N*-difluoromethylide; *N*-trifluoromethyl-imidazole

1. Introduction

Recently, the introduction of the difluoromethylene moiety into organic compounds has attracted much attention due to the biological properties exhibited by *gem*-difluoro compounds as compared to their non-fluorinated analogs [1–3]. Among various methods for the synthesis of such compounds, the transformations of nucleophilic difluoromethylene synthons, i.e. 1,1-(difluoroalkyl)silanes, difluoroenoxysilanes, carbalkoxydifluoromethylene and dialkoxy phosphinyldifluoromethylene zinc, copper and silicon derivatives play a rising role in synthesis of geminal difluoromethylene compounds with a broad spectrum of biological activity [1–9]. In contrast to the extensively investigated chemistry of the aforementioned derivatives, little is known about heteroaryl-*N*-difluoromethyl anions, heteroarylium-*N*-difluoromethylides or their trimethylsilyl derivatives. Introduction of the heteroaryl-*N*-difluoromethyl moiety into organic or organoelement compounds may induce new interesting biological properties. Just recently tetrakis(dimethylamino)ethylene (TDAE) was successfully applied for the generation of heteroaryl-C-difluoromethylanions and heteroaryldifluoromethylation of carbonyl compounds [10,11] and for the synthesis of potent non-nucleosidic HIV-1 reverse transcriptase inhibitors (NNRTIs) [12].

Searching for synthetic methods for heteroaryl-*N*-difluoromethyl-anions we decided to broaden our study on the catalytic *N*-bromodifluoromethylation of 4-dimethylaminopyridine, which resulted in the synthesis of the first *N*-bromodifluoromethylated heterocyclic compounds [10–13],

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where a chain carbenic mechanism involving a 4-dimethylaminopyridinium difluoromethylide intermediate was proposed for the reaction with CF_2Br_2, in contrast to a radical pathway for $BrCF_2CF_2Br$ [13]. To the best of our knowledge, it was the first indication of the generation and participation of a nitrogen difluoromethylide in the reaction [14–16]. Iminiodifluoromethanides formed by the reaction of difluorocarbene (from CF_2Br_2 and excess of lead powder in the presence of Bu_4NBr) with benzaldehyde and benzophenone imines underwent regioselective 1,3-dipolar cycloaddition to aldehydes giving oxazolidine derivatives [16,17]. *N*-methylides including pyridinium-*N*-dichloromethylide are of considerable importance for stereoselective synthesis of heterocycles via 1,3-cycloaddition reactions with electron deficient alkenes and alkynes [18–20]. Moreover, *N*-bromodifluoromethylated heterocycles are useful precursors for *N*-trifluoromethylated derivatives [10]. There is a growing interest for *N*-perfluoroalkylated heterocyclic systems, e.g. (4-chloro-benzyl)-(2-chloro-9-trifluoromethyl-9H-purin-6-yl)-amine being an inhibitor of cyclin dependent kinase 2 [21].

2. Results and discussion

2.1. Electrochemistry

Some of the derivatives synthesized in this work have been studied by cyclic voltammetry, in acetonitrile (CH_3CN) and *N*,*N*-dimethylformamide (DMF) as solvent with NBu_4PF_6 as supporting electrolyte. The reduction potentials of the halogenodifluoro-methylated compounds were measured, in order to establish their ability to be involved in single electron transfer reactions of synthetic utility. Cyclic voltammetry of the 4-dimethylamino-pyridinium-*N*-bromodifluoromethyl bromide (**1**) shows two irreversible reduction steps in CH_3CN or DMF at respective potentials close to -0.89 and -1.54 V versus saturated calomel electrode (SCE; peak potentials at 0.2 V/s on a glassy carbon electrode). The first reduction step corresponds to the uptake of 1.6 electrons (as compared to the one-electron oxidation wave of ferrocene) and to the cleavage of the carbon–bromine bond and the second reduction step, located at a more negative potential, corresponds to the reduction of the 4-dimethylamino-pyridinium-*N*-difluoromethyl bromide, as was shown with comparison to an authentic sample (peak potential at 0.2 V/s $= -1.55$ V versus SCE). This was also confirmed by a preparative electrolysis in CH_3CN containing 0.1 M Bu_4NPF_6, at a carbon felt cathode, at a potential close to -0.92 V versus SCE giving after consuming close to 1.5 F/mol of starting material, a major product identified as the 4-dimethylamino-pyridinium-*N*-difluoromethyl bromide [^{19}F NMR: $\delta_F = -94.9$ (d, $^2J_{HF} = 58.0$ Hz)]. The reduction of 4-dimethylammonium-pyridinium-*N*-CF_2CF_2Br bromide occurs at more negative potentials close to -1.18 V versus SCE and -1.42 V versus SCE. As observed for the monobromodifluoromethylated compound, the second reduction step corresponds to the reduction of the $-NCF_2CF_2H$ pyridinium derivative. These studies indicate that the cleavage of the C–Br bonds is relatively easy (positive reduction potentials) and, therefore, electron transfer reactions using the TDAE as reductive reagent should be conceptually feasible, as already demonstrated in our earlier work [7,8].

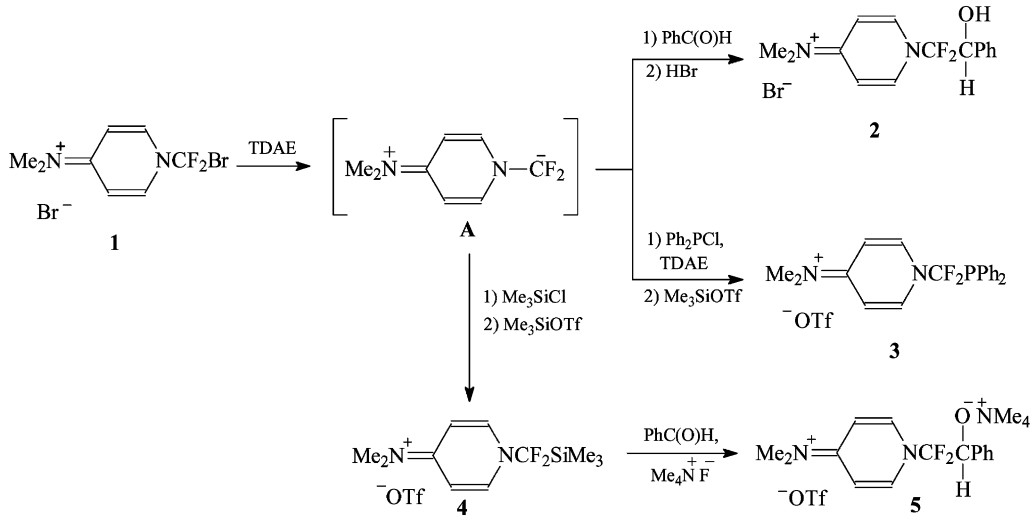
2.2. Generation and reactions of heteroarylium-*N*-difluoromethylides

4-Dimethylamino-pyridinium-*N*-difluoromethylide (**A**) was generated in situ using TDAE and trapped in the presence of the electrophile. With benzaldehyde as a solvent 1-(1,1-difluoro-2-hydroxy-2-phenyl-ethyl)-4-dimethylamino-pyridinium bromide (**2**) was obtained in 46% isolated yield (88% ^{19}F NMR). Chlorodiphenyl phosphine and chlorotrimethylsilane were able to trap intermediate **A** followed by the exchange of chloride for triflate as counterion providing water soluble 1-(difluoro-diphenylphosphanyl-methyl)-4-dimethylamino-pyridinium triflate (**3**) (67%) and 1-(difluoro-trimethylsilyl-methyl)-4-dimethylamino-pyridinium triflate (**4**) (53%), which reacted with benzaldehyde to give tetramethylammonium 1-(1,1-difluoro-2-phenyl-ethylat)-4-dimethylamino-pyridinium triflate (**5**) and trimethylfluorosilane when using a stoichiometric amount of tetramethylammonium fluoride. In solvents like CH_2Cl_2 or CH_3CN compound **1** and excess of TDAE react rapidly and exothermally to give the corresponding *N*-difluoromethyl derivative, 1-difluoro-methyl-4-dimethylamino-pyridinium bromide [10], as the only fluorinated product (Scheme 1, presenting only the quinoidal mesomeric form [10] of the heterocycle).

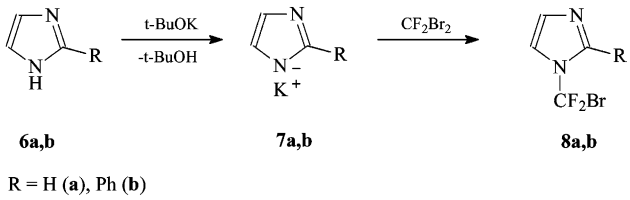
2.3. Synthesis of the *N*-bromodifluoromethyl heterocycles

Deprotonation of imidazoles **6a**,**b** with potassium *tert*-butylate followed by the reaction with dibromodifluoromethane produces *N*-bromodifluoromethyl imidazoles **8a**,**b**. This method provides an important possibility to generate a bromodifluoromethyl fragment at the heterocyclic nitrogen, contrary to previous reports on the interaction of the imidazolyl anion with CF_3Br or R^FI leading only to a mixture of 2- and 4-perfluoroalkyl substituted imidazoles without *N*-perfluoroalkylation [22]. One might anticipate a halogenophilic reaction of the imidazolyl anion **7a** with CF_2Br_2 generating an imidazole-*N*-difluoromethyl anion succeeded by the formation of 1-bromodifluoromethyl-imidazole (**8a**) similarly to the interaction of dihalodifluoromethane with PhO^- and PhS^- [23] (Scheme 2).

Surprisingly, the counterion of the imidazolyl anion drastically influenced the reaction with CF_2Br_2, with Li^+ or Na^+ the reaction proceeded slowly at room temperature and was accelerated by a small quantity of Zn powder which also



Scheme 1.



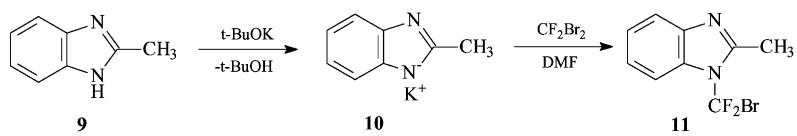
Scheme 2.

increases the amount of the 1-difluoromethyl-imidazole by-product, e.g. 2-methyl-benzimidazolyl sodium reacts with 200% excess of CF_2Br_2 (THF, 20°C, 2d) to afford 1-bromodifluoromethyl-2-methylbenzimidazole (**11**) in 12% isolated yield. This reaction under the same conditions in acetonitrile gave 32% ^{19}F NMR yield. When this work was in progress, brief communications describing a synthesis of *N*-bromodifluoromethylated benzimidazole derivatives and *N*-bromodifluoromethyl imidazole under reaction conditions mentioned in our previous publication [10] was published [24,25], where, contrary to our work, the yield of **8a** and **11** have been reported to be 9 and 46%, respectively, using zinc as a catalyst and sodium salts of imidazole and 2-methylbenzimidazole in acetonitrile. At room temperature without a catalyst in our case, the reaction of CF_2Br_2 with imidazolyl potassium (**7a**) and 2-methyl-benzimidazolyl potassium (**10**) lead to **8a** in 43% yield (2d, THF), in 71% yield (12 h, DMF) and **11** in 70% yield (DMF), respectively. Only negligible amounts (1 mol%) of *N*-difluoromethylated heterocyles were obtained (Scheme 3).

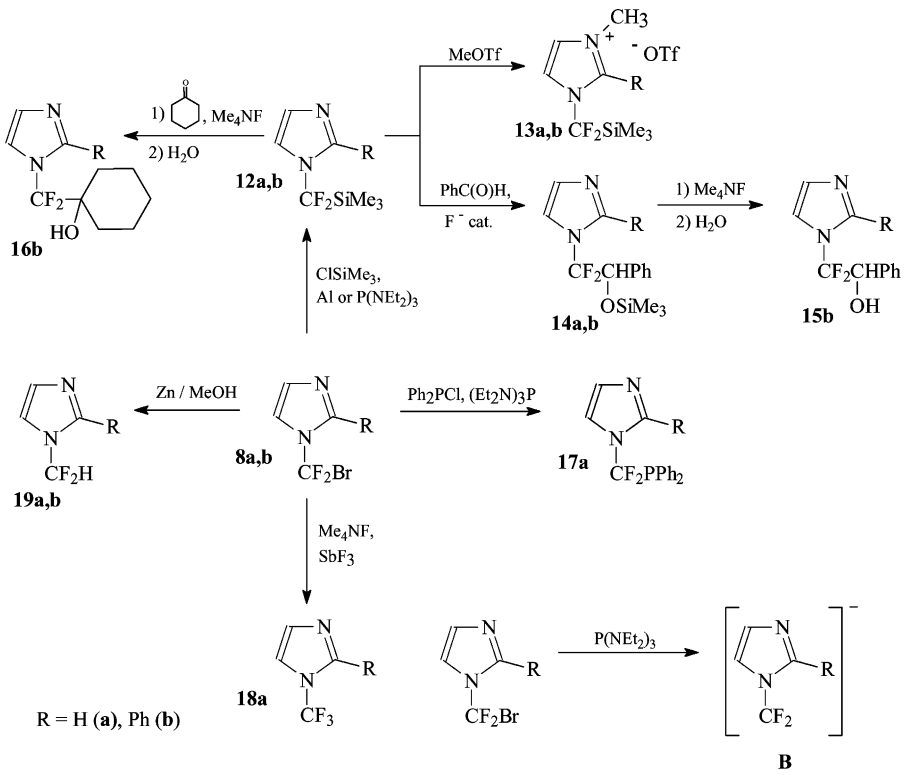
2.4. Generation of heteroaryl-N-difluoromethyl anions and their derivatives

The imidazol-*N*-difluoromethyl anion (**B**) and 2-methyl-1-difluoromethyl-benzimidazole anion had to be generated in situ from 1-bromodifluoromethyl-imidazole (**8a**) [26], 1-difluoromethyl-2-phenyl-imidazole (**8b**) [26] and 1-difluoromethyl-2-methyl-benzimidazole (**11**) [24] using tris(-diethylamino)phosphine under Marchenko–Ruppert reaction conditions [27,28] (Schemes 4 and 5) and trapped in the presence of the appropriate electrophile, namely, benzaldehyde, chlorotrimethylsilane and chlorodiphenylphosphine (Scheme 4).

In the presence of a 10-fold excess of Me_3SiCl in CH_2Cl_2 at −70°C, the reaction yielded imidazol-1-yl-difluoromethyltrimethylsilane (**12a**), 2-phenyl-imidazole-1-yl-difluoromethyl-trimethylsilane (**12b**) and 2-methyl-benzimidazole-1-yl-difluoromethyl trimethylsilane (**20**) (Scheme 5) in 85, 75 and 82%, isolated yields, respectively [26]. These compounds have been easily prepared with aluminium powder and one-fold excess of chlorotrimethylsilane in monoglyme or *N*-methyl-pyrrolidone [29], in 71, 75 and 73% yields, respectively. They, in the presence of a catalytic amount of fluoride, formed imidazol-1-difluoromethyl anions which could be trapped with benzaldehyde to give the 1-(1,1-difluoro-2-phenyl-2-trimethylsiloxy-ethyl)-imidazoles (**14a**,**b**). Compound **14b**, after hydrolysis furnished the corresponding alcohol **15b** (Scheme 4). The reactions of heteroaryl-*N*-difluoromethyltrimethylsilanes

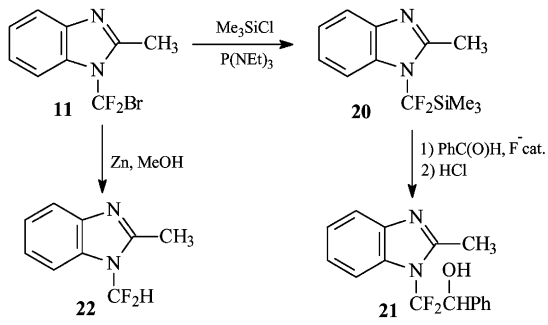


Scheme 3.



Scheme 4.

with enolizable ketones, e.g. cyclohexanone, was successful with a stoichiometrical amount of tetramethylammonium fluoride. In contrast to trifluoromethyltrimethylsilane, $CF_2=CFSiMe_3$, $(EtO)_2(O)PCF_2SiMe_3$ and $C_6F_5SiMe_3$ give carbanion addition products only with aldehydes, with enolizable ketones, silylated enols only [30–32]. All these reactions proceed using fluoride ion catalysis. If only 1 mol% of Me_4NF or KF was added to the silane monoglyme solution of **12b** and cyclohexanone at either 0°C or at ambient temperature, the main reaction product formed was 1-difluoromethyl-2-phenyl-imidazole (**19b**) (99%). The target 1-(2-phenyl-imidazol-1-yl-1,1-difluoromethyl)-1-cyclohexanol (**16b**) was observed only as an impurity (1%) in the ^{19}F NMR spectrum. Whereas an equimolar amount of Me_4NF favors the formation of the carbanion addition product and after hydrolysis **16b** was obtained in 64% (70% ^{19}F NMR) yield, a one-fold excess of cyclohexanone improves the yield to 77% (83% ^{19}F NMR) (Scheme 4).



Scheme 5.

Hydrolysis of 1-(1,1-difluoro-2-phenyl-2-trimethylsiloxy-ethyl)-2-methyl-benzimidazole yielded 2-(2-methyl-benzimidazole)-1-yl-2,2-difluoro-1-phenyl-ethanol (**21**) (81% yield). In addition, the 1-difluoromethyl-2-methyl-benzimidazole anion could be produced by reductive debromination of **11** [24] using TDAE in benzaldehyde as a solvent to give 2-(2-methyl-benzimidazole)-1-yl-2,2-difluoro-1-phenyl-ethanol (**21**) (Scheme 5).

Obviously, the electron withdrawing effect of the heterocyclic nuclei rendered the heteroaryl-*N*-CF_2 substituted alcohols stable towards hydrolysis, unlike compounds containing the Alk_2NCF_2 moiety which proved to be soft fluorinating agents for the substitution of alcoholic hydroxy groups [33]. 1-(1,1-Difluoro-2-hydroxy-2-phenyl-ethyl)-3,3-diphenyl-aziridine-2-carboxylic acid ethyl ester, the only example of a heteroaryl-*N*-difluoromethyl carbinol was recently isolated in 5% yield from a complex mixture resulting from the reaction of the corresponding iminiodifluoromethylide with benzaldehyde [16]. Anionic imidazole-*N*-difluoromethylation of Ph_2PCl furnished imidazol-1-yl-difluoromethyl diphenylphosphine (**17a**) (78% yield) (Scheme 5). Compound **8a** was successfully fluorinated using antimony trifluoride to furnish 1-trifluoromethylimidazole (**18a**). 1-Difluoromethylimidazole (**19a**) (Scheme 4) or 1-difluoromethyl-2-methyl-benzimidazole (**22**) could be obtained in 95% yield by reduction of *N*-bromodifluoromethyl derivatives with Zn

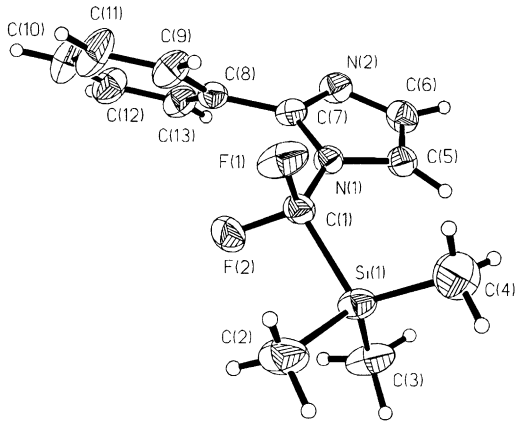


Fig. 1. Molecular structure of **12b** (thermal ellipsoids with 50% probability). Selected bond lengths (pm) and angles (°) Si(1)–C(2) 185.3(4), Si(1)–C(1) 193.8(4), F(1)–C(1) 138.3(4), F(2)–C(1) 137.5(4), N(1)–C(7) 138.8(4), N(1)–C(5) 139.4(4), N(1)–C(1) 144.2(4), N(2)–C(7) 132.1(4), N(2)–C(6) 137.7(5), C(3)–Si(1)–C(2) 112.2(2), C(2)–Si(1)–C(1) 101.41(17), C(7)–N(2)–C(6) 106.3(3), F(2)–C(1)–F(1) 104.9(3), F(2)–C(1)–N(1) 106.3(3), N(1)–C(1)–Si(1) 121.3(2).

powder in a methanol/water mixture at room temperature [34] (Scheme 5).

2.5. Crystal structure of 2-phenyl-imidazole-1-yl-difluoromethyltrimethylsilane (*12b*)

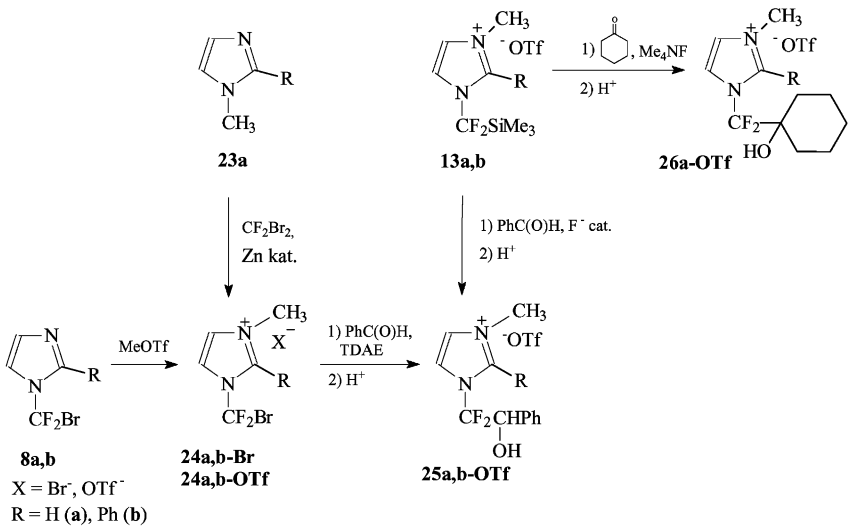
The molecular structure of imidazole **12b** exhibited a relatively long Si(1)–C(1) (193.8(4) pm) bond (see Fig. 1), slightly longer than the comparable Si–C bond in bis(trifluoromethyl) trimethylsiliconate [35] or in trifluoromethyltriphenylsilane [36]. The angles and bond lengths in the imidazole ring correspond to ''normal'' imidazole-rings [37]. The CF_2SiMe_3 unit is essentially tetrahedral, whereas the angle N(1)–C(1)–Si(1) 121.3(2)° is considerably larger than expected.

2.6. Heteroarylium-N-difluoromethylides

Similarly to DMAP [10,11], 1-methyl-imidazole (**23a**) reacted rapidly with dibromodifluoromethane in CH_3CN under TDAE, Zn or Cu powder catalysis [13] to yield 1-methyl-3-bromodifluoromethyl-imidazolium bromide (**24a-Br**) (75% isolated yield). Similar triflate salts **24a**,**b-OTf** have been prepared in 100% yield by bromodifluoromethylation of imidazoles **6a**,**b** followed by methylation in the 3-position using methyl triflate. 3-Methyl-imidazolium-*N*-difluoromethylide generated from 1-methyl-3-bromodifluoromethyl-imidazolium triflate (**24-Otf**) in the presence of TDAE reacted with benzaldehyde like 4-dimethylaminopyridinium-*N*-difluoromethylide. After hydrolysis 1-(1,1-difluoro-2-hydroxy-2-phenyl-ethyl)-3-methyl-imidazolium triflate (**25a-Otf**) was obtained. The generation of 3-methyl-imidazolium-*N*-difluoromethylides can also be easily realized by reacting imidazolium-1-yl-difluoromethyltrimethylsilane triflates (**13a**,**b**) under fluoride catalysis. The corresponding 2-phenyl-imidazolyl-1-difluoromethyl anion was generated and its derivatives were produced under the same conditions. Like heteroaryl-*N*-difluoromethyltrimethylsilanes, 1-trimethylsilyldifluoromethyl-3-methyl-imidazolium triflate (**13a**) and cyclohexanone in presence of equimolar amounts of tetramethylammonium fluoride reacted to give 1-(1,1-difluoro-1-cyclohexanol-1-yl-methyl)-3-methyl-imidazolium triflate with 76% (86% ^{19}F NMR), **26a-OTf** after hydrolysis. In the case of tetramethylammonium fluoride catalysis only heteroarylium-*N*-difluoromethyl derivatives were observed (Scheme 6).

3. Experimental

All reactions were performed under nitrogen in carefully dried solvents. Mass spectra were recorded on a Finnigan



Scheme 6.

MAT 8222 spectrometer under EI and FAB conditions, for the covalent and ionic derivatives, respectively. NMR spectra were recorded on a Bruker DPX-200 spectrometer operating at 200.13 for ^{1}H (TMS), 188.31 for ^{19}F ($CClF_3$), 50.32 MHz for ^{13}C (TMS), some ^{13}C NMR spectra were recorded on a Bruker AMX-360 spectrometer at 90.56 MHz (TMS). Compounds **8a**,**b**, **12a**,**b**, **14a**,**b**, **15b**, **20**, **26a-OTf** were prepared according to [26], for compound **11** see also [24]. Cyclic voltammetry was performed using a 'home-made' potentiostat [38] with a positive feedback Ohmic drop compensation and a Tacussel GSTP4 signal generator. The working electrode was a glassy carbon (Tokai Corporation) disc (3 mm diameter) and the reference electrode a SCE. The supporting electrolyte was tetrabutylammonium hexafluorophosphate (NBu_4PF_6; Fluka puriss). For purification of solvents used for cyclic voltammetry cf. [7,8].

*3.1. 1-(1,1-Difluoro-2-hydroxy-2-phenyl-ethyl)-4-dimethylamino-pyridinium bromide (**2**)*

To a solution of 2.62 g (7.89 mmol) of **1** and 4.18 g (39.5mmol) of benzaldehyde in 15 ml benzonitrile was added at −20°C in 1.58 g (7.89 mmol) of TDAE, stirred at −20°C for 1 h and for 1 h at ambient temperature. After filtrating-off $TDAE^{2+}$ $2Br^{-}$, 20 ml water was added, then the remaining water evaporated and the residue recrystallized from acetonitrile. Yield of 2 1.3 g (46%), mp 225°C; ^{1}H NMR (CD_3CN) $\delta = 3.3$ (s, CH_3), 4.7 (s, CH), 5.5 (s, OH), 7.1 (s, CH), 7.4 (s, CH), 8.3 (s, CH); ^{19}F NMR δ (CD_3CN) = −91.9 (dd, $J_{FF} = 202.7$, $^{3}J_{FH} = 3.6$ Hz), −101.3 (dd, $J_{FF} = 202.7$, $^{3}J_{FH} = 3.6$ Hz); ^{13}C NMR δ (CD_3CN) = 41.2 (s, CH_3), 73.2 (m, CH), 121.0 (t, CF_2, $J_{CF} = 270.5$ Hz), 108.0–157.8 (m); HRMS calcd. for $C_{15}H_{17}N_2F_2O^{+}$ 279.13089; found 279.13250; anal. calcd. for $C_{15}H_{17}N_2F_2OBr$: C 50.15, H 4.77, F 10.58; found: C 50.25, C 4.85, F 10.7%.

*3.2. Typical procedure for **3**, **4**, **25a**,**b-OTf***

To a solution of 2.74 g (25.3 mmol) of chlorotrimethylsilane and 0.84 g (2.53 mmol) of **1** in 15 ml benzonitrile was added at −20°C in 0.51 g (2.53 mmol) of TDAE, stirred at −20°C for 1 h and for 1 h at ambient temperature. After filtrating-off $TDAE^{2+}$ $2Br^{-}$, trimethylsilyl triflate 0.42 g (2.53 mmol) was added and the solution stirred for additional 15 min at ambient temperature. After evaporation of the solvent under reduced pressure, the residue was recrystallized from THF. Yield of **4** 0.53 g (53%).

*3.3. 1-(Difluoro-diphenyl-phosphanyl-methyl)-4-dimethylamino-pyridinium triflate (**3**)*

Yield 67%; mp 115–116°C; ^{1}H NMR δ (CD_3CN) = 3.2 (s, CH_3), 6.8 (d, CH, $J_{HH} = 8.3$ Hz), 8.0 (d, CH, $J_{HH} = 8.3$ Hz); ^{19}F NMR δ (CD_3CN) = −80.4 (s, CF_3), −82.2 (d, CF_2, $^{2}J_{PF} = 70.7$ Hz); ^{31}P NMR δ (CD_3CN) = 15.7 (t, 1P); HRMS calcd. for $C_{20}H_{20}N_2F_2P^{+}$ 357.13322; found 357.132221.

*3.4. 1-(Difluoro-trimethylsilyl-methyl)-4-dimethylamino-pyridinium triflate (**4**)*

Yield 53%; mp 117–118°C; ^{1}H NMR δ ($CDCl_3$) = 0.3 (s, CH_3), 3.3 (s, CH_3), 7.2 (d, CH, $J_{HH} = 7.8$ Hz), 8.0 (d, $J_{HH} = 8.3$ Hz), ^{19}F NMR δ ($CDCl_3$) = −79.5 (s, CF_3), −92.9 (s, CF_2); ^{13}C NMR δ ($CDCl_3$) −5.0 (CH_3), 40.6 (CH_3), 120.7 (q, CF_3, $J_{CF} = 321.0$ Hz), 125.6 (t, CF_2, $J_{CF} = 303.7$ Hz), 108.6–157.3 (m); HRMS calcd. for $C_{11}H_{19}N_2F_2Si^{+}$ 245.12856; found 245.12877; anal. calcd. for $C_{12}H_{19}N_2F_5SiO_3S$: C 36.54, H 4.86, F 24.08; found C 36.48, H 4.79, F 24.0%.

*3.5. 1-(1,1-Difluoro-2-hydroxy-2-phenyl-ethyl)-3-methyl-imidazolium triflate (**25a-OTf**)*

Yield 47%; mp 112–113°C; ^{1}H NMR δ ($CDCl_3$) = 3.9 (s, CH_3), 4.7 (s, CH), 5.5 (s, OH), 7.6 (s, CH), 7.7 (s, CH), 9.2 (s, CH); ^{19}F NMR δ ($CDCl_3$) −80.5 (s, CF_3), −86.9 (dd, CF_2, $J_{FF} = 209.8$, $^{3}J_{FH} = 3.5$ Hz), −98.3 (dd, CF_2, J_{FF} 209.8, $^{3}J_{FH}$ 14.1 Hz); ^{13}C NMR (□) ($CDCl_3$) = 39.3 (s, CH_3), 72.5 (t, CH, $^{2}J_{CF} = 31.9$ Hz), 129.3 (t, $J_{CF} = 275.3$ Hz), 124.1 (s, CH), 121.9 (q, $J_{CF} = 320.8$ Hz), 129.5–141.9 (m); HRMS calcd. for $C_{12}H_{13}N_2F_2O^{+}$ 239.22316; found: 239.22738.

*3.6. 1-(1,1-Difluoro-2-hydroxy-2-phenyl-ethyl)-2-phenyl-3-methyl-imidazolium triflate (**25b-OTf**)*

Yield 54%; mp 122–123°C; ^{1}H NMR δ ($CDCl_3$) = 3.8 (s, CH_3), 4.5 (s, CH), 5.7 (s, OH), 7.2–7.7 (m, 7H); ^{19}F NMR δ ($CDCl_3$) = −80.4 (s, CF_3), −82.3 (dd, $J_{FF} = 201.8$, CF_2, $^{3}J_{FH} = 3.4$ Hz), −92.8 (dd, CF_2, $J_{FF} = 219.3$, $^{3}J_{FH} = 13.1$ Hz); ^{13}C NMR (□) ($CDCl_3$) = 40.1 (s, CH_3), 85.2 (t, CH, $^{2}J_{CF} = 28.1$ Hz), 135.2 (t, $^{1}J_{CF} = 289.4$ Hz), 121.8 (q, $^{1}J_{CF} = 320.7$ Hz), 124.5–145.1 (m); HRMS calcd. for $C_{18}H_{17}N_2F_2O^{+}$ 315.31498; found: 315.31453.

*3.7. Tetramethylammonium 1-(1,1-difluoro-2-phenyl-ethylat)-4-dimethylamino-pyridinium triflate (**5**)*

Yield 32%; mp 254–256°C; ^{1}H NMR δ (CD_3CN) = 3.1 (s, CH_3), 3.2 (s, CH_3), 4.7 (s, CH), 7.2 (s, CH), 7.4 (s, CH), 8.3 (s, CH); ^{19}F NMR δ (CD_3CN) = −80.4 (s, CF_3), −93.8 (dd, $J_{FF} = 200.1$, $^{3}J_{FH} = 3.0$ Hz), −103.6 (dd, $J_{FF} = 200.1$, $^{3}J_{FH} = 13.8$ Hz); ^{13}C NMR δ (CD_3CN) = 40.3 (s, CH_3), 56.3 (s, CH_3), 120.9 (q, CF_3, $J_{CF} = 321.1$ Hz), 125.6 (t, CF_2, $J_{CF} = 303.7$ Hz), 107.4–159.1 (m); anal. calcd. for $C_{20}H_{28}F_5N_3O_4S$: C 47.90, H 5.63, F 18.94; found: C 47.85, H 5.69, F 19.01%.

3.8. 1-Difluoromethyl-2-methyl-benzimidazole (**11**) [24]

Yield 70%; mp 34–37°C; bp 68–70°C/0.005 Torr; ^{1}H NMR δ ($CDCl_3$) = 2.7 (t, CH_3, $^5J_{FH}$ = 2.9 Hz), 7.3–7.7 (m, Ar); ^{19}F NMR δ ($CDCl_3$) = −27.9 (s, CF_2); ^{13}C NMR δ ($CDCl_3$) = 16.6 (t, CH_3, $^4J_{CF}$ = 4.5 Hz), 109.2 (t, CF_2Br, J_{CF} 307.4 Hz), 112.3 (t, C-CH_3, $^3J_{CF}$ = 5.3 Hz), 119.8–149.3 (Ar, m); HRMS calcd. for $C_9H_7N_2F_2{}^{79}Br$ 259.97607; found 259.97648.

3.9. Typical procedure for **12a,b** [34], **17a**, **20** [31]

To a solution of 0.59 g (3 mmol) of **8a** and 3.6 g (33 mmol) of Me_3SiCl in 9 ml CH_2Cl_2 was added dropwise in 0.82 g (3.3 mmol) tris(diethylamido)phosphite at −70°C. After stirring for 1 h at this temperature, 0.5 h at ambient temperature and pumping off of the solvent, the crude product was extracted from the residue with 3×5 ml pentane and recrystallized from hexane. Yield of **12a** 0.49 g (85%), colorless oil.

3.10. Imidazol-1-yl-difluoromethyl-diphenyl-phosphine (**17a**)

Yield 78%; mp 80–82°C; ^{1}H NMR δ (CD_3CN) = 7.1 (dd, CH, $^3J_{HH}$ = 2.2, $^4J_{HH}$ = 1.0 Hz), 7.3 (m, CH), 7.3–7.7 (m, Ar) 7.9 (s, CH), ^{19}F NMR δ (CD_3CN) = −72.9 (d, CF_2, $^2J_{PF}$ = 79.3 Hz); ^{31}P NMR δ (CD_3CN) = −10.5 (t); HRMS calcd. for $C_{16}H_{13}N_2F_2P$: 302.07844; found: 302.07867.

3.11. 2-Phenyl-benzimidazole-1-yl-2,2-difluoro-1-phenyl-ethanol (**21**) [24]

To a solution of 4.0 g (15.7 mmol) of **20** and 8.32 g (78.5 mmol) of benzaldehyde in 20 ml monoglyme 0.04 g tetramethylammonium fluoride [39] was added and the mixture stirred for 20 h. The solvent and excess of benzaldehyde were evaporated and the residue was treated with 50 ml 10% hydrochloric acid. The precipitate was filtrated-off and washed with a sodium hydrogencarbonate solution, then extracted with hot chloroform. After evaporation of chloroform the product was recrystallized from a hexane/chloroform (1/1) mixture. Yield 3.7 g (81%); ^{1}H NMR δ ($CDCl_3$) = 2.3 (t, CH_3, $^5J_{FH}$ = 2.9 Hz), 5.3 (dd, CH), 6.8 (d, OH, $^4J_{FH}$ = 5.4 Hz), 7.1–7.6 (m, Ar); ^{19}F NMR δ ($CDCl_3$) = −86.5 (d, CF_2, J_{FF} = 217.3 Hz), −92.1 (dd, $^1J_{FF}$ = 217.2, $^3J_{FH}$ = 12.1 Hz); ^{13}C NMR δ ($CDCl_3$) = 16.8 (t, CH_3, $^4J_{CF}$ = 4.5 Hz), 73.8, 74.1 (AB system, CH, J_{AB} = 30.9 Hz), 113.3 (t, $^3J_{CF}$ = 5.3 Hz), 121.2 (t, CF_2, $^1J_{CF}$ = 262.2 Hz), 119.6–151.6 (m, Ar); HRMS calcd. for $C_{16}H_{14}ON_2F_2$: 288.10792; found: 288.10742.

3.12. Typical procedure for **13a,b**, **24a,b-OTf**

To a solution of 0.95 g (3.57 mmol) of **12b** in 5 ml pentane was added dropwise in 0.61 g (3.75 mmol) methyl triflate. The precipitate was filtrated-off and washed with 10 ml of pentane. Yield of **13b** 1.53 g.

3.13. 1-Trimethylsilyldifluoromethyl-3-methyl-imidazolium triflate (**13a**)

Yield 100%; mp 62–63°C; ^{1}H NMR δ ($CDCl_3$) = 0.0 (s, CH_3), 3.6 (s, CH_3), 7.1 (dd, $^3J_{HH}$ 2.3 Hz, $^4J_{HH}$ 0.8 Hz, CH), 7.1 (m, CH), 7.7 (s, CH); ^{19}F NMR δ ($CDCl_3$) = −79.6 (CF_3), −78.9 (CF_2); ^{13}C NMR δ ($CDCl_3$) = −3.4 (CH_3), 39.0 (s, CH_3), 121.6 (q, J_{CF} = 322.5 Hz), 121.5 (t, J_{CF} = 233.1 Hz); HRMS calcd. for $C_8H_{15}N_2F_2Si^+$: 205.26143; found: 205.26135.

3.14. 1-Trimethylsilyldifluoromethyl-2-phenyl-3-methyl-imidazolium triflate (**13b**)

Yield 100%; mp 75–76°C; ^{1}H NMR δ ($CDCl_3$) = 0.1 (s, CH_3), 3.7 (s, CH_3), 7.5–7.8 (m, 7H); ^{19}F NMR δ ($CDCl_3$) = −79.6 (CF_3), −82.8 (CF_2); ^{13}C NMR δ ($CDCl_3$) = −3.6 (CH_3), 37.7 (s, CH_3), 121.6 (q, J_{CF} = 322.5 Hz), 123.1 (t, J_{CF} = 242.1 Hz), 119.7–145.3 (m); HRMS calcd. for $C_{14}H_{19}N_2F_2Si^+$: 281.12634; found: 281.12598.

3.15. 1-Bromodifluoromethyl-3-methyl-imidazolium triflate (**24a-OTf**)

Yield 100%; mp 49–51°C; ^{1}H NMR δ ($CDCl_3$) = 3.9 (s, CH_3), 7.6 (s, CH), 7.9 (s, CH), 9.3 (s, CH); ^{19}F NMR δ ($CDCl_3$) = −34.5 (s, CF_2), −80.6 (s, CF_3); ^{13}C NMR δ ($CDCl_3$) = 37.9 (CH_3), 108.0 (t, CF_2, J_{CF} = 309.8 Hz), 118.3 (CH), 121.9 (q, CF_3, J_{CF} = 320.9 Hz), 126.8 (s, CH), 137.0 (s, CH); HRMS calcd. for $C_5H_6N_2F_2{}^{79}Br^+$ 210.96824; found 210.97041.

3.16. 1-Bromodifluoromethyl-2-phenyl-3-methyl-imidazolium triflate (**24b-OTf**)

Yield 100%; mp 64–65°C; ^{1}H NMR δ ($CDCl_3$) 3.8 (s, CH_3), 7.3–8.0 (m, 7H); ^{19}F NMR δ ($CDCl_3$) −30.2 (s, CF_2Br), 79.6 (s, CF_3); ^{13}C NMR δ ($CDCl_3$) 36.8 (s, CH_3), 116.0 (q, J_{CF} 321.0 Hz), 108.6 (t, J_{CF} 308.3 Hz), 100.5–144.6 (m, Ar); anal. calcd. for $C_{12}H_{10}N_2O_3F_5SBr$: C 32.97, H 2.31, F 21.73; found C 32.72, H 2.42, F 21.5.

3.17. 1-Trifluoromethyl-imidazole (**18a**)

To a solution of 1.37 g (7.65 mmol) of antimony trifluoride was added 1.5 g (76.5 mmol) **8a**. The mixture was heatedat 60°C for 24 h and the product extracted with hot hexane. After evaporating hexane 0.31 g (30%), bp 63–64°C; ^{1}H NMR δ ($CDCl_3$) = 7.2 (dd, CH, $^3J_{HH}$ = 2.2, $^4J_{HH}$ = 1.0 Hz), 7.3 (m, CH), 7.9 (s, CH), ^{19}F NMR δ ($CDCl_3$) = −58.5 (CF_3); ^{13}C NMR δ ($CDCl_3$) = 115.3 (q, CF_3, J_{CF} = 319.4 Hz), 116.0 (s, CH), 130.9 (s, CH),

133.9 (s, CH); HRMS calcd. for $C_4H_3N_2F_3$ 136.07612; found 136.07635.

3.18. Typical procedure for **19a,b**, **22**

In a 10 ml methanol/water (1/1) mixture to 0.7 g (3.6 mmol) **8a** were added 0.6 g (9.2 mmol) zinc and stirred for 24 h. The mixture was refluxed and extracted with 5×10 ml hot hexane. Recrystallization from hexane gave 0.4 g 19a (95%).

3.19. 1-Difluoromethyl-imidazole (**19a**)

At bp 156–157°C (155–156°C) [23]; ^{19}F NMR δ ($CDCl_3$) −93.0 (d, $^2J_{FH} = 60.4$ Hz).

3.20. 1-Difluoromethyl-2-phenyl-imidazole (**19b**)

Yield 95%; mp 67–68°C (61–62°C) [23]; ^{19}F NMR δ ($CDCl_3$) = −92.0 (d, $^2J_{FH} = 60.4$ Hz).

3.21. 1-Difluoromethyl-2-methyl-benzimidazole (**22**)

Yield 95%; bp 73°C/0.01 Torr (102°C/1.4 Torr) [24]; ^{19}F NMR δ ($CDCl_3$) = −96.1 ($^2J_{FH} = 58.6$ Hz).

3.22. X-ray crystallographic structure determination of 2-phenyl-imidazole-1-yl-difluoromethyl trimethylsilane (**12b**)

Data were collected at 173(2) K on a Siemens P4-diffractometer with a graphite monochromator (Mo Kα radiation, $\lambda = 71.073$ pm). The instrument was equipped with a Siemens low temperature unit LTII. The structures were solved by Direct Methods and anisotropically refined based on F^2 using the SHELX-97 program package. The C–H hydrogen atoms were placed in calculated positions, assigned common isotropic thermal parameters and allowed to ride on their parent atoms. $C_{13}H_{16}F_2N_2Si$ (266.37), 0.5 mm × 0.3 mm × 0.15 mm (recrystallized from pentane), monoclinic *C2/c*, $a = 2349.9(2)$, $b = 673.00(10)$, $c = 1774.9(2)$ pm, $\alpha = 90°$, $\beta = 93.39°$, $\gamma = 90°$, $V = 2.8021(6)$ nm^3, Z 8, $D_{calcd.} = 1.263$ Mg/m^3, Absorption coefficient 0.175 mm^{-1}, F(0 0 0) 1120, Θ 2.30–25°, reflections collected 3208, independent reflections 2464 [$R_{int} = 0.0228$], full-matrix least-squares on F^2, data/restraints/parameters 2464/0/171, goodness-of-fit on F^2 1.052, final R indices [$I > 2\sigma(I)$] $R_1 = 0.0617$, $wR_2 = 0.1547$, R indices (all data) $R_1 = 0.0936$, $wR_2 = 0.1722$, largest diffraction peak and hole 0.318 and −0.453 electrons/Å^3. Crystallographic data excluding structure factors for the structure in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC 159332. Copies of the data can be obtained free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

4. Conclusions

A convenient synthesis of new *N*-CF_2Br heterocyclic compounds (and their *N*-CF_3 derivatives) has been found and their chemical and electrochemical reactivity studied. 1,3-Dipolar cycloaddition reactions of 4-dimethylaminopyridinium-1-difluoromethylide and 3-methyl-imidazolium-1-difluoromethylide with electron deficient (fluorinated) alkenes and alkynes and other examples of anionic heteroaryl-*N*-difluoromethylation reactions with heteroaryl-*N*-difluoromethyltrimethylsilanes will be published in due course. Similarly the generation of the N–CF_2 radicals and their synthetic reactions will be studied.

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References

[1] M.J. Tozer, T.F. Herpin, Tetrahedron 52 (1996) 8619.
[2] R. Filler, Y. Kobayashi, L. Yagupolskii, Organofluorine Compounds in Chemistry and Biomedical Applications, Elsevier, Amsterdam, 1993.
[3] O. Lefebvre, T. Brigaud, C. Portella, Tetrahedron 55 (1999) 7233.
[4] D.J. Burton, Z.-Y. Yang, Tetrahedron 48 (1992) 189.
[5] W. Qiu, D.J. Burton, Tetrahedron Lett. 37 (1996) 2745.
[6] G.K.S. Prakash, A.K. Yudin, Chem. Rev. 97 (1997) 757.
[7] C. Burkholder, W.R. Dolbier Jr., M. Médebielle, J. Org. Chem. 63 (1998) 5385.
[8] C. Burkholder, W.R. Dolbier Jr., M. Médebielle, Tetrahedron. Lett. 39 (1998) 8853.
[9] V.P. Kukhar, V.A. Soloshonok, Fluorine-containing Amino Acids: Synthesis and Properties, Wiley, Chichester, 1994.
[10] A. Kolomeitsev, R.-M. Schoth, E. Lork, G.-V. Röschenthaler, J. Chem. Soc., Chem. Commun. (1996) 335.
[11] D.J. Burton, in: G.O. Olah, R.D. Chambers, G.K.S. Prakash (Eds.), Synthetic Fluorine Chemistry, Wiley, New York (1992) p. 209.
[12] C. Burkholder, W.R. Dolbier, Jr., M. Médebielle, S. Ait-Mohand, in press.
[13] R.-M. Schoth, E. Lork, G.-V. Röschenthaler, A. Kolomeitsev, J. Fluorine Chem. 84 (1997) 41.
[14] D.J. Burton, R.D. Howells, P.D. Vander Valk, J. Am. Chem. Soc. 99 (1977) 4830.
[15] V.V. Orda, I.I. Maletina, L.M. Yagupolskii, J. Fluorine Chem. 54 (1991) 378.
[16] M.S. Novikov, A.F. Khlebnikov, A. Krebs, R.R. Kostikov, Eur. J. Org. Chem. (1998) 133.
[17] M.S. Novikov, A.F. Khlebnikov, A.E. Masalev, R.R. Kostikov, Tetrahedron Lett. 38 (1997) 4187.
[18] A.F. Khlebnikov, M.S. Novikov, R.R. Kostikov, in: A.R. Katritzky (Ed.), Advance Heterocyclic Chemistry, Academic Press, San Diego, 1996.
[19] E. Chateauneuf, R.P. Johnson, M.M. Kirchhoff, J. Am. Chem. Soc. 112 (1990) 3217.

[20] R. Bonneau, Y.N. Romashin, M.T.H. Liu, S.E. MacPherson, J. Chem. Soc., Chem. Commun. (1994) 509.
[21] S.R. Schow, R.L. Mackman, C.L. Blum, E. Brooks, A.G. Horsma, Bioorg. Med. Chem. Lett. 7 (1997) 2697.
[22] M. Médebielle, J. Pinson, J.-M. Savéant, J. Am. Chem. Soc. 113 (1991) 6872.
[23] C. Wakselman, A. Lantz, in: R.E. Banks, B.E. Smart, J.C. Tatlow (Eds.), Organo-fluorine Chemisry (Principles and Commercial Applications), Plenum Press, New York, 1994, p. 177.
[24] L.M. Yagupolskii, D.V. Fedyuk, Tetrahedron Lett. 41 (2000) 2265.
[25] L.M. Yagupolskii, D.V. Fedyuk, K.I. Petko, V.I. Troitskaya, V.I. Rudyk, V.V. Rudyuk, J. Fluorine Chem. 106 (2000) 181.
[26] G. Bissky, V.I. Staninets, A.A. Kolomeitsev, G.-V. Röschenthaler, Synletters (2001) 374.
[27] A.P. Marchenko, G.K. Bespal'ko, E.S. Kozlov, A.M. Pinchuk, J. Gen. Chem. USSR (English Trans.) 51 (1981) 1422.
[28] I. Ruppert, K. Schlich, W. Volbach, Tetrahedron Lett. 25 (1984) 2195.
[29] J. Grobe, J. Hegge, Synletters (1995) 641.
[30] M. Fujita, M. Obayashi, T. Hiyama, Tetrahedron 44 (1988) 4135.
[31] J. Nieschalk, D. O'Hagan, J. Chem. Soc., Chem. Commun. 7 (1995) 719–720.
[32] B.A. Gostevskii, O.A. Kruglaya, O.A. Albanov, N.S. Vyazynkin, J. Organomet. Chem. 187 (1980) 157–166.
[33] N.N. Yarovenko, M.A. Raksha, J. Gen. Chem. USSR (English Trans.) 29 (1959) 2125.
[34] V.G. Poludnenko, O.B. Didinskaya, A.F. Podzharskii, M.M. Gil'burd, Khim. Heterocycl. Compounds (English Trans.) 18 (1982) 1696.
[35] A. Kolomeitsev, G. Bissky, E. Lork, V. Movchun, E. Rusanov, P. Kirsch, G.-V. Röschenthaler, J. Chem. Soc., Chem. Commun. (1999) 1107.
[36] H. Beckers, D.J. Brauer, H. Bürger, C.J. Wilke, J. Organomet. Chem. 356 (1988) 31.
[37] S.M. Carrera, Acta Cryst. 20 (1966) 783.
[38] D. Garreau, J.-M. Savéant, J. Electroanal. Chem. 35 (1972) 309.
[39] A.A. Kolomeitsev, F.U. Seifert, G.-V. Röschenthaler, J. Fluorine Chem. 71 (1995) 47.