DIPOLAR CYCLOADDITION OF *N*-OXIDES OF AZINES AND AZOLES TO DIFLUOROALKENES

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Abstract. *1,3-Dipolar cycloaddition of perfluoroalkenes and 1,1-difluorostyrenes with nitrones and N-oxides of azines and azoles allows to obtain various heterocyclic products, such as fluoroalkyl heterocycles, amides and esters of α-heteroarylcarboxylic acids, β-lactams or unsymmetrical bis(heteroaryl)methanes. NMR characterisation of the key intermediate, α-heteroaryl acyl fluoride, provides evidence for the mechanism proposed for cycloaddition of N-oxides and fluoroalkenes.*

Contents

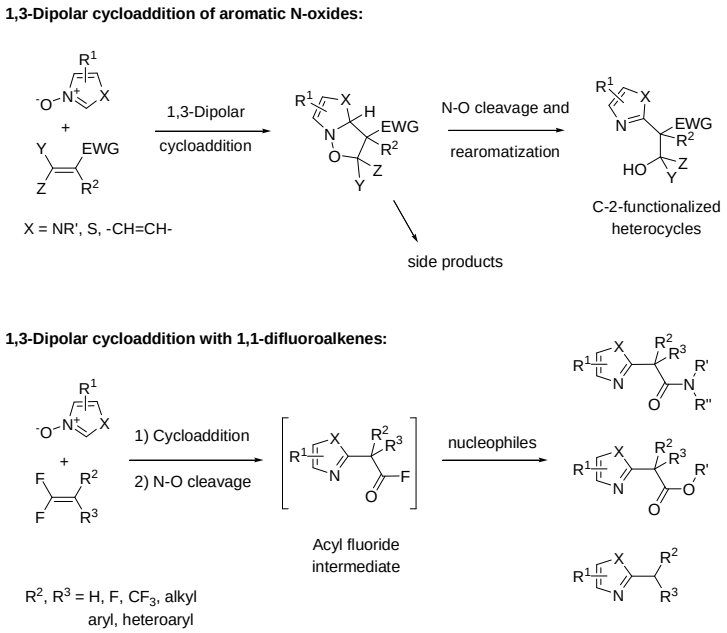
1. Introduction

Development of new efficient methods for the synthesis of highly functionalized nitrogen heteroaromatic systems remains one of the central challenges of modern synthetic organic chemistry.[1] A great number of practical synthetic methods is based on assembly of the heterocyclic unit from acyclic precursors.[2] In recent years, however, methods that allow selective replacement of ring hydrogen atom with a desired substituent are gaining increasing importance. Transition metal-catalyzed C–H activation reactions[3] of both azines[4] and azoles[5] have been studied extensively. Other important and useful approaches to functionalization of a hydrogen-substituted position of a heteroaromatic ring include nucleophilic vicarious or oxidative substitution of hydrogen,[6,7] radical substitution[8] and selective lithiation.[9] Recently, an efficient reaction sequence which allows functionalisation of C-2 position of complex pyridine and other azine substrates with nucleophiles via 2-fluoro derivatives has been reported.[10] Among more classical,

though still actively developed methods, Chichibabin-type reactions[11] and nucleophilic addition to heterocycles activated at nitrogen atom by alkylation or acylation should be mentioned.[12]

N-Oxides of nitrogen heteroaromatics are readily available for both five- and six-member systems.[13] They have rich chemistry and offer wide possibilities in terms of preparation of highly functionalized heterocyclic derivatives.[14] *N*-Oxides of both azoles[15] and azines[16] are good substrates for C–H activation reactions, metalation with strong bases[9a] or nucleophilic substitution of hydrogen,[6a,17] but they are also capable of undergoing nucleophilic *cine* substitution with metaloorganic reagents[18] or weaker nucleophiles,[19,20] when the oxygen atom acts as a leaving group, usually after its appropriate activation.

Another transformation available for aromatic *N*-oxides is dipolar cycloaddition, with *N*-oxide acting as a 1,3-dipole.[21] This Account will summarize our work on the development of a particular case of cycloaddition of *N*-oxides to terminal difluoroalkenes.[22] This reaction is distinguished by the fact that it leads in a selective and predictable manner to substitution of hydrogen in the heterocyclic ring of both azoles and azines with formation of a new carbon-carbon bond (Scheme 1). It allows preparation of diverse heterocyclic products, such as fluoroalkylated heterocycles, α-heteroaryl esters and amides, or bis(heteroaryl)methanes which can be used, for example, as ligands.



Scheme 1

2. Functionalisation of nitrogen heterocycles via 1,3-dipolar cycloaddition of *N*-oxides

1,3-Dipolar cycloaddition is yet another class of processes by which a new bond is formed to the carbon atom in the heteroaromatic ring vicinal to the basic nitrogen atom (Scheme 1, top). Initially, cycloaddition to dipolarophiles containing a double or triple bond generates, respectively, isoxazolidines or isoxazolines in which the original heterocyclic ring is no longer aromatic. Formation of these adducts may

be stepwise or concerted, depending on the structure of substrates and, in particular, capability of dipolarophile to undergo nucleophilic addition and stabilise the resulting negative charge.[23] In some cases isoxazolidine adducts are stable and final products, but much more often they undergo further transformations in which aromaticity of azine or azole substrate is restored.[21]

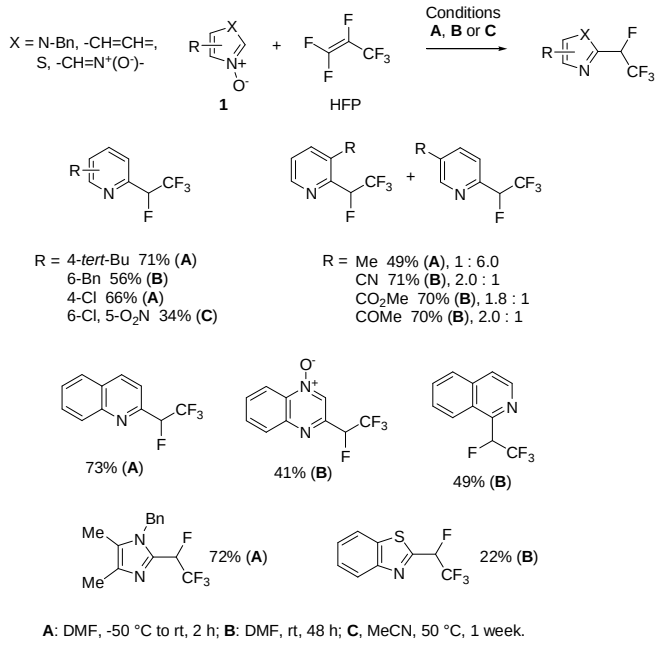
Dipolar cycloaddition is a general process as it occurs for both azine and azole *N*-oxides, and it also introduces the new substituent selectively into C-2 substitution, unless the cycloadduct undergoes a sigmatropic rearrangement.[24] It is also a transition metal-free process and it usually occurs under close to neutral conditions. For these reasons, cycloaddition approach could be useful for installing new substituents into the aromatic rings of *aza*-heterocycles and for late-stage functionalization of even complex substrates, provided that initial isoxazolidine adducts are selectively transformed into C-2 substituted products.

Some synthetically useful processes of this kind have been described in the literature. Cycloaddition of azine *N*-oxides to multiple carbon-nitrogen bonds of imidoyl chlorides[25a,b] or triflates,[25c] isocyanates[26] and isonitriles activated by TMSOTf[27] is an important method of selective amination of C-2 position. Cycloaddition of pyridine *N*-oxides with benzyne followed by a sigmatropic rearrangement leads to 3-(o-hydroxyaryl)pyridine derivatives.[24b] The outcome of reactions of azine *N*-oxides with electron poor double and triple carbon-carbon bonds depends strongly on the structure of the substrates.[24a,25a,28] Isoquinoline *N*-oxides give the expected 1-alkylated isoquinoline derivatives upon cycloaddition with alkyl acrylates.[29] Cycloaddition of quinazoline *N*-oxide with a strain-activated alkene has been reported to be followed by Cu(II)-promoted cleavage of the azine ring, leading selectively to complex heterocyclic products.[30] Cycloaddition strategy for C-2 functionalization has been even utilized successfully on a complex substrate - nebularine *N1*-oxide, a nucleoside analogue containing a purine *N*-oxide fragment. Reaction with 3-phenyl-2-propynenitrile yielded product containing a 1-cyano-2-hydroxy-2-phenylvinyl substituent in the purine six-membered ring.[31] Reaction between quinoline *N*-oxide and a 2-fluro-2-fluoroalkylacrylate gave C-2 substitution product, formation of which could be explained by the general pathway shown in Scheme 1.[32]

Some of the above reactions occur for imidazole *N*-oxides as well, providing imidazoles with new substituents at C-2. Amination can be achieved by reaction with isocyanates and isothiocyanates according to a stepwise cycloaddition mechanism.[33] Reactions with unsaturated carboxylic esters[34] or 2,2-bis(trifluoromethyl)ethene-1,1-dicarbonitrile[35] allow to introduce a carbon substituent, and the reaction with 2,2,4,4-tetramethylcyclobutane-1,3-dithione gives imidazole-2-thiones.[36] Benzimidazole *N*-oxide reacts with acetylene mono- and dicarboxylates,[37] as well as isocyanates and isothiocyanates.[38] Dipolar cycloaddition followed by isoxazoline ring opening has been even observed for the reaction of non-aromatic 4,5-dihydroimidazole *N*-oxide with dimethyl acetylenedicarboxylate.[39]

3. 1,3-Dipolar cycloaddition of *N*-oxides and simple perfluoroalkenes

The reaction between *N*-oxides and perfluoroalkenes was described for the first time over 40 years ago by Mailey and Ocone, who reported that pyridine *N*-oxide and its simple derivatives react with hexafluoropropene (C_3F_6, HFP) under relatively harsh conditions (autoclave, elevated temperature and pressure) to give 2-(1,2,2,2-tetrafluoroethyl) derivatives in moderate yields (Scheme 2).[40] Among the gaseous products of these reactions, carbon dioxide and difluorophosgene were detected. Later, these findings were confirmed by Banks, Haszeldine and co-workers.[41]



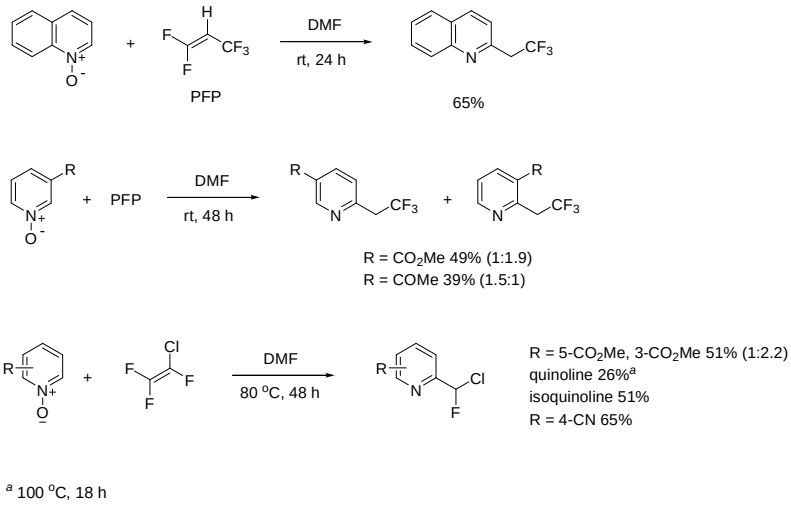
A: DMF, -50 °C to rt, 2 h; **B**: DMF, rt, 48 h; **C**, MeCN, 50 °C, 1 week.

Scheme 2

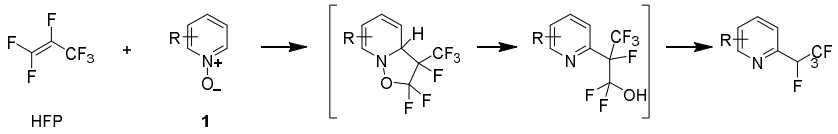
As aromatic and heteroaromatic compounds with perfluoroalkyl[42] or partially fluorinated alkyl groups[43] in the ring are important as modern pharmaceuticals and other biologically active compounds, this reaction attracted our attention as a simple and potentially useful method of synthesis of azines and azoles selectively fluoroalkylated at the position vicinal to the basic nitrogen atom. We found that the reaction of *N*-oxides with perfluorpropene can be performed at relatively mild conditions, in a polar solvent such as DMF at room temperature and using glass pressure tubes with Teflon valves instead of an autoclave.[44] A variety of pyridine *N*-oxides could be used (Scheme 2), although those containing electron-withdrawing substituents reacted sluggishly, requiring prolonged reaction time (48 h). Unsymmetrically substituted pyridine *N*-oxides containing electron withdrawing substituents gave mixtures of isomeric products with 2,3-substituted compounds as the major products, while for 3-methylpyridine C-6 substitution predominated, probably for steric reasons. The process proved to be general in terms of the heterocyclic systems, as apart from substituted pyridines it gave good results with quinolines, isoquinolines and azoles. Indeed, for these substrates the reaction was particularly facile, which can be attributed to their relatively low resonance stabilisation energy. Pentafluoropropene (CF_2=$CHCF_3$, PFP) and chlorotrifluoroethene could be used instead of HFP, giving the expected 2-(2,2,2-trifluoroethyl)- or chlorofluoromethyl-substituted heterocycles (Scheme 3).[44b]

In the early works cited above it was postulated that in the course of the reaction the initial dipolar cycloaddition of *N*-oxide to perfluoroalkene leads to a difluoroisoxazolidine cycloadduct which then undergoes cleavage of the weak N-O bond with concomitant restoration of the aromaticity of the azine ring.[40,41] The resultant α,α-difluoroalcohol decomposes with loss of difluorophosgene to give the observed

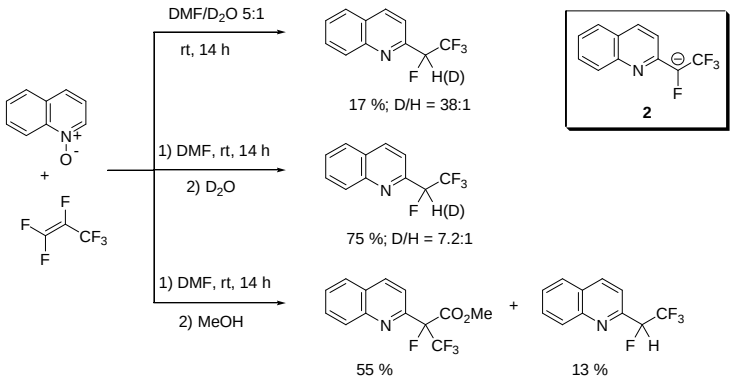
product with a $CHFCF_3$ substituent (Scheme 4). To verify this hypothesis, a series of experiments were performed, some of which are shown in Scheme 5.[45]



Scheme 3



Scheme 4

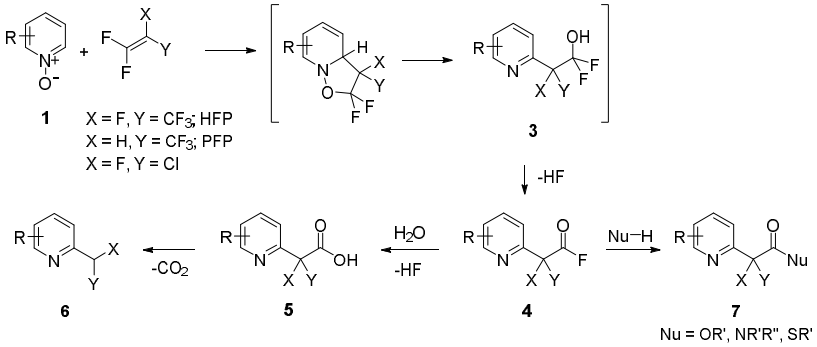


Scheme 5

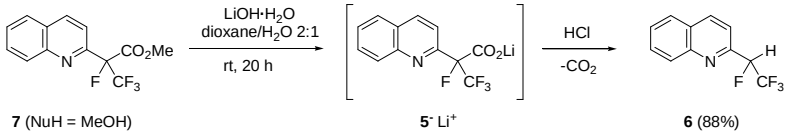
A reaction of quinoline *N*-oxide with HFP conducted in a 5:1 DMF-D_2O mixture gave the product with a high deuterium content in the fluoroalkyl substituent, D:H=38:1 as determined by the ^1H and ^{13}C NMR spectra. It would suggest that the alcohol intermediate must be long-leaved enough for the H/D exchange to

occur in the OH group. A long lived carbanion **2** is improbable since it is expected to undergo fast elimination of fluoride, and the appropriate quinolinyl-substituted trifluoroalkene was not observed. However, another two experiments of Scheme 5 were more informative. Reaction in which D_2O was added *at the end* of the reaction gave highly deuterated tetrafluoroethyl product as well, and a reaction finished by adding MeOH before a standard aqueous work-up gave methyl ester of 2-quinolinylperfluoropropionic acid in good yield, together with some tetrafluoroethylquinoline. These results indicate that the initially formed alcohol does not decompose with loss of COF_2 as soon as it is formed, but rather it loses HF to give a stable acyl fluoride **4**. This fluoride is accumulated in the reaction mixture until a nucleophile such as MeOH or D_2O is added, to give, respectively, an ester or a carboxylic acid.

α-Heteroarylacetic acids are relatively unstable,[46] and this instability may be further enhanced by the presence of strongly electron withdrawing CF_3 group. Therefore, the carboxylic acid **5** undergoes fast decarboxylation to the tetrafluoroethyl derivative **6**. This product is deuterated if the formation of acid and its decarboxylation occurs in the presence of D_2O. The updated reaction mechanism which follows from the above discussion is depicted in Schemes 6 and 7. Further support is provided by the fact that basic hydrolysis of methyl 2-quinolinylperfluoropropionate and subsequent acidification gives the respective tetrafluoroethyl product under very mild conditions (no heating). The existence of the acyl fluoride as the dominating species in the reaction mixture was later confirmed by its direct observation with NMR experiments (see Section 6.3).



Scheme 6

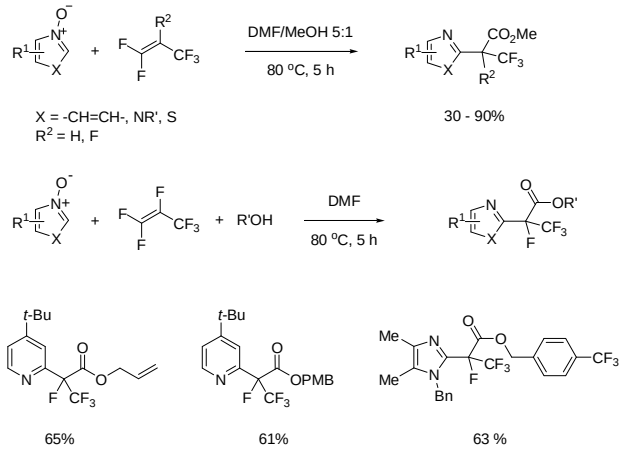


Scheme 7

4. Reaction of *N*-oxides and perfluoroalkenes in the presence of nucleophiles

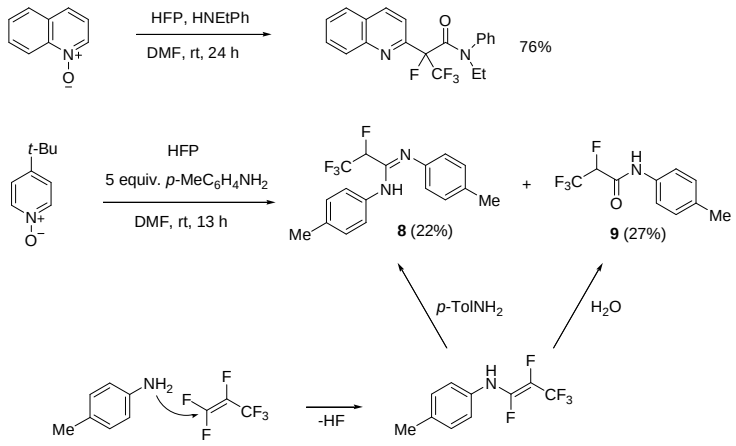
Elucidation of the mechanism of the reaction between aromatic *N*-oxides and perfluoroalkenes had important synthetic consequences as it enabled us to apply it for the preparation of various derivatives of fluorinated α-heteroarylcarboxylic acids instead of just simple 2-fluoroalkyl heterocycles. The most

straightforward application was reaction of *N*-oxides of various heterocylic systems with perfluroalkenes in the presence of MeOH in DMF at 80 °C which gave α-heteroaryl perfluoropropionic methyl esters in good yields; more complex alcohols can be used as well (Scheme 8).[45]



Scheme 8

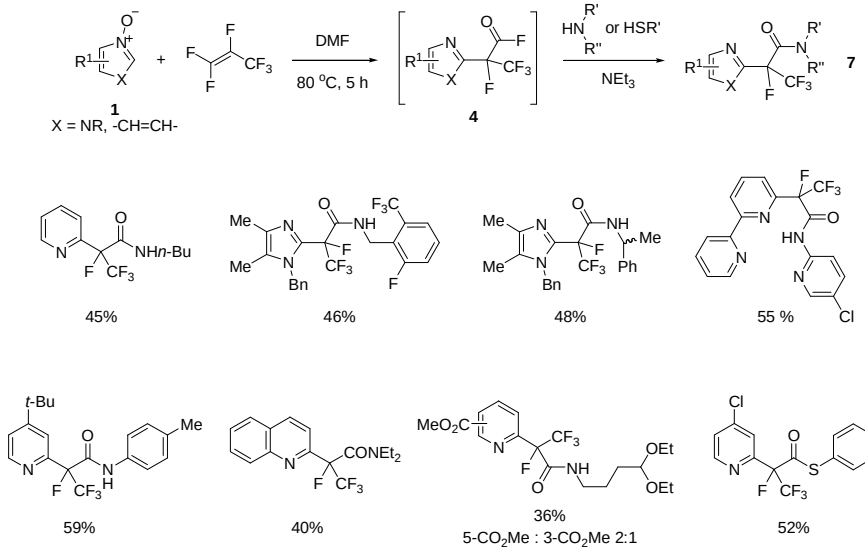
Synthesis of amides is more complicated as many amines are nucleophilic enough to react directly with electrophilic perfluoroalkenes, which leads to partial or even exclusive formation of aminoalkenes and amides without the heterocyclic unit via nucleophilic addition of amine to the double bond of perfluoroalkene, elimination of fluoride and hydrolysis.[47] The reaction of quinoline *N*-oxide with HFP and poorly nucleophilic *N*-ethylaniline in DMP at RT can be performed by mixing all the reactants already at the beginning of the reaction and the expected α-(2-quinolinyl)perfluoropropionamide is formed in good yield (76% after 24 h; Scheme 9).



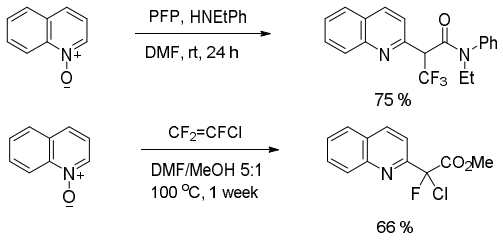
Scheme 9

Reaction of 4-*tert*-butylpyridine *N*-oxide with HFP and 4-toluidine in DMF at RT gives only a mixture of aminoalkene **8** and the product of hydrolysis, amide **9**.

On the other hand, a two-step protocol, in which *N*-oxide and HFP are first reacted in DMF to generate the acyl fluoride, and then an amine and NEt_3 are added at 0 °C, gives the expected α-heteroaryl perfluoropropionic amides in good yields. This procedure allows to obtain a broad variety of α-heteroaryl-substituted perfluoropropionic acid amides from both azines and azoles, HFP or PFP and primary and secondary amines, aliphatic and aromatic. Using a thiophenol as the quenching nucleophile provides a thioester (Scheme 10). Less electrophilic fluoroalkenes PFP and CF_2=CFCl give amides in a simple one-pot procedure (Scheme 11).



Scheme 10

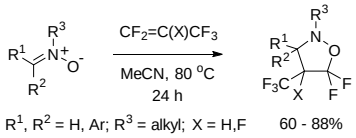


Scheme 11

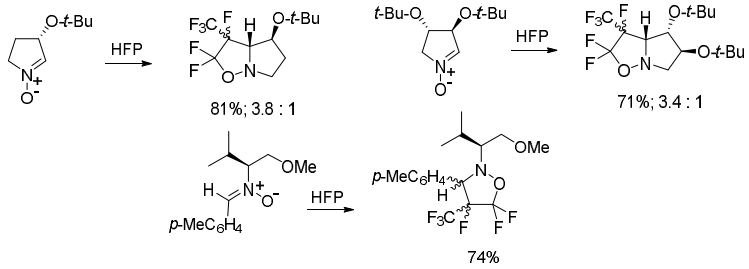
5. 1,3-Dipolar cycloaddition of perfluoroalkenes and nitrones

Dipolar cycloaddition of perfluoroisobutene and nitrones, which can be considered acyclic analogues of *N*-oxides, has been reported by Knunyants et al. in the early seventies.[48] This reaction follows a similar pathway as cycloaddition to *N*-oxides, only the initial cycloadduct, a partially fluorinated isoxazolidine, is a

stable compound and does not undergo spontaneous cleavage of N=O double bond, probably because in this case this process is not accompanied by rearomatization of a heterocyclic ring. We found that both HFP and PFP react readily with C-aromatic and aliphatic nitrones in MeCN at 80 °C, 24 h, giving 5,5-difluoro-4-trifluoromethylisoxazolidines in good yields and moderate diastereoselectivity, in most cases from 2:1 to 3:1 (Scheme 12).[49] Cyclic nitrones with a bulky *tert*-butoxy group undergo cycloaddition exclusively at the less hindered side of the ring, giving mixtures of only two out of the four possible diastereoisomers (Scheme 13).

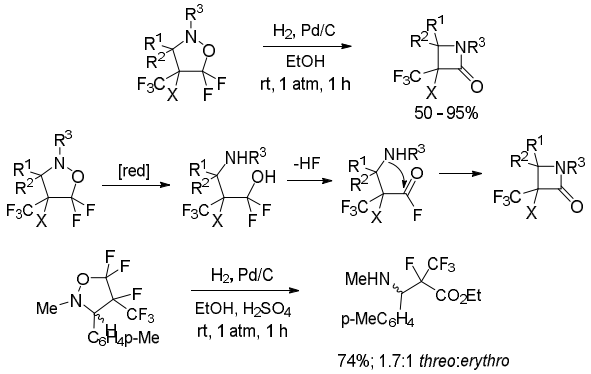


Scheme 12



Scheme 13

Attempts to deprotonate C-3 carbon (the one adjacent to nitrogen) and induce heterolytic cleavage of the N-O bond in isoxazolidines obtained from HFP and PFP failed. However, this bond can be cleaved under Pd-catalysed hydrogenation conditions to reveal an amine and α,α-difluoroalcohol function (Scheme 14).



Scheme 14

We were pleased to find that the reaction does not stop at this point as difluoroalcohol undergoes elimination of HF to an acyl fluoride, which in turn spontaneously acylates the amine nitrogen of the same molecule to provide a trifluoromethylated β-lactam. Although β-lactams have very wide and important applications in medicinal chemistry, and selective fluorination has been found to impose interesting properties on biologically relevant small molecules,[42a,50] selectively fluorinated β-lactams have been investigated only to a small extent and there are few methods of their preparation.[51] A general approach is a [2+2] Staudinger cycloaddition of fluoroalkyl-substituted ketenes and imines.[52] The method presented in Scheme 14 is fairly general and employs very mild reaction conditions (no acid or basic catalysts nor transition metals used). Considering that most isoxazolidines could be separated into diasteroisomers prior to hydrogenation step, our synthesis of CF_3-substituted β-lactams is also highly stereoselective.

Performing the hydrogenation reaction in the presence of protic acid, H_2SO_4 or HCl, prevents the formation of a β-lactam. As the amino group is protonated under these contidions, the acyl fluoride intermediate reacts with EtOH solvent to give a β-aminoacid methyl ester, rather than acylate the amine group in an intramolecular fashion (Scheme 14).[49] The intramolecular reaction is probably slow also because it involves formation of a four-membered ring, which is a disfavoured process according to the Baldwin rules.[53]

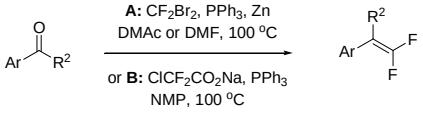
6. 1,3-Dipolar cycloaddition of *N*-oxides and 1,1-difluoroalkenes

6.1. Preparation of α-aryl-α-heteroarylacetic esters

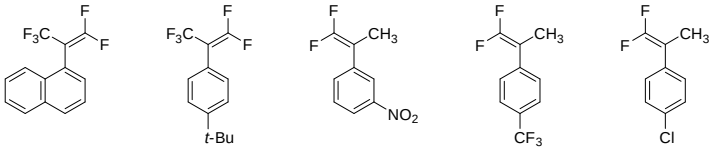
It appeared interesting to broaden further the scope of the cycloaddition of *N*-oxides and perfluoroalkenes by replacing perfluoroalkenes with terminal 1,1-difluoroalkenes. This concept was expected to allow the elaboration of a general method of functonalization of azines and azoles with aliphatic substituents of any given structure, containing an ester or amide functionality, selectively at position adjacent to nitrogen (see Scheme 1). Difluoroalkenes are currently available by many methods, primarily using Wittig[43c,54] and Julia-type[55] difluoroolefination, Pd-catalyzed reactions of difluorovinylmetal reagents[56] and many other reactions.[57]

In particular, thermal decomposition of sodium chlorodifluoacetate, which is a readily available, easy to handle and environmentally benign source of fluorine, in the presence of PPh_3 at 100 °C is a simple and efficient protocol for transforming carbonyl compounds into 1,1-difluoroalkenes, as described for the first time by Fuqua and co-workers (Scheme 15).[54a]

A reaction between imidazole *N*-oxide, 1,1-difluoro-2-(4-bromophenyl)ethene and MeOH at elevated temperature (70 °C) indeed yields α-imidazolyl-α-arylacetic acid methyl ester,[58] formation of which is expected on the basis of the mechanism analogous to that proposed earlier for cycloaddition of *N*-oxides to HFP and other perfluoroalkenes. Optimization of the conditions revealed that in this case the best results are obtained in moderately polar solvents such as THF, dioxane, AcOEt or acetone. In THF at 70 °C, several imidazole derivatives can be obtained from imidazole *N*-oxides and 1,1-difluorostyrenes of different electronic character and containing a three- or four-substituted double bond, with little or no side products (Scheme 16). The reaction is faster for electron poor styrenes, while electron rich ones react sluggishly, with pyrrole-derived difluoroalkene giving only 13% of α-imidazolyl-α-pirrolylacetamide, but 93% based on recovered starting alkene.

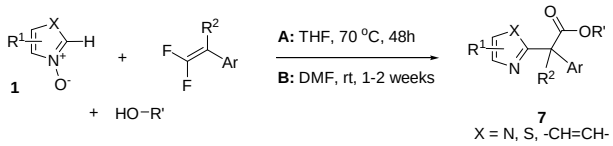


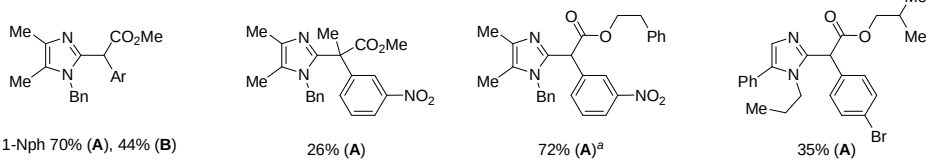
Ar = 1-naphthyl 29% (A), 61% (B); 2-naphthyl 89% (B); 4-*t*-BuC$_6$H$_4$ 70% (A), 73% (B); 4-ClC$_6$H$_4$ 34% (A); 4-BrC$_6$H$_4$ 84% (A), 65% (B); 2,3-Cl$_2$C$_6$H$_3$ 44% (A); 4-MeO$_2$CC$_6$H$_4$ 56% (A), 69% (A); 3-O$_2$NC$_6$H$_4$ 65% (B); 4-O$_2$NC$_6$H$_4$ 28% (A); 4-NCC$_6$H$_4$ 33% (A), 21% (B); 4-CF$_3$C$_6$H$_4$ 29% (B); 4-MeOC$_6$H$_4$ 49% (B); 2-thiophenyl 24% (B); *N*-MOM-2-pyrrolyl 15% (B)



58% (A) 59% (B) 46% (B) 26% (B) 19% (B)

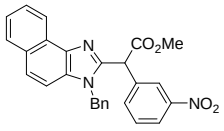
Scheme 15



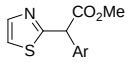


Ar = 1-Nph 70% (**A**), 44% (**B**); 4-BrC$_6$H$_4$ 72% (**A**), 47% (**B**); 2,3-Cl$_2$C$_6$H$_3$ 87% (**A**), 51% (**B**); 4-MeO$_2$C$_6$H$_4$ 50% (**A**); 3-O$_2$NC$_6$H$_4$ 65% (**A**),[a] 74% (**B**); 4-NCC$_6$H$_4$ 92% (**A**); 2-thienyl 45% (**A**); 1-MOM-2-pyrrolyl 13% (**A**)[b]

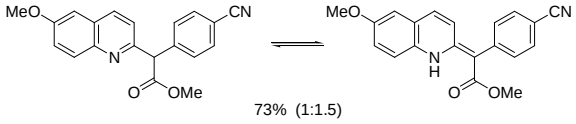
26% (**A**) 72% (**A**)[a] 35% (**A**)



91% (**A**)



Ar = 4-BrC$_6$H$_4$ 22% (**A**)[c]; 3-O$_2$NC$_6$H$_4$ 43% (**A**)[c]



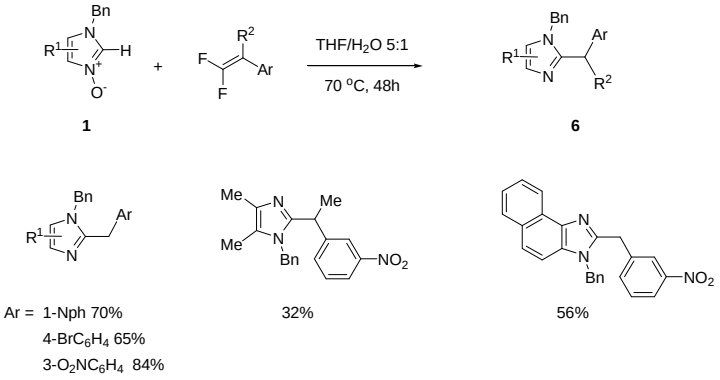
73% (1:1.5)

[a] 40 °C. [b] 93% based on recovered s.m. [c] 50 °C, 4 days

Scheme 16

The esters can be obtained from thiazole and azine oxides as well. Regrettably, aliphatic 1,1-difluoroalkenes, for example 1,1-difluoro-1-nonene, fail to react with imidazole *N*-oxides and MeOH even after 1 week at 100 °C, in DMF or THF under pressurized conditions.

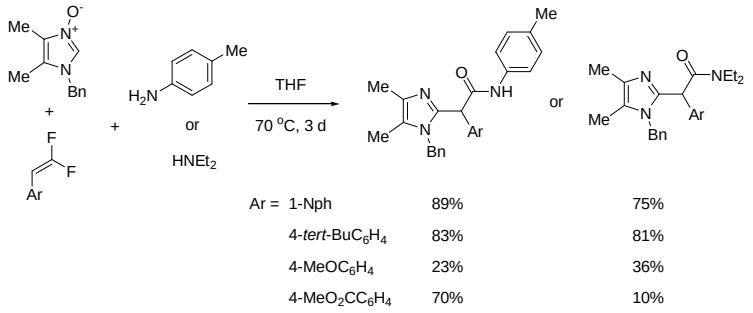
Performing the reaction in the presence of water instead of alcohol is a simple method of preparation of 2-benzylated azoles (Scheme 17).[58]



Scheme 17

6.2. Preparation of α-aryl-α-heteroarylacetamides

Dipolar cycloaddition of 1,1-difluorostyrenes and *N*-oxides is general enough to be employed for the assembly of structurally diverse amides containing an azine or azole heterocyclic unit, an aryl group, an amine part with various aliphatic or aromatic substituents, and a quarternary all-carbon centre at α position to the amide group, if the starting alkene is four-substituted.[59] As 1,1-difluorostyrenes are generally less electrophilic than HFP, it is possible to perform a three component reaction of *N*-oxide, difluorostrene and amine simply by heating all the reactants together, preferably in a moderately polar oxygen-containing solvent like THF (Scheme 18).

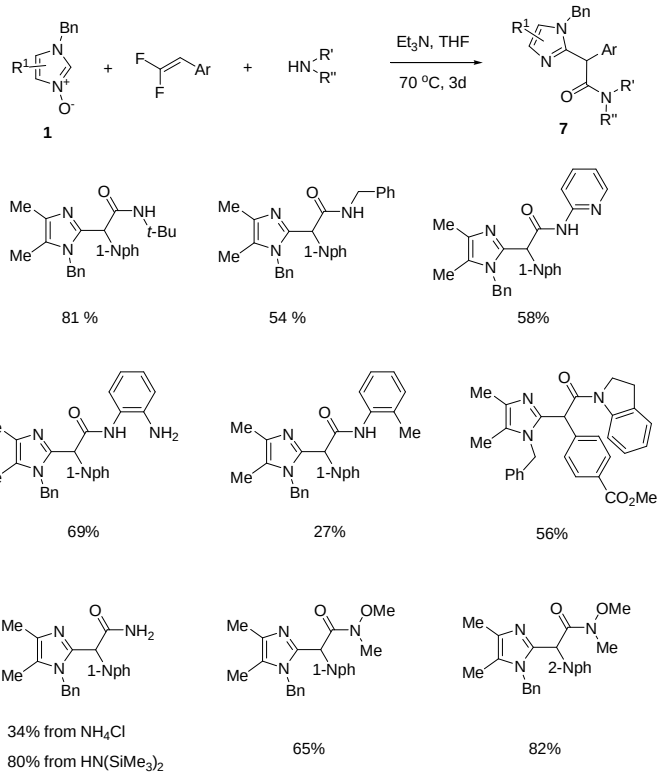


Scheme 18

Reactions of 1-benzyl-4,5-dimethylimidazole 3-oxide with 1,1-difluorostyrenes and two amines of different nucleophility, 4-toluidine and diethylamine provide expected acetamides in high yields, except for

a methoxy-substituted difluorostyrene, which displays low activity, and 4-methoxycarbonyl-substituted difluorostyrene, which is very active but tends to react directly with diethylamine, giving mainly addition-elimination products, similarly to HFP (Scheme 18).[47]

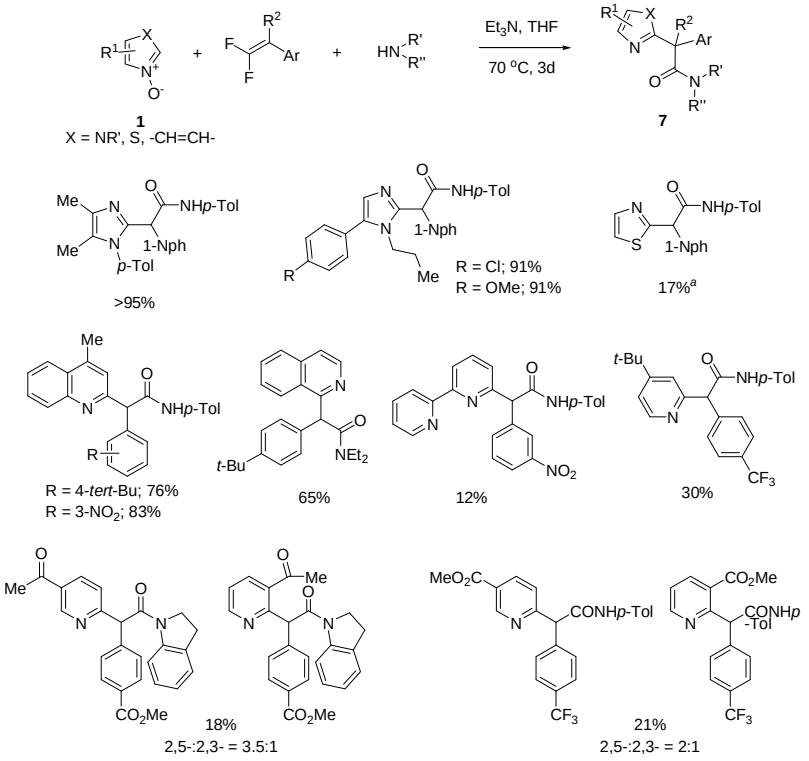
α-Heteroarylamides can be prepared for various primary and secondary amines, both aliphatic and aromatic (Scheme 19). Anilines containing an additional substituent in the *ortho* position of the ring are less active and give mixtures of amides and 2-alkylimidazoles **6**, which do not contain the amine part nor the amide functionality. On the other hand *o*-phenylenediamine gives selectively the product of acylation of only one amine group. *N*,*O*-Dimethylhydroxylamine as nucleophile provides Weinreb amides in good yields. Primary amides can be obtained using ammonium salts such as NH_4Cl with excess of triethylamine, or better hexamethyldisilazane, which gives much higher yields. The two trimethylsilyl groups bound to nitrogen are presumably cleaved by HF liberated during the reaction between *N*-oxide and difluorostyrene.[60] The reaction is readily scalable, giving high yields of α-imidazolylamides at a scale more than 20 times larger (10 mmol of 1,1-difluorostyrene). Pyrrole exhibited too low nucleophilicity to give an acylation product.



Scheme 19

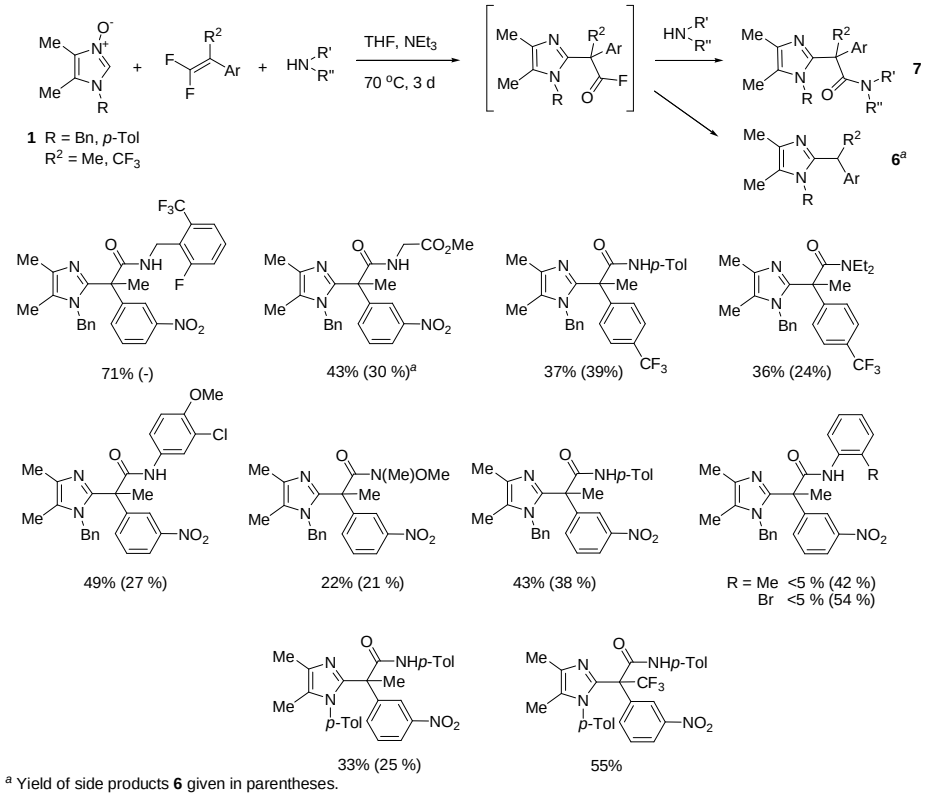
The reaction is general in terms of the heterocylic system, as *N*-oxides of quinoline and isoquinoline provide the respective α-heteroarylamides in good yields as well (Scheme 20). Reaction of thiazole *N*-oxide is less efficient due to limited stability of the oxide and the respective amide at elevated temperature. *N*-

Oxides of pyridines are much less active than their analogues containing condensed aromatic rings, as large quantities of difluorostyrenes are recovered and α-(2-pyridyl)amides are obtained only in low yields. In the reactions with 1,1-difluorostyrenes unsymmetrically substituted pyridine *N*-oxides containing an electron withdrawing substituent at C-3 position give 2,5-disubstituted isomers in preference to 2,3-substituted ones. Notably, the expected mixture of isomeric products can be obtained from 3-acetylpyridine *N*-oxide, which would be difficult to functionalize in the ring via most of the currently available synthetic methods, especially those involving strongly basic conditions, due to its acidic α-protons and a reactive carbonyl group.



Scheme 20

Efficient assembly of quaternary all-carbon centres,[61] particularly those substituted with a trifluoromethyl group,[62] is an important issue in synthetic organic chemistry. Reactions of tetrasubstituted 1,1-difluorostyrenes lead to products containing a quaternary centre at α position in moderate yields (Scheme 21).[59] These alkenes and the corresponding acyl fluoride intermediates formed after cycloaddition with *N*-oxides are much less active than it was the case with three-substituted difluorostyrenes, as elevated temperature (100 °C) is necessary to obtain good conversion, and the expected amides **7** are formed along with significant quantities of benzylated imidazoles **6**.



[a] Yield of side products **6** given in parentheses.

Scheme 21

6.3. Investigation of the mechanism

The reaction of *N*-oxides and 1,1-difluorostyrenes presumably proceeds according to the mechanism proposed earlier in Scheme 6 for simple perfluoroalkenes. The first step is either a concerted or a stepwise 1,3-dipolar cycloaddition, leading to an isoxazolidine intermediate, in analogy to isoxazolidines isolated and characterized in the reactions between HFP and PFP with nitrones.[48,49] For the reactions of *N*-oxides with dipolarophiles, both pathways are possible, depending on the structure of the reactants.[23] A stepwise cycloaddition usually results in the formation of side products, such as deoxygenated imidazoles or 2-imidazolones, when the substrate is an imidazole *N*-oxide.[35,36,63] No such products have been observed in the reactions of azine and azole *N*-oxides with 1,1-difluorostyrenes and amines or alcohols. Moreover, these reactions proceed well in solvents of various polarity, although moderately polar solvents like THF, AcOEt or acetone are the most efficient.

Finally, *N*-oxides of pyridines with an EWG at C-3 position give mainly the less sterically hindered 2,5-substituted amides (Scheme 20). This is in contrast to the recently described cycloaddition of *N*-oxides of azines with isonitriles, where the preference for 2,3-substituted products was explained by a stepwise cycloaddition mechanism and faster addition of the negatively-charged carbon atom to the ring position bearing a higher positive charge.[27] Similarly, in the reactions of the same 3-EWG-substituted *N*-oxides with

HFP the more sterically congested 2,3-substituted isomers were the major products (see Schemes 2 and 3). HFP is much more electrophilic than difluorostyrenes, which is evidenced for example by its higher activity towards amines, thus it could promote a stepwise mechanism by stabilizing the negative charge by a strong inductive effect of five β-fluorine atoms.

The above considerations suggest that the cycloaddition reaction between *N*-oxides and difluorostyrenes is close to a concerted process. Other observations are in agreement with this conclusion. Activity of *N*-oxides of various heterocycles generaly corresponds to their relative resonance stabilisation energy (imidazoles>quinolines, isoquinolines>pyridines) because cycloaddition involves dearomatization of the heteroaromatic ring. Four-substituted difluorostyrenes, both methyl- or trifluoromethyl substituted ones, react sluggishly because in the rate-determining step the two new bonds to the two carbon atoms of the double bond are formed simultaneously, instead of a nucleophilic attack of the *N*-oxide oxygen on the terminal CF_2 group. The rate of the formation of only one bond, between the *N*-oxide oxygen and the CF_2 carbon atom would be influenced by electronic factors of substituents at the $F_2C=C(R)Ar$ bond, but not by the steric hindrance of an additional substituent present at the other carbon of double bond. Finally, faster reaction observed for electron-rich *N*-oxides and electron poor 1,1-difluorostyrenes can be explained if it is controlled by HOMO of the *N*-oxide and LUMO of the alkene.

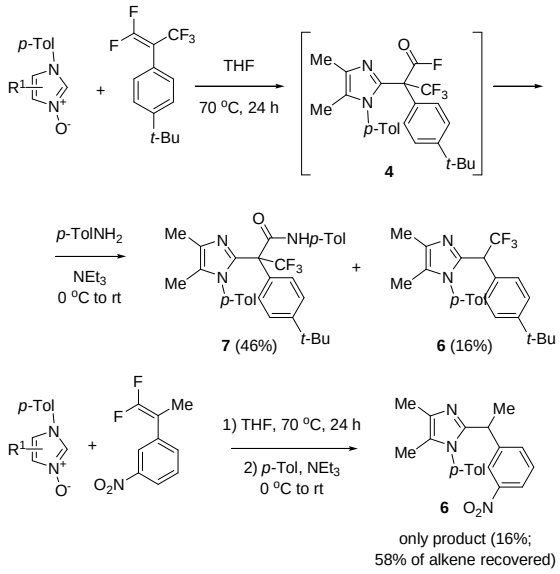
According to the mechanism illustrated in Scheme 6, cycloaddition is followed by elimination of a proton and cleavage of the weak N-O bond, which restores aromaticity of the heteroaromatic ring, leading to an α,α-difluoroalcohol. This labile intermediate can lose difluorophosgene to give a 2-benzylated azine or azole **6**, or undergo elimination of HF to give an acyl fluoride intermediate **4**. The former path of decomposition of α,α-difluoroalcohol is probably of little importance or even does not occur at all, since the amount of 2-benzylated heterocylic side products **6** which would be formed in this process depends strongly on activity of nucleophile present in the reaction mixture; with sufficiently active nucleophiles compounds **6** are not observed at all. It means that the efficiency of amide or ester formation depends on the competition between two processes available to the acyl fluoride: decomposition and reaction with nucleophile.

Lifetime of acyl fluoride intermediate seems to depend strongly on the nature of substituents at its α carbon atom. In the previously described reactions of perfluoroalkenes HFP and PFP this intermediate is sufficiently stable to perform the reaction in two steps. On the other hand, reactions of *N*-oxides with difluorostyrenes $CF_2=CHAr$ provide esters and amides only in a one-pot procedure, but a two stage protocol described earlier for perfluoroalkens does not work, giving only benzylation products **6**. In these reactions the intermediate acyl fluoride decomposes during the reaction unless it can be immediately quenched with nucleophile.

The main structural difference between acyl fluorides which are intermediates in the formation of α-aryl-α-heteroarylamides and those generated from *N*-oxides and, for example, HFP, is the presence of the bulky and strongly electron withdrawing trifluoromethyl group. Thence, the intermediate in the reaction between *N*-oxide and 2-aryl-perfluoropropene is expected to be relatively stable. This is indeed the case, as the reaction between imidazole *N*-oxide, CF_3-substituted difluorostyrene and 4-toluidine shown in Scheme 22 can be performed in two stages: first, generation of acyl fluoride (**4**) at 70 °C for 24 h, then quenching with 4-toluidine. The stability of the intermediate acyl fluoride does not depend on whether the α carbon atom is tertiary or quaternary, as a similar two step-protocol with tetrasubstituted difluorostyrene containing

Me group instead of CF_3 at the double bond produces only decarboxylated product of type **6** (Scheme 22, bottom).

Stability and structure of acyl fluoride **4** could be verified by NMR spectroscopy of the reaction mixture, when substrates from Scheme 22 were added in equimolar amounts to deuterated THF and heated to 70 °C in an NMR tube.[59] Already after 30 min the respective α-CF_3-substitured acyl fluoride was the predominating species in the solution, with only small amounts of alkene (fluoride:alkene ratio 3.3:1) and traces of decarboxylation product **6**. The presence and identity of acyl fluoride **4** was confirmed by its characteristic signals in the ^{19}F NMR (doublet of the CF_3 group at -64.01 ppm, $^4J_{FF}$=11.7 Hz, quartet of the COF fluorine atom at 43.61 ppm, $^4J_{FF}$=11.9 Hz) and ^{13}C NMR (COF carbon doublet at 156.7 ppm, $^1J_{CF}$=370.5 Hz, doublet of quartets of α-carbon at 64.6 ppm, $^2J_{CF}$=48.4 Hz, 26.4 Hz) spectra. The signals in ^1H NMR were similar to those observed for the final amide product, but they occurred at different chemical shift values. The observed signals are in good agreement with those found in the literature for aliphatic acyl fluorides,[64] particularly CF_3CH_2COF.[65]

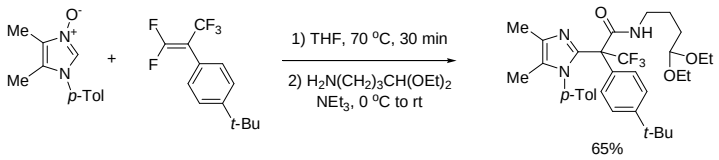


Scheme 22

Taking into account that, according to NMR measurements, conversion of substrates into fluoride **4** is nearly accomplished already after 30 min, it is possible to synthesize efficiently a sensitive amide derivative from 4-aminobutyric aldehyde diethyl acetal. The reaction gives a good yield of the expected amide, whereas a one pot protocol leads only to a complicated mixture of products (Scheme 23).[59]

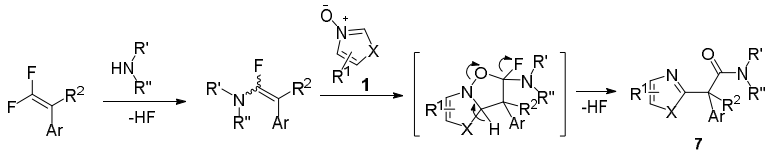
Preparation of α-heteroarylamides and esters from *N*-oxides, fluoroalkenes and amines or esters is accompanied by the formation of a new stereogenic centre. This stereocentre is formed at the cyloaddition step and it would be interesting to control its configuration, particularly if the new synthetic method is to be applied in medicinal chemistry. It could be achieved by introducing chiral substituents to either of the

reaction partners, *N*-oxide or 1,1-difluoroalkene. So far, such attempts have met with difficulties as introduction of bulky stereodiscriminating groups is deteriorating for the reaction rate and yield, but diastereoselectivity remains moderate. Some of the more promising results of this research will be reported in due course.



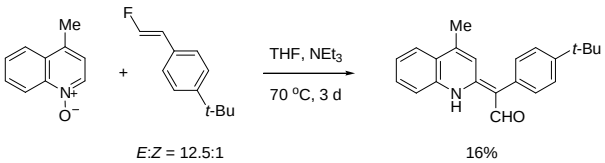
Scheme 23

An alternative mechanism for the formation of amides from *N*-oxides, difluoroalkenes and amines could be envisioned, in which amine and difluoroalkene react first according to nucleophilic addition–elimination pathway and subsequent cycloaddition of resulting aminoalkene and *N*-oxide (Scheme 24). This mechanism is improbable for a few reasons. First, all attempts to react *N*-oxides with 2-aminoperfluoropropenes performed in our laboratory failed, leading only to substrate recovery. Second, strongly electrophilic 1,1-difluorostyrenes (for example with Ar=4-$MeO_2CC_6H_4$) as well as HFP do react with amines to give 1-amino-1-fluoroaleknes and 1,1-diaminoalkenes, but these products are unreactive towards *N*-oxides; their formation appears to be rather a side process. Finally, the presence of an acyl fluoride intermediate has been in one case confirmed spectroscopically.



Scheme 24

On the basis of the mechanism depicted in Scheme 6, a reaction between monofluorostyrene and *N*-oxide is expected to give an α-aryl-α-heteroarylacetaldehyde derivative. This is indeed the case, as a reaction of 4-methylquinoline *N*-oxide and 1-fluoro-2-(4-*tert*-butylphenyl)styrene (as a 12.5:1 mixture of *E* and *Z* isomers) gives 16% of α,β-unsaturated aldehyde (Scheme 25).[59]

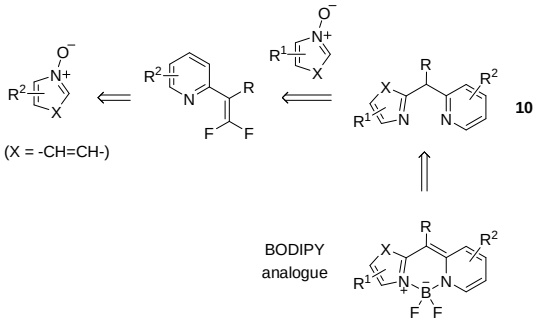


Scheme 25

This moderate yield reflects much lower activity of monofluorostyrenes compared to 1,1-difluorostyrenes, as under the same reaction conditions 1,1-difluoro-2-(4-*tert*-butylphenyl)styrene and the same *N*-oxide, in the presence of *p*-toluidine gave the appropriate α-(2-quinolinyl)acetamide in 76% yield (see Scheme 20).

7. 1,3-Dipolar cycloaddition of *N*-oxides and heteroaryl difluoroalkenes in the synthesis of bis(heteroaryl)methane ligands

The reaction between azole or azine *N*-oxides and difluoroalkenes described above introduces a new group into the hetrocyclic ring, in the position adjacent to the basic nitrogen. If this new substituent contained a carbon atom and another heterocyclic ring with an appropriately placed basic nitrogen atom, the product would have chelating properties. This would be the case if the difluoroalkene partner of the cycloaddition contained a heterocyclic ring connected directly to the double bond (Scheme 26).

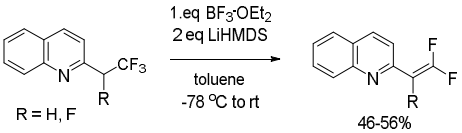


Scheme 26

The reaction would be thus a method of assembling chelating *N,N* ligands from, in principle, any two heterocyclic units. Bis(heteroaryl)methanes of the general structure **10**, in which both heterocyclic units are identical are well known and have wide applications, mainly in coordination chemistry[66] and catalysis,[67] or medicinal chemistry.[68] On the other hand, similar compounds with two different units, especially those containing both a six- and a five-membered ring, are much more rare.[69] The methods of their preparation are few and include addition of lithiated heterocycles to heteroarenecarbaldehydes and ketones[70] or some Pd-catalyzed coupling reactions.[71] Bis(pyridyl)methanes containing two pyridine rings can be also obtained by S_NAr reaction between 2-halopyridines and carbanions derived from 2-cyanomethylpyridines.[72] This method was used by Kubota and co-workers in the synthesis of a new class of BODIPY (boron dipyrromethene) analogues containing two differently substituted pyridine rings instead of pyrrole rings.[73] The complexes obtained after complexation with BF_3 exhibited promising optical properties such as larger Stokes shift and enhanced fluorescence in the solid state. A few more examples of BODIPY analogues based on unsymmetrical ligands,[74] particularly those containing pyridine units,[75] have been reported recently. We envisioned that it might be useful to elaborate a general and transition metal-free, cycloaddition-based approach to unsymmetrical bis(heteroaryl)methanes and investigate the optical properties of the respective boron fluoride complexes.

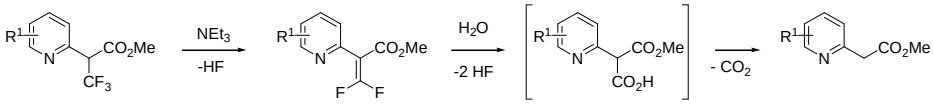
The results summarized in the previous sections suggest that the aim of obtaining various unsymmetrical bis(heteroaryl)methanes can be simply attained by employing heterocyclic analogues of 1,1-difluorostyrenes with appropriate heteroaromatic groups, for example 2-pyridyl. Unfortunately, preparation of 2-(2',2'-difluorovinyl)heteraromatic derivatives required for the cycloaddition reaction turned out to be far from straightforward. Simple methods of difluoromethylation of carbonyl compounds, such as reaction with CF_2Br_2 or $ClCF_2CO_2Na$ and PPh_3, fail for 2-pyridine carboxyaldehyde or 2-acetylpyridine due to instability of both substrates and products under the reaction conditions. 2-(2',2'-Difluorovinyl)pyridine has been accessed via Pd-catalyzed coupling reactions of difluorovinyl organometallic reagents,[56a,e] but these methods did not suit our purpose of developing a synthetic method that would be possibly general in terms of heterocyclic systems, as well as operationally simple and practical. We also preferred to avoid the use of transition metal catalysts as they would be likely difficult to remove from the final, chelating bis(heteroarylmethane).

As described in the initial sections of this Account, cycloaddition of perfluorinated alkenes and *N*-oxides is a general, mild and transition metal-free method of preparation of heteroaromatics with partially fluorinated alkyl substituents such as $CHFCF_3$ and CH_2CF_3 (see Section 3). We envisioned that elimination of HF from these compounds under basis conditions could provide an easy access to appropriate difluorovinyl heterocycles. Unfortunately, the proton in the tri- or tetrafluoroethylazines turned out not to be acidic enough for deprotonation with tertiary amines or even DBU. Careful optimization of the elimination reaction revealed that 2-(trifluorovinyl)quinoline could be obtained in moderate yield using LiHMDS and $BF_3{\cdot}OEt_2$ in toluene, and 2-(2',2'-difluorovinyl)quinoline by using LiHMDS in THF (Scheme 27).[63]



Scheme 27

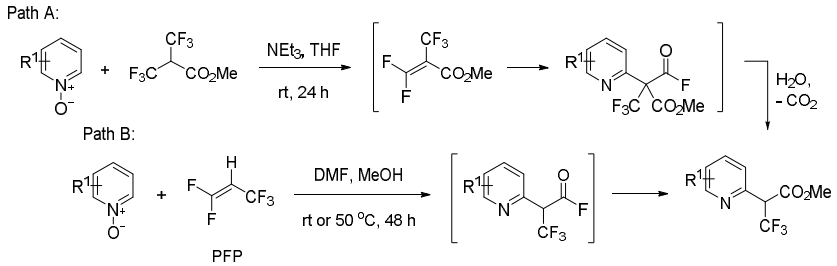
Both fluorovinyl derivatives of quinoline turned out to be moderately stable and difficult to purify, but they could be used in cycloaddition reactions with *N*-oxides of quinoline or imidazole to give the expected unsymmetrical bis(heteroaryl)methanes in low or moderate yield. However, practical difficulties of the above synthetic sequence led us to develop an improved approach. We decided to prepare heterocycles with a $CH(CF_3)CO_2Me$ substituent at C-2, in which acidity of the α proton would be enhanced by the presence of the ester group.[63] Deprotonation and subsequent elimination of fluoride was expected to occur in the presence of a weak base such as NEt_3 and provide electron-poor difluoroacrylates **11** (Scheme 28).



11

Scheme 28

The required derivatives with a $CH(CF_3)CO_2Me$ group can be accessed from *N*-oxides via two different variants of dipolar cycloaddition of an *N*-oxide to a fluoroalkene: (i) reaction with PFP, in which the acyl fluoride intermediate is intercepted with MeOH, (ii) reaction with methyl perfluorometacrylate, in which hydrolysis and decarboxylation of acyl fluoride intermediate removes the redundant carbon atom (Scheme 29). The latter approach is more efficient in terms of yields and from the practical point of view as perfluorometacrylate is generated in situ from 2H-perfluoroisobutyric methyl ester, a compound which is liquid and readily available. PFP used in the former method is gaseous and considerably more expensive. Unfortunately, both approaches failed to provide derivatives of imidazole with a $CH(CF_3)CO_2Me$ group at C-2. Elimination of HF from azines bearing the $CH(CF_3)CO_2Me$ group is facile, but the resulting difluoroacrylates **11** are impossible to isolate after standard aqueous work-up as they undergo immediate nucleophilic addition of water to the terminal CF_2 group, followed by its hydrolysis to a carboxy group and decarboxylation (Scheme 29).



4-methylquinoline *N*-oxide	36% (A), 82% (B)	R^1 = 3-CO_2Me	23% (A)
isoquinoline *N*-oxide	42% (A)	R^2 = 4-Cl	36% (A)
6-methoxyquinoline *N*-oxide	51% (A), 71% (B)		

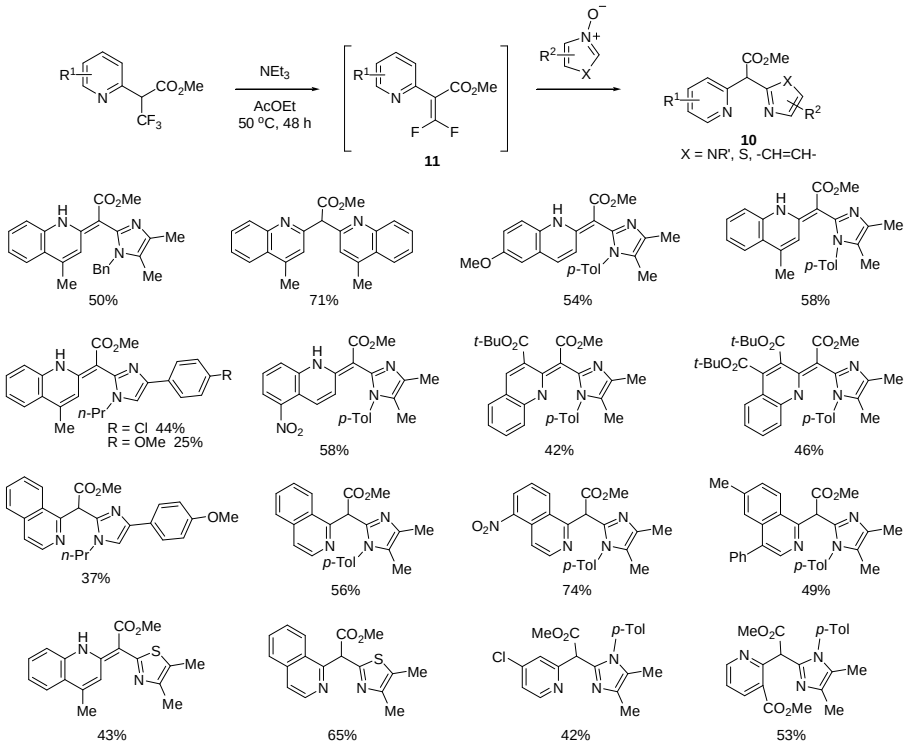
Scheme 29

However, this was not a serious obstacle as **11** could be generated in situ in the presence of *N*-oxides. Under optimized conditions (dry AcOEt, NEt_3, 50 °C) we were able to obtain in moderate yields various bis(heteroaryl)acetic acid methyl esters containing substituted azine and azole rings connected to the central "meso" carbon (Scheme 30).[63]

In the syntheses of the products depicted in Scheme 30 and employing imidazole *N*-oxides the respective deoxygenated imidazoles were formed as side products. It suggests that, unlike cycloaddition reactions with difluorostyrenes, cycloaddition of *N*-oxides to strongly electrophilic 2-heteroarylacrylates might be a stepwise cycloaddition, and the adduct formed after nucleophilic attack of the *N*-oxide oxygen atom might undergo unwanted side reactions apart from the desired cyclisation to an isoxazolidine intermediate.

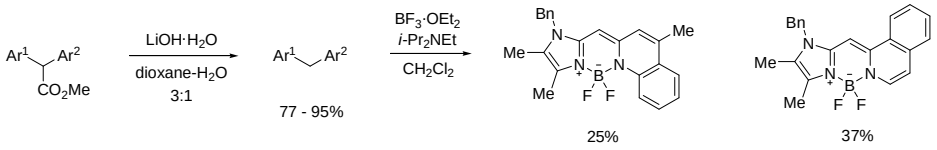
The products in Scheme 30 containing a quinoline or pyridine ring exist largely or exclusively as tautomers with an exocyclic double bond between the meso carbon and the azine ring and a proton attached to the azine nitrogen. The ratio of tautomers reflects relative resonance stabilisation energy of different heteroaromatic rings. Such NH tautomers are presumably stabilised by an intramolecular hydrogen bond between N-H and CO_2Me groups, as well as conjugation with the ester group. In contrast to compounds with

an sp^3 meso carbon, they are coloured (yellow or orange) and possess bands in the visible light region of their UV-Vis spectra.



Scheme 30

Attempts of complexating some of bis(heteroaryl)acetic acid esters with boron trifluoride lead to complicated mixtures of products, because of concomitant deesterification and decarboxylation induced by BF_3, and probably also concurrent formation of complexes in which boron is complexed to an oxygen atom of CO_2Me and one of nitrogen atoms. However, methoxycarbonyl group can be readily removed in a controlled manner using $LiOH \cdot H_2O$. The resultant bis(heteroarylmethanes) smoothly undergo complexation with BF_3 to give the respective complexes which can be considered BODIPY analogues with an azole and azine. The complexes of in Scheme 31 have limited chemical stability, but they exhibit strong fluorescence excited by 365 nm UV irradiation.



Scheme 31

8. Conclusions

1,3-Dipolar cycloaddition of azine and azole *N*-oxides and terminal difluoroalkenes (perfluoroalkenes, 1,1-difluoro- and 1-monofluorostyrenes) is a fairly general and practical method of selective functionalisation of C-2 position of heteroaromatic ring. Under mild and transition metal-free conditions it provides heterocycles with complex, partially fluorinated substituents in the ring, or structurally diverse derivatives of α-heteroaryl carboxylic acids, including those with all-carbon quaternary centres. However, further work is necessary to elaborate an efficient diastereoselective version of the reaction. The mechanistic proposal for the reaction has been confirmed by spectroscopic characterisation of the key intermediate, an α-heteroaryl acyl fluoride. Cycloaddition of fluoroalkenes to nitrones, following a slightly different pathway, allows to prepare α-trifluoromethyl β-lactams. Cycloaddition of highly active and electrophilic, in situ generated heteroaryl-substituted difluoroacrylates is a versatile synthetic method of assembling various five- and six-membered heterocyclic systems into unsymmetrical *N,N* ligands with potential use in coordination chemistry or search for fluorescence dyes with novel molecular architecture.

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