SYNTHESIS AND USE OF HALODIFLUOROMETHYL HETEROCYCLES

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Abstract. *In view of the expanding interest in fluorinated heterocycles, the installation of a fluoroalkyl group in a molecule represents a challenging task in organic synthesis. Nowadays, convenient strategies for introducing CF_2X groups are still on demand because halodifluoromethylated compounds are useful synthetic intermediates in medicinal and agrochemistry, and in electronic materials. This review collects different strategies for incorporating selectively the halodifluoromethyl moiety either into simple aromatic and aliphatic heterocycles or into structural analogs of biologically active heterocyclic compounds. Moreover, given the importance of organofluorine compounds in organic and medicinal chemistry, the exchange reaction of halogen (Br, Cl) on the halodifluorinated group with different nucleophiles has proved to be useful for the formation of trifluorinated and gem difluorinated linked compounds.*

Contents

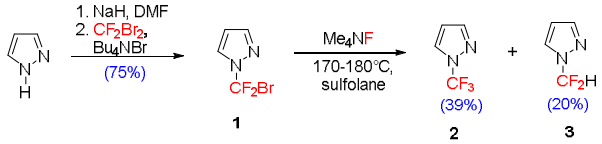
1. Introduction

Introduction of a *gem*-difluoromethyl or a α-halo-α,α-difluoromethyl moiety into organic molecules has been shown to enhance biological activities as the CF_2 group can affect physico-chemical properties of organic compounds.[1] Among the several approaches for the introduction of a difluorinated moiety into organic molecules, methods for the direct difluoromethylation as well as difluoromethylenation have been provided in recent years.[2] However, more generally, the difluoro methylene functionality has received less attention respect to monofluorinated and trifluoromethyl units.[3] In contrast, methods for the introduction of halodifluoromethyl units (CF_2X) are rather rare. The introduction of the α-halo-α,α-difluoromethyl (CF_2X) moiety is not a simple synthetic operation, especially in the case of heterocycles. In this review the most useful methods to install this versatile group on different aromatic and non aromatic heterocycles have been examined. A general approach includes the direct introduction of the CF_2X unit, usually CF_2Br, on a preformed heterocycle. Alternatively, viable heterocyclic syntheses involving cyclization reactions from building blocks containing the CF_2Br group have been also described. Moreover, we collected herein either methods for introducing the aforementioned group or the main exploitation of the CF_2X group, usually based on the displacement of the halogen atom (X) with arenolates or hydrogen or a fluorine atom, in order to synthesize *gem*-difluoromethylene linked molecules, CF_2H group and CF_3 group also in radiolabeled form.

2. Synthesis and use of halodifluoromethyl-substituted pyrazoles

2.1. *N*-CXF_2 substituted pyrazoles

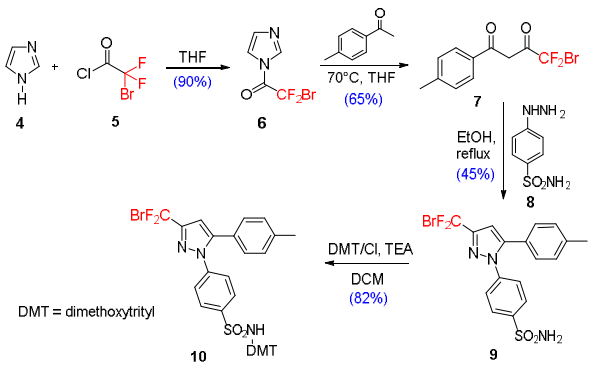
As part of ongoing research programme by Yagupolskii concerning the preparation of *N*-bromodifluoromethyl azoles, an easy method for dibromofluoromethylation of pyrazole was developed.[4] The optimized protocol relied on the reaction of the sodium salts of pyrazole with CF_2Br_2 in the presence of catalytic amount of tetrabutylammonium bromide and DMF as solvent. The reaction led to the formation of pyrazole **1** in satisfactory yield. The fluorination of **1** with Me_4NF in sulfolane, as solvent, furnished the corresponding trifluoromethylated adducts **2** along with discrete amount of difluoromethylated pyrazole **3** (Scheme 1).



Scheme 1. Synthesis of *N*-bromodifluoromethylpyrazoles and substitution of bromine by fluorine.

2.2. *C*-CXF_2 substituted pyrazoles

The halodifluoromethylation of C-substituted pyrazoles represents an important way to prepare precursors for radiolabeling of relevant drugs. The research group of Kumar developed the synthesis of the precursor of [^{18}F]celecoxib **11**, a selective COX-2 inhibitor, in four steps with 22% overall yield. The reaction of 2-bromo-2,2-difluoroacetyl chloride **5** with imidazole **4** gave the corresponding imidazolyl ethanone **6** which was subjected to the coupling reaction with 4'-methyl acetophenone affording the β-diketone **7** in 65% yield. The pyrazole synthesis was finalized by the condensation reaction of the ketone **7** with 4-hydrazinobenzenesulfonamide **8** in ethanol as solvent. The subsequent protection of pyrazole-sulfonamide **9** with dimethoxytrityl (DMT) group resulted in the formation of DMT-protected 4-[3-(bromodifluoromethyl)-5-*p*-tolylpyrazol-1-yl]benzenesulfonamide **10** (Scheme 2).[5]

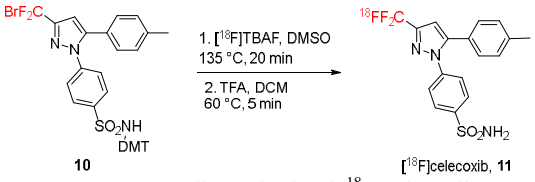


Scheme 2. Synthesis of the celecoxib precursor.

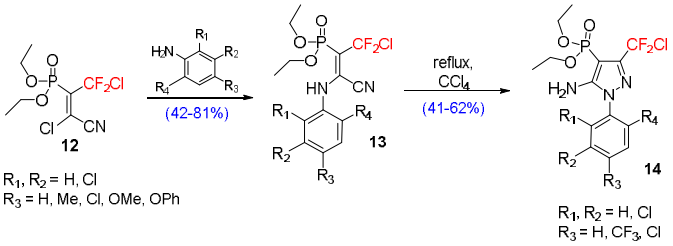
This precursor **10** was subjected to Br/[^{18}F] displacement reaction by treatment with [^{18}F]TBAF in DMSO for 20 min at 135 °C, with subsequent deprotection of sulfonamide (Scheme 3). In this work, interesting PET studies on rodent have been performed showing bone labeling, while PET studies in baboon demonstrated retention of radioactivity in the brain region. This radiolabeling method occurred with high specific activity and could be applied for human purposes.

In a more recent work, Shidlovskii *et al.* reported a feasible pyrazole synthesis by treatment of freshly prepared 2-chloro-2-chlorodifluoromethyl-1-cyano-1-diethoxyphosphorylethylene **12** with different anilines, and subsequent cyclization step of enamines intermediates **13**, yielding 5-amino-1-aryl-4-diethoxyphosphoryl-3-chlorodifluoromethyl-pyrazoles **14**. These pyrazoles resulted quite

interesting as new heterocyclic compounds having both editable chlorodifluoroalkyl and diethoxyphosphoryl groups (Scheme 4).[6]

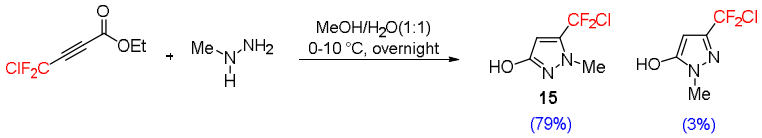


Scheme 3. Radiosynthesis of [^{18}F]celecoxib.



Scheme 4. Synthesis of 3-chlorodifluoromethyl substituted pyrazoles.

A straightforward route to 5-perfluoroalkyl pyrazoles has been developed by B. Hamper in 1990. When perfluoroalkylacetilenic esters reacted with methylhydrazine in methanol/water or dichloromethane at low temperature (below 0 °C), 1-methyl-3-hydroxy-5-perfluoroalkylpyrazoles formed in good yield and regioselectivity. It was demonstrated the effect of the acetylene structure on the regioselectivity. Among all the fluorinated synthesized pyrazoles, it was possible to isolate the product **15** bearing the -CF_2Cl group in 5 position in good yield and regioselectivity (Scheme 5).[7]



Scheme 5. Synthesis of 5-chlorodifluoromethyl pyrazoles.

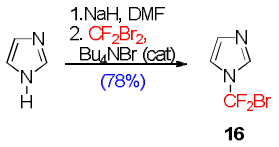
3. Synthesis and use of *N*-halodifluoromethyl-substituted imidazoles

Yagupolskii *et al.* developed a synthetic procedure, as previously reported for pyrazoles (see Scheme 1), for the insertion of bromodifluoromethyl moiety on the nitrogen atom of imidazoles.[4] The protocol was based on the treatment of imidazole with NaH for the generation of the corresponding sodium salt, and subsequent reaction with CF_2Br_2 in DMF. The preparation of *N*-bromodifluoromethyl imidazole **16** was achieved in high yield in presence of tetrabutylammonium bromide as catalyst. In this work, the crucial role of the counterion of the imidazole anion was investigated. Indeed, the reaction proceeded slowly when Li^+ or Na^+ were used as counterions and, it was accelerated by the presence of zinc dust which, however, was also responsible for the formation of byproducts (Scheme 6).

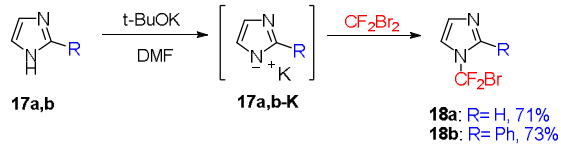
Alternatively, the same authors proposed a catalyst-free approach by using imidazolyl potassium salts **17a,b-K** and CF_2Br_2 in DMF, affording satisfactory yields of product **18a,b** (Scheme 7).

The obtained bromodifluoromethyl derivatives **18a,b** were treated with tetrakis(dimethylamino)ethylene (TDAE) generating the corresponding *N*-difluoromethyl anions which were trapped with the appropriate electrophiles. By producing the *N*-difluoromethyl anions in the presence of an excess of Me_3SiCl in CH_2Cl_2 at -70 °C, imidazol-1-yl-difluoromethyltrimethylsilane **19**, and 2-phenyl-imidazole-1-yl-difluoromethyl-trimethylsilane **20** were synthesized. By adding a catalytic amount

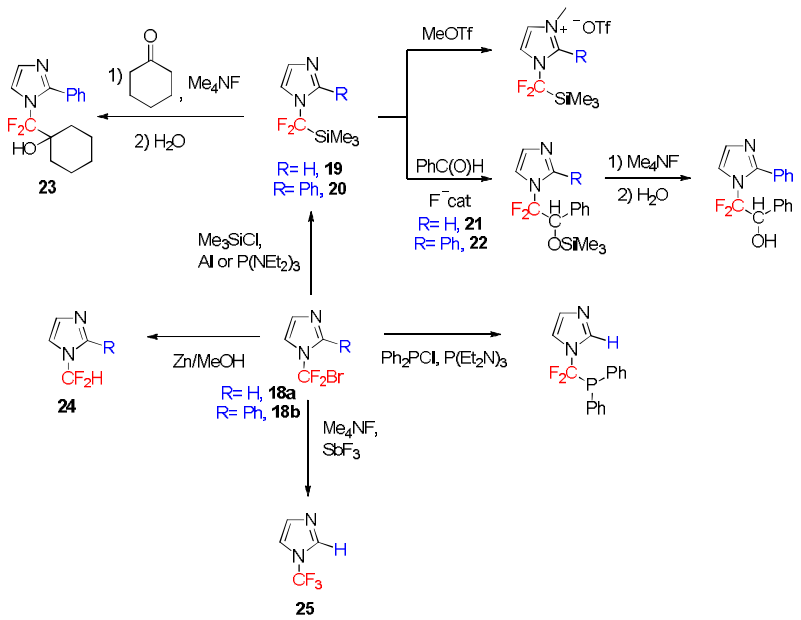
of fluoride source to **19** and **20**, the corresponding imidazole-1-difluoromethyl anions were generated and subsequently reacted with benzaldehyde, furnishing 1-(1,1-difluoro-2-phenyl-2-trimethylsiloxyethyl)-imidazoles **21-22**. Instead, by means of stoichiometric amount of fluoride source, the anion formed from heteroaryl-*N*-difluoromethyltrimethylsilane **20** was able to trap an enolizable ketone as cyclohexanone, furnishing difluorohydrine **23**. As shown in Scheme 8, the derivatives **18a** and **18b** were also employed in other interesting transformations, such as the reduction with Zn powder to obtain the corresponding difluoromethylated compound **24** or the *N*-CF_3 derivative **25** through the Br/F exchange.



Scheme 6. Synthesis of *N*-bromodifluoromethyl imidazole with Bu_4NBr.



Scheme 7. Catalyst-free synthesis of the *N*-bromodifluoromethyl imidazole.

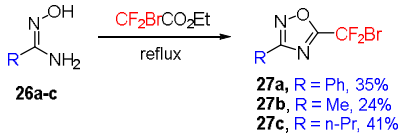


Scheme 8. Usefulness of *N*-bromodifluoromethyl heterocycles **18a,b**.

4. Synthesis and use of 5-(bromodifluoromethyl)-1,2,4-oxadiazoles

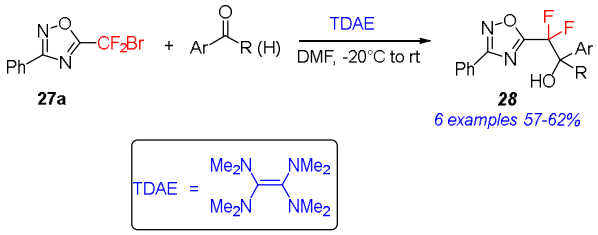
A facile synthesis of CF_2Br-substituted oxadiazoles was carried out in one step by reaction of commercially available CF_2BrCO_2Et with amidoximes **26a-c**, that were readily available by reaction of the appropriate nitriles with hydroxylamine. Three different 5-(bromodifluoromethyl)-1,2,4-oxadiazoles **27a-c**

were synthesized. Although the isolated yields were very low, the one-step procedure resulted extremely convenient mostly offering the possibility for providing the scale-up of the reaction (Scheme 9).[8]



Scheme 9. Synthesis of 5-(bromodifluoromethyl)-1,2,4-oxadiazoles.

The carbon-bromine bond of these compounds **27a-c** was found to be highly reactive in electrochemical single electron transfer (SET) transformations.[9,10] In these reactions, tetrakis(dimethylamino)ethlylene (TDAE) was used as an effective reducing agent to generate stable difluoromethyl heterocyclic anions which have been exploited in the reaction with a series of aldehydes and ketones furnishing novel β,β-difluoro-α-heteroarylated alchools **28**. When TDAE was added to a solution of **27a** and the electrophile in anhydrous DMF at -20 °C, a deep red color immediately developed, probably due to the formation of a charge transfer complex. By warming the solution to room temperature, the complex gradually decomposed producing the corresponding 2-(difluoromethyl)heterocyclic anion which reacted with the electrophile. The oxidation of TDAE in these conditions was clearly demonstrated by the recovery of $[TDAE]^{2+}2Br^-$ by simple filtration at the end of the reaction (Scheme 10).



Scheme 10. Tetrakis(dimethylamino)ethylene (TDAE) as a useful reducing agent of some bromodifluoromethyl heterocycles.

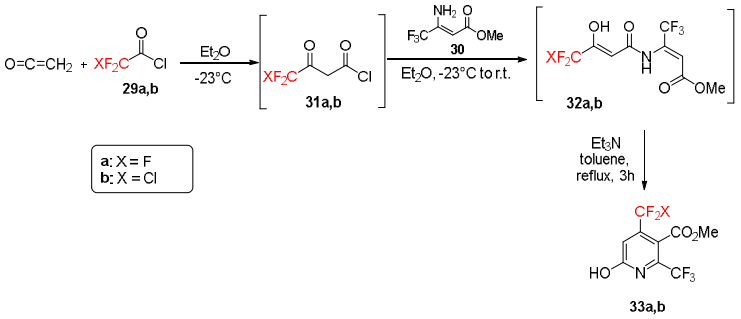
5. Synthesis and use of halodifluoro-substituted pyridines

5.1. *C*-CXF_2 substituted pyridines

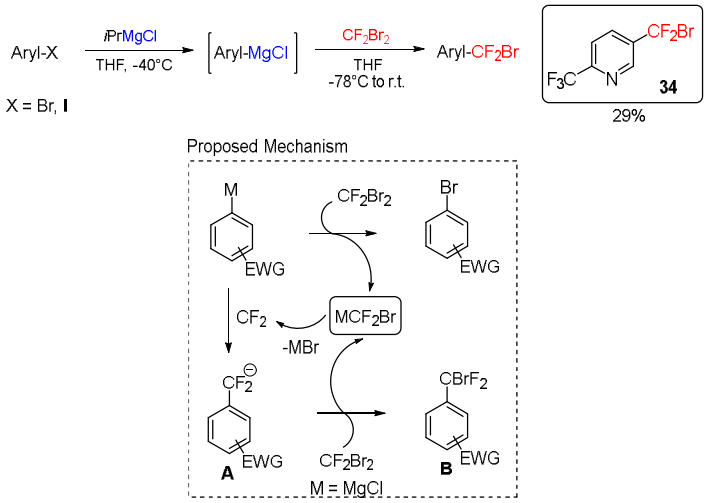
The synthesis of pyridines bearing the CF_2X group can be realized through two different ways: a) a cyclocondensation reaction between a halodifluoroacetoacetyl chloride and a β-aminobutenoate; b) the introduction of CXF_2 group *via* the direct bromodifluoromethylation of pyridine or metalated pyridine. In 1993, Goure *et al.* described a two steps, one pot, synthesis of perfluoroalkylated pyridines based on the cyclocondensation approach.[11] In particular, the reaction of ketene with trifluoroacetyl chloride **29a**, followed by the addition of methyl 3-amino-4,4,4-trifluoro-2-butenoate **30** to the resultant ethereal solution of 4,4,4-trifluoroacetoacetyl chloride **31a** followed by warming to ambient temperature, afforded enamineamide **32a** in good yield. Treatment of **32a** with 1.2 equivalents of triethylamine in 3 h gave the 2-hydroxy-4,6-bis(trifluoromethyl)pyridine-5-carboxylate **33a**. When chlorodifluoroacetyl chloride **31b** was involved as starting material, methyl 4-(chlorodifluoromethyl)-2-hydroxy-6-(trifluoromethyl)-pyridine-5-carboxylate **33b** was obtained in satisfactory yield (Scheme 11).

Moreover, Shiosaki *et al.* in 2014 proposed a new bromodifluoromethylation using aromatic metalated reagents and CF_2Br_2 as haloalkylating agent.[12] Despite the more reactive lithiated analogues, aryl Grignard reagents containing electron-withdrawing groups, such as CN, CO_2Me, SF_5, SO_2Ar, CF_3, and halides resulted suitable substrates for this particular functionalization. The metalated species, generated by bromine or iodine/metal exchange after addition of 1.06 equivalents of *i*-PrMgCl to a solution of halogenated aromatic compound in THF, was reacted with CF_2Br_2 (1.2 equivalents) in THF to afford the desired product. It was demonstrated that this bromodifluoromethylation proceeded *via* a carbene-mediated mechanism as

described in Scheme 12 (M=MgCl), in which the intermediate aryldifluoromethyl anion **A** was stabilized by an electron-withdrawing group (EWG) through inductive and resonance effects, eventually affording the desired product **B**. In the scope of the reaction, although in low yield, one example of pyridine as heteroaromatic cycle **34** was reported.



Scheme 11. Synthesis of 4-chlorodifluoromethyl substituted pyridines.



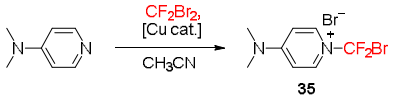
Scheme 12. Bromodifluoromethylation of pyridines by using organomagnesium reagents.

5.1. *N*-CXF_2 substituted pyridines

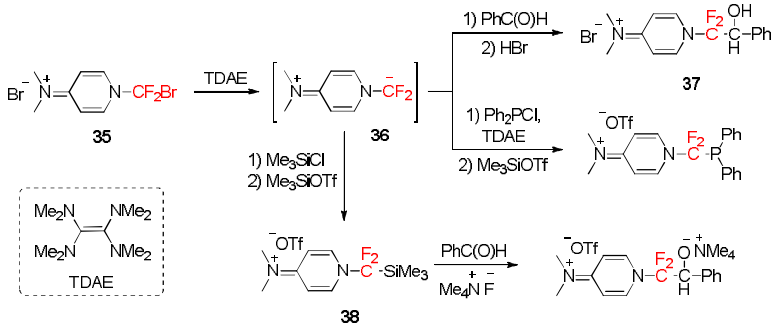
In 1996, the first example of *N*-perhalogenoalkylated pyridine derivatives by a copper-catalyzed *N*-bromodifluoromethylation of 4-dimethylaminopyridine (DMAP) was presented by Röschenthaler and co-workers.[13] A chain carbenic mechanism, involving the generation of the 4-dimethylaminopyridinium difluoromethylide intermediate, was proposed for the reaction of DMAP with CF_2Br_2 to yield *N*-(bromodifluoromethyl)pyridinium bromide **35** (Scheme 13).

Later, inspired by Médebielle's work, Bissky *et al.* proposed the generation of 4-dimethylaminopyridinium-*N*-difluoromethylide **36** in the presence of different electrophiles by reacting **35** with TDAE (tetrakis(dimethylaminoethlylene).[14] Using benzaldehyde as reaction solvent, 1-(1,1-difluoro-2-hydroxy-2-phenyl-ethyl)-4-dimethylaminopyridinium bromide **37** was isolated in 46% yield. Other electrophiles were effectively employed to trap the intermediate **36**, such as chlorodiphenyl phosphine. Moreover, 1-(difluorotrimethylsilyl-methyl)-4-dimethylamino-pyridinium triflate **38** was obtained by the reaction of **36** with chlorotrimethylsilane followed by a triflate/chloride counterion exchange

reaction. The compound **38** was reacted with benzaldehyde and tetramethylammonium fluoride to access tetramethylammonium 1-(1,1-difluoro-2-phenylethyl)-4-dimethylamino-pyridinium (Scheme 14).



Scheme 13. Synthesis of pyridinium bromide.



Scheme 14. Generation and reactions of heteroarylium-*N*-difluoromethylides.

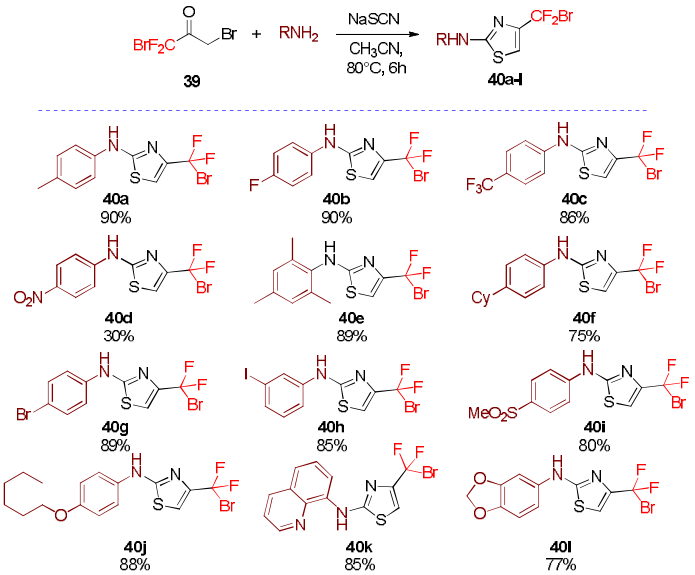
6. Synthesis and use of halodifluoromethyl-substituted thiazoles

A new synthetic strategy for the synthesis of 4-bromodifluoromethyl-2-amino thiazoles based on the use of 1,3-dibromo-1,1-difluoro-2-propanone **39** as new synthon was carried out by Luisi *et al.* This useful synthon was prepared starting from the commercial available ethyl 1-bromo-1,1-difluoroethanoate with methylmagnesium bromide, in diethyl ether at -78 °C (76% yield), followed by bromination step with trifluoroacetic acid (TFA) as solvent, at 40 °C for 16 h (80% yield). With this dibromodifluoroketone **39** in hand, the synthesis of 4-bromodifluoromethyl-thiazoles **40a-l** was developed, by reacting **39** with several aromatic amines and in the presence of sodium thiocyanate (Scheme 15).[15] As reported in Scheme 15, the reaction worked well with several aromatic amines being tolerant to different substituents on the aromatic ring. The presence of a strong electron-withdrawing group as in the case of the *p*-nitroaniline provided low yield of the corresponding thiazole **40d**. In striking contrast, the reaction was not significantly affected by the presence of fluoro, trifluoromethyl and methylsulfonyl groups, affording derivatives **40b**, **40c** and **40i** in good yields. The presence on the aromatic ring of electron-donating substituents was also tolerated, leading to derivatives **40j** and **40l** in high yields.

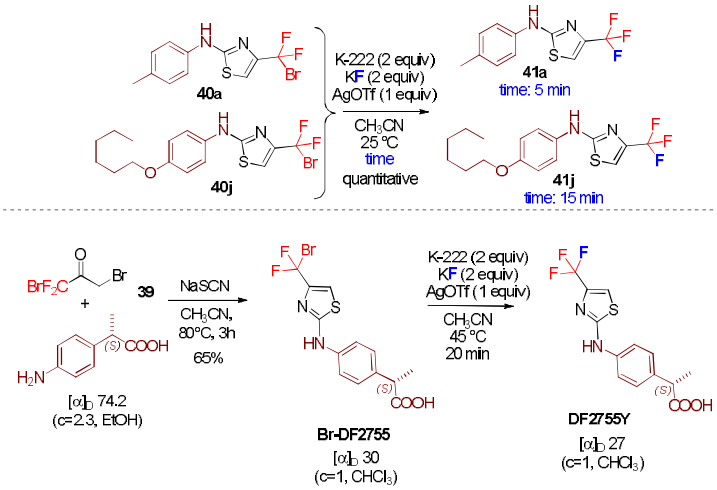
These new compounds are amenable to a Br/F exchange reaction by a nucleophilic substitution with fluorine anion. Derivatives **40a** and **40j** were used as test compounds and subjected to reaction under "cold" conditions using KF as source of fluoride ions, kryptofix® 222 as cryptand for potassium cation, AgOTf as promoter in acetonitrile at room temperature (Scheme 16). As reported in Scheme 16, the reaction performed very well providing the exchange products **41a** and **41j** quantitatively in only 5-15 minutes. Nicely, the observed short reaction time for complete Br/F exchange, could potentially be useful for a late stage ^{18}F radiolabeling experiment. The strategy was applied to the preparation of **Br-DF2755**, precursor of the biologically relevant **DF2755Y**.

7. Synthesis and use of 2-(bromodifluoromethyl)benzoxazoles

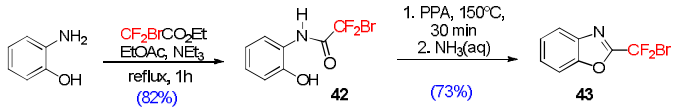
In 1999, a two-step preparation of 2-(bromodifluoromethyl)benzoxazole **43** was reported by Burkholder and Médebielle.[7] A solution of 2-aminophenol, ethyl bromodifluoroacetate, and trimethylamine in ethyl acetate was heated to access 2-bromo-2,2-difluoro-*N*-(2-hydroxyphenyl)acetamide **42** in high yield. By heating the amide **42** in the presence of PPA (polyphosphoric acid), the facile cyclization of the latter was achieved giving the desired benzoxazole **43** in 73% of yield (Scheme 17).



Scheme 15. Synthesis of bromodifluoromethyl thiazoles by cyclization of synthon **39** with amines and thiocyanate.



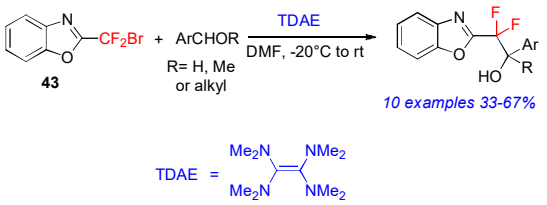
Scheme 16. Examples of Br/F exchange reaction.



Scheme 17. Synthesis of 2-(bromodifluoromethyl)benzoxazole.

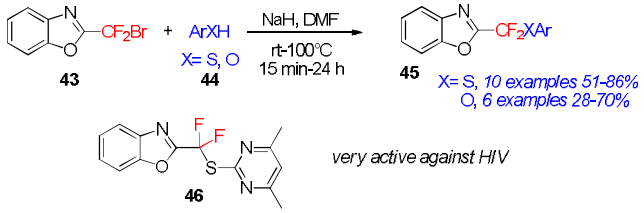
The carbon-bromine bond of the compound **43** was found to be highly reactive in single electron transfer (SET) transformations.[9,10] As previously reported in Scheme 10, TDAE (tetrakis(dimethylaminoethlylene) was able to generate stable difluoromethyl heterocyclic anions which

have been exploited to react with a series of aldehydes and ketones furnishing novel β,β-difluoro-α-heteroarylated alchools (Scheme 18). Therefore, 2-bromodifluoromethyl benzoxazoles were employed as starting material for the preparation of a large spectrum of compounds for biological screening against HIV. In particular, some *gem*-difluoromethyl benzoxazoles were evaluated in the preliminary screen of the in vitro Anti-AIDS Drug Discovery Program at the National Cancer Institute.[16]



Scheme 18. Tetrakis(dimethylamino)ethylene (TDAE) as a useful reductant of some bromodifluoromethyl heterocycles.

The same authors also reported the effective displacement of bromide from the CF_2Br group of 2-(bromodifluoromethyl)benzoxazole **43** by using the anions of heterocyclic thiols and phenolic compounds as nucleophiles **44**.[17] The authors proposed an $S_{RN}1$ mechanism involving a SET chain process for these transformations rather than a simple S_N2 mechanism which is prevented by the presence of the alpha fluorine atoms. This hypothesis was confirmed by the observation that the reaction was inhibited in the presence of 1,4-dinitrobenzene. Some of the compounds **45** obtained by this method were found to be active against HIV, especially the compound **46** (Scheme 19).



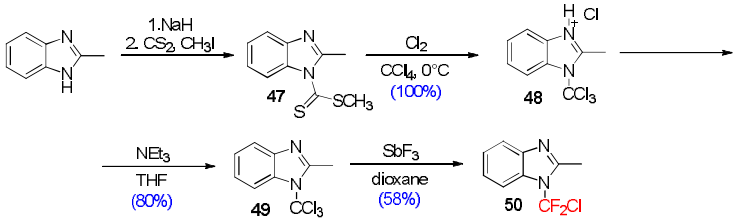
Scheme 19. The $S_{RN}1$ reactions of 2-(bromodifluoromethyl)benzoxazole with the anions derived from heterocyclic thiols and phenolic compounds.

8. Synthesis and use of *N*-bromo- and *N*-chlorodifluoromethyl benzimidazoles

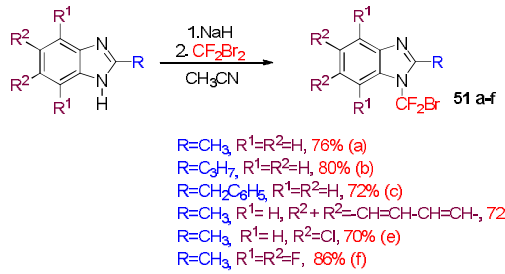
In 2000, Yagupolskii and co-workers reported the preparation of different *N*-halodifluoromethyl heterocycles.[18] Among these derivatives, the *N*-sodium salt of 2-methylbenzimidazole, obtained by reaction with NaH, was reacted with carbon disulfide and methyl iodide furnishing compound **47**. The following chlorination of (methylthio)thiocarbonyl moiety of **47** with Cl_2 gave access, after treatment of the hydrochloride salt **48** with triethylamine, to 2-methyl-1-trichloromethylbenzimidazole **49**. By refluxing a mixture of SbF_3 and **49** in dioxane, the displacement of two chlorine atoms with fluorine was achieved, obtaining, after distillation, 1-chlorodifluoromethyl-2-methylbenzimidazole **50** in 58% yield (Scheme 20).

Another approach to prepare 1-halodifluoromethylbenzimidazoles was presented by Yagupolskii. In particular, the sodium salts of various 2-substituted benzimidazoles were treated with CF_2Br_2 in the presence of zinc dust, giving the corresponding 1-bromodifluoromethylbenzimidazoles **51a-f** (Scheme 21).

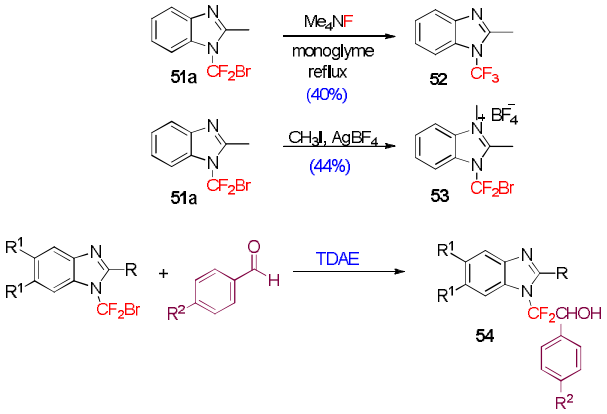
By heating 1-bromodifluoromethyl-2-methylbenzimidazole **51a** in the presence of tetramethylammonium fluoride or SbF_3, the transformation of **51a** into the corresponding trifluoromethylated analog **52** was achieved (Scheme 22). Furthermore, by adding **51a** and methyl iodide to a solution of $AgBF_4$ in dichloroethane, the salt **53** was obtained. Interestingly, the reaction of 1-bromodifluoromethylbenzimidazoles with aromatic aldehydes in the presence of TDAE gave access to compounds **54** interesting from a biological point of view.



Scheme 20. Preparation of 1-chlorodifluoromethyl-2-methylbenzimidazole **50**.



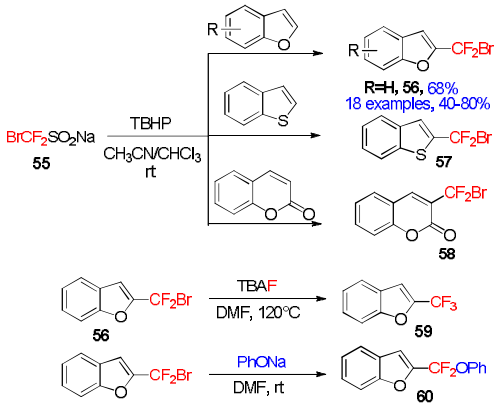
Scheme 21. Preparation of various CF_2Br-containing benzimidazoles.



Scheme 22. Different applications of 1-bromodifluoromethylbenzimidazoles.

9. Synthesis and use of bromodifluoromethyl benzofurans

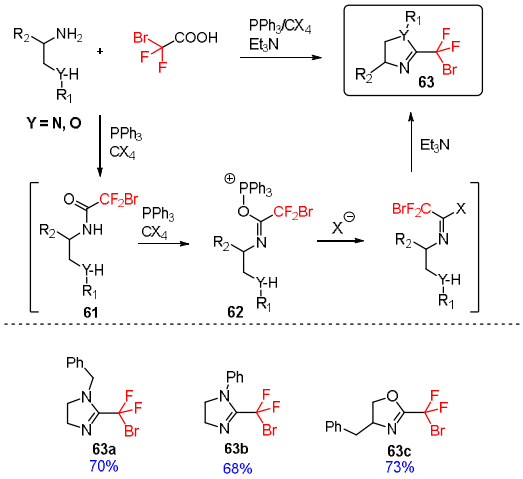
Recently, the use of bromodifluoromethanesulfinate **55** as a radical bromodifluoromethylating reagent for the preparation of CF_2Br-containing heteroaromatics was provided by Qing.[19] By using benzofuran as the model substrate, a careful screening of the reaction conditions was conducted. Using a mixture of CH_3CN and $CHCl_3$ with a ratio of 1:2, in the presence of TBHP as oxidant at room temperature the highest yield of desired bromodifluoromethylated product **56** was observed (Scheme 23). Under these conditions, the scope of the reaction was explored by using benzofurans bearing either electron-donating and electron-withdrawing groups. When 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) was added to the reaction mixture, the formation of desired products was not observed confirming a radical mechanism for this process. The developed bromodifluomethylation procedure was also extended to benzo[b]thiophene and 2*H*-chromen-2-one obtaining the corresponding bromodifluoromethylated heterocycles **57** and **58** in moderate yields. Moreover, by treating **56** with TBAF in DMF at 120 °C the trifluoromethylated product **59** was synthesized. Finally, the reaction of 2-(bromodifluoromethyl)-5-(*tert*-butyl)benzofuran with PhONa in DMF at room temperature furnished (aryloxy)difluoromethylated product **60** in high yield.



Scheme 23. Bromodifluoromethylation of heteroaromatics with sodium bromodifluoromethansulfinate.

10. Synthesis and use of bromodifluoromethyl substituted 1,3-imidazolines and 1,3-oxazolines

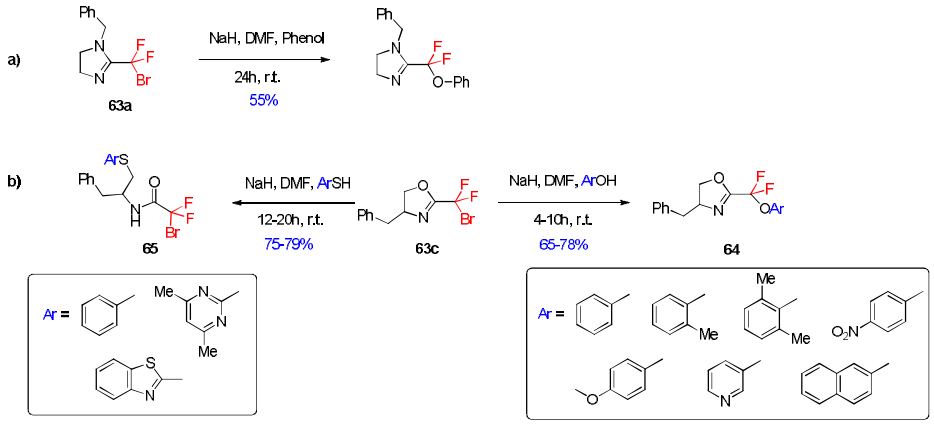
A straightforward one-pot procedure for the synthesis of 1,3-imidazolines and 1,3-oxazolines bearing fluorinated alkyl groups was developed by Jiang *et al.*[20] Among different *gem*-difluoromethylene moieties, 2-bromodifluoromethyl group was introduced in 2-position of 1,3-imidazolines and 1,3-oxazolines. The synthesis of these heterocycles was performed by refluxing in CCl_4 or in toluene at 90 °C in the presence of 3 equivalents of CBr_4, Ph_3P, and excess of Et_3N, *N*-monosubstituted ethane-1,2-diamines or 2-amino-3-phenylpropanol with fluorinated carboxylic acids to generate 2-fluoroalkyl-1,3-imidazolines or 2-fluoroalkyl-1,3-oxazolines **63**, respectively (Scheme 24). The reactions were carried out in a one-pot process with good to excellent isolated yields. The postulated mechanism of this tandem process was supported experimentally by isolation of the fluorinated amide intermediates **61**, which was then converted to imidoyl halide intermediates **62** in the presence of PPh_3/CX_4, followed by a rapid intramolecular cyclization to the desired products **63**.



Scheme 24. Bromodifluoromethylation of 1,3-imidazolines and 1,3-oxazolines.

2-Bromodifluoromethyl-1,3-imidazoline **63a**, was successfully used in the synthesis of *gem*-difluoromethylene linked compounds to be used in biological studies, by reaction with phenol in the presence of NaH/DMF likely involving a typical SET mechanism (Scheme 25, a). The reaction of

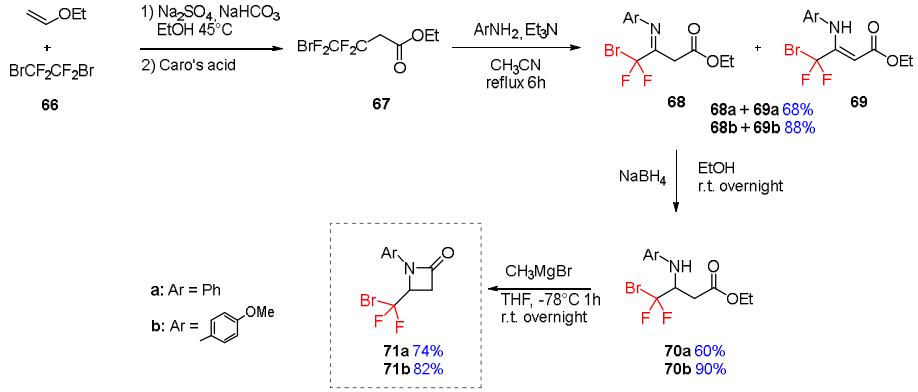
2-bromodifluoromethyl-1,3-oxazoline **63c** with phenolate disclosed that a *gem*-difluoromethylene-linked 1,3-oxazoline-contaning phenyl ether **64** could be obtained exclusively. Interestingly, 4-benzyl-2-bromodifluoromethyl-1,3-oxazoline **63c** reacted with arenethiols to provide biologically interesting fluoromethylated secondary carboxamides **65** through a nucleophilic ring-opening process at the C5 position of 1,3-oxazoline (Scheme 25, b).[21]



Scheme 25. Reaction of 2-bromodifluoromethyl 1,3-imidazoline and 1,3-oxazoline with sodium arenolates.

11. Synthesis and use of bromodifluoromethyl substituted β-lactams

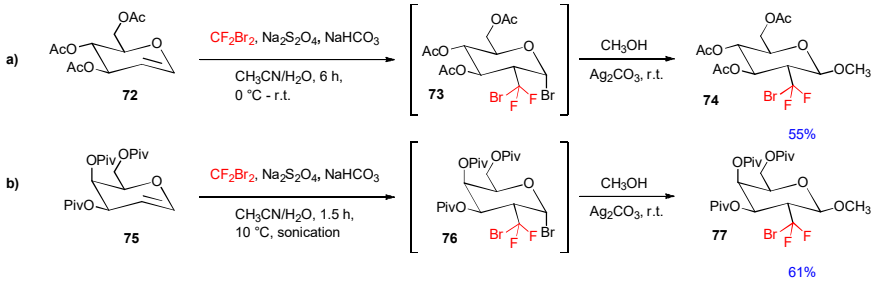
In 2006, Wang *et al.*, reported an efficient synthetic route to obtain β-bromodifluoromethyl-lactams as useful precursors to afford *gem*-difluoromethyene-substituted β-lactams.[22] These nitrogenated heterocycles are intriguing compounds due to the CH_2/CF_2 transposition which has been recognized as a valuable way in the blockage of metabolic processes. Reaction of $BrCF_2CF_2Br$ **66** with ethyl vinyl ether gives ester **67** (Scheme 26). The subsequent dehydrohalogenation of **67** with Et_3N in refluxing CH_2Cl_2, followed by substitution of the fluorine with the aromatic amines gave the desired imines **68** together with its tautomer enamine **69**. $NaBH_4$ in EtOH can easily reduce these two tautomers at room temperature. Ring closures of the β-amino esters **70** using methylmagnesium bromide to remove the hydrogen on the nitrogen atom smoothly led to the desired $BrCF_2$-containing β-lactams **71** in good yields (Scheme 26).



Scheme 26. Synthetic route to bromodifluoromethyl lactams.

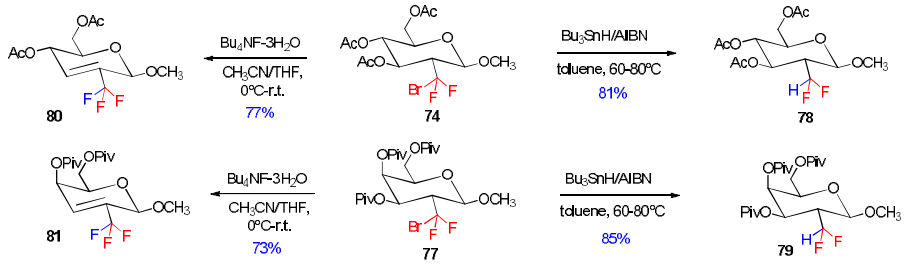
12. Synthesis and use of bromodifluoromethyl substituted sugars

The bromodifluoromethyl groups can be installed at the C2 carbon of methyl β-D-glycosides.[23] This strategy relies on the fluoroalkylation of glucals and galactals with dibromodifluoromethane *via* the 2-C-bromodifluoromethyl-substituted glycosyl bromides, followed by glycosylation to the methyl β-D-glycosides. The procedure for the addition of dibromodifluoromethane to the 3,4,6-tri-*O*-acetyl-D-glucal **72** was carried out in acetonitrile/water (5:3 v/v) in presence of sodium dithionite, yielding the 3,4,6-tri-*O*-acetyl-2-bromodifluoromethyl-2-deoxy-β-D-glucopyranosyl bromide **73** as the major product. The latter furnished the methyl β-D-glucoside **74** by adding a methanolic suspension of silver carbonate (Scheme 27).



Scheme 27. Synthesis of fluorinated monosaccharides.

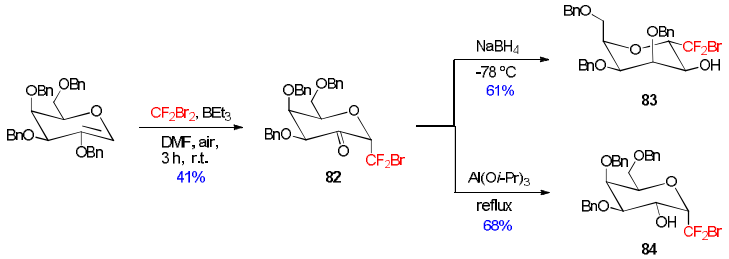
Compounds **74** and **77** are attractive building blocks for their potential linking through difluoromethylenic unit allowing an efficient synthesis of glycoconjugate analogues, but they should also be suitable precursors for syntheses of 2-deoxy-2-difluoromethyl or 2-deoxy-2-trifluoromethyl derivatives of sugars by replacing the bromine atom with hydrogen and fluorine. By treatment of the glycosides **74** and **77** with tributylstannane in toluene, the corresponding 2-deoxy-2-difluoromethyl derivatives **78** and **79** were obtained in good yields. Instead, by treatment of the compounds **74** and **77** with an excess of tetrabutylammonium fluoride trishydrate (TBAF·3H_2O) in acetonitrile (Scheme 28), pseudoglycals **80** and **81** were isolated in good yields. The formation of **80** and **81** could be explained by the elimination of HBr promoted by fluoride ion that, subsequently, attacks the exocyclic difluoromethylene group with simultaneous formation of the double bond due to the elimination of the acyl group at 3 position.



Scheme 28. Transformation of 2-bromodifluoromethyl monosaccharides.

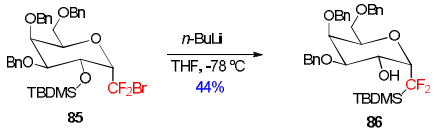
An interesting addition of bromodifluoromethyl radical to 2-benzyloxyglycals gave rise to the formation of 2-ketohexopyranosides which can be reduced affording α-C-glycosides in satisfactory overall yields with complete diastereoselectivity for each step.[24] The addition of dibromodifluoromethane to this electron-rich double bond occurred efficiently giving 2-oxogalactoside **82** as the sole reaction product in DMF as solvent at room temperature and in presence of BEt_3 and air (Scheme 29). The simple sodium borohydride mediated reduction of galactose derivative afforded CF_2-glycoside **83** having an α-D-taloside configuration with a $^1C4$ conformation for the most populated conformer, as ascertained by NMR analysis.

Very low temperatures (-78 °C) were required to avoid the simultaneous reduction of the bromodifluoromethyl group. Because this reaction was presumably under kinetic control, that is, it proceeded through an attack of the hydride on the least-hindered face, the use of a thermodynamically controlled reduction reaction was able to reverse the selectivity. In fact, by the Meerwein-Ponndorf-Verley (MPV) reaction (aluminum isopropoxide at reflux in isopropanol), the α-CF_2-D-galactoside **84** formed as sole product and an X-ray diffraction study confirmed the configuration at the C2 position (Scheme 29).



Scheme 29. Stereoselective reduction of the 2-oxogalactoside.

The presence of CF_2Br groups at the pseudo-anomeric position allowed efficient Br/Li-exchange/nucleophilic-addition sequences. As a matter of fact, Br/Li exchange on OTBS-derivative **85** (TBS=*tert*-butyldimethylsilyl) was performed, which resulted in a migration of the TBS group from the O2 to C1' atoms to provide the corresponding CF_2TBS derivative **86** in moderate yield (Scheme 30). These transformations open the way for the synthesis of fluorinated C-glycosidic analogues of glycoconjugates.



Scheme 30. Br/Li exchange promoting CF_2TBS derivative formation.

13. Conclusions

In conclusion, CXF_2-substituted heterocyclic motifs show widespread application in organic synthesis, materials, and pharmaceutical chemistry. Considering the reported work, different approaches have taken place in the installation of a halodifluoromethyl group over the past decade, but we found that there are still some aspects needing to be thought deeply, such as the types of novel reaction, mechanistic models, substrate scope and so on. As representative approaches in CF_2X insertion, the synthetic methods, employing a cyclization reaction starting from halodifluoroalkyl compounds as key building blocks, have been utilized as the mainstream strategy. On the other hand, however, the availability of preformed heterocycles as well as the dihalodifluoromethane derivatives allows to an alternative approach using the organometallic strategy, which enable the direct introduction of CXF_2 group on many heterocycles with more flexible variation on the substructures of the starting materials, and/or improved product selectivity. While the overall synthetic methods are yet scarce and old, extensive efforts in devising much more different methods on the synthesis of this CXF_2 heterocycles by employing structurally diverse and easily available substrates are therefore still highly demanding. Moreover, these aforementioned heterocycles are precursors of useful derivatives by exploitation of the CF_2X group, usually based on displacement of halogen atom (X) with an arenolate, a hydrogen and a fluorine atom. We believe that in this context further ground-breaking discoveries can be expected with certainty in the near future.

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