Chemistry of *N*-fluoropyridinium salts

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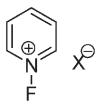
This *tutorial review* deals with developments in the chemistry of *N*-fluoropyridinium salts in the past decade, including both synthetic and mechanistic aspects. Three distinct types of transformations including: i) fluorination reactions, ii) carbenoid behavior and iii) *cine*-/*tele*-substitution involving *N*-fluoropyridinium cation are exemplified. Procedures for fluorination of carbanions and benzenoid aromatics along with hetarylation processes yielding 2- and 4-substituted pyridines are referenced. Several new discoveries in the area, including three-component condensation reactions of *in situ* generated *N*-fluoropyridinium fluoride are described.

Introduction

In our search for a convenient and manageable "electrophilic" fluorinating agent, we stumbled upon two observations by Simons[1] and Meinert[2] who reported the reaction of molecular F_2 with pyridine in $CFCl_3$ at temperatures <-70 °C to yield a white suspension. Its analysis revealed an apparent 1 : 1 ratio of Py/F_2 (contrary to the bis-coordinated complexes of pyridine with other halogens) in the complex. This led the authors to assign it a $[PyF]^+F^-$ structure. Later on, the existence of both i) the N–F bond and ii) quaternary positively charged N atom were confirmed by several independent analytical techniques. At the time, neither author attempted to use the product **1a** for fluorination. The suspension of an intermediate *N*-fluoropyridinium fluoride **1a** decomposed upon warming to afford 2-fluoro- and 2-chloropyridines. Several teams reported similar observations and exploited this "hetarylation" step further.[3,4] Umemoto's team in Japan was successful in tackling the stability problem of **1a**. Namely, they developed an elegant protocol for the *in situ* conversion of the fluoride **1a** into the respective BF_4 or OTf salts **1b** and **1c** based on anion exchange with a Lewis acid, a Brønsted acid, or the alkali metal salt of an acid.[5,6]



1a, X = F
1b, X = BF4
1c, X = OTf

Several alternatives including treatment of **1a** with $BF_3{\cdot}OEt_2$ or a direct reaction of F_2 with *N*-(TMS)pyridinium triflate have been introduced.[6] "Nucleofugic" counterions stabilize **1** resulting in highly crystalline materials with melting points >180 °C. Several zwitterionic *N*-fluorinated pyridines have been reported as well.[7]

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Physical properties and stability

N-Fluoropyridinium salts including **1b,c** are stable under anhydrous conditions. Dried solvents, including CH_2Cl_2, THF and MeCN were found to be the optimal media for conducting chemistries of **1**. In general, respective triflates are soluble in organic solvents providing better reaction control and enhanced yields of the target products. In our hands, all salts **1** with ClO_4^- counterion were shock and temperature sensitive leading to a violent decomposition if handled improperly. DMSO, DMF and NMP caused decomposition of **1b** to yield 2-pyridone as a major product. Salt **1c** was reported to have a half-life of 13 days in D_2O.[6]

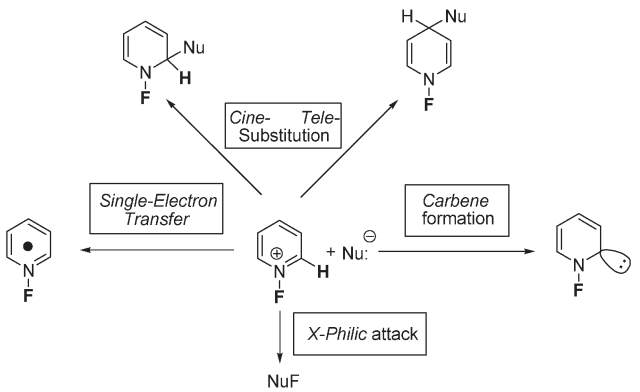
Consistent with its molecular structure, salts **1** are strong oxidizing agents. Namely, they promote I^-/I_2 conversion. This protocol was used synthetically for the selective introduction of *in situ* generated "electrophilic" iodine at the α-carbonyl position in various aryl alkyl ketones.[8] Electrochemical studies of the *N*-fluoropyridinium cation revealed that, as opposed to the respective *N*-alkyl pyridinium salt, its reduction is irreversible resulting in decomposition.[9]

A crystal structure of **1c** was described. Notably, the N–F bond length is 1.357Å, suggesting strong back donation of

p-electrons of the fluorine atom to the nitrogen of the ring.[10] The F^+ detachment energy values of *N*-fluoropyridinium salts were determined using functional B3LYP hybrid level theory. The calculated value of 266 kcal mol^{-1} suggest that the pure electrophilic nature of fluorination with *N*-fluoropyridinium salts is an unlikely event.[11]

Reactivity: general outlook

In addition to their potential as a fluorinating agents, *N*-fluoropyridinium salts display several alternative reactivity pathways.[3,4] These include i) single-electron transfer (SET), ii) nucleophilic aromatic *cine-*/*tele-* substitution and iii) base-induced 2-proton abstraction and formation of a tentative "carbene" intermediate. SET pathway has been introduced as an alternative to the "X-philic attack"[12] at the fluorine atom suggested earlier to rationalize the results of "electrophilic" fluorination.[4] Nucleophilic aromatic *cine-*/*tele*-substitution reaction, when the position bearing a leaving/nucleofugal group and the position of a new substituent in the product are nonadjacent, has been proposed to explain the "aberrant" behavior of carbanions derived from nitroalkanes in their reactions with **1**.[4] Acidity of a proton at C2 may be responsible for a base-induced conversion of **1** into the respective carbene intermediate.[4]



Evidence accumulated to date suggests that i) the course of the reaction is determined by the nature of both the nucleophile and **1**, in addition, ii) the majority of reactivities of **1** could be rationalized in terms of several simultaneous mechanisms. Despite of the high reactivity of *N*-fluoropyridinium salts, there are numerous synthetically useful transformations allowing for both selective fluorination and hetarylation of substrates. In this review, we will focus on recent practical developments since the last comprehensive treatise on the subject.[4]

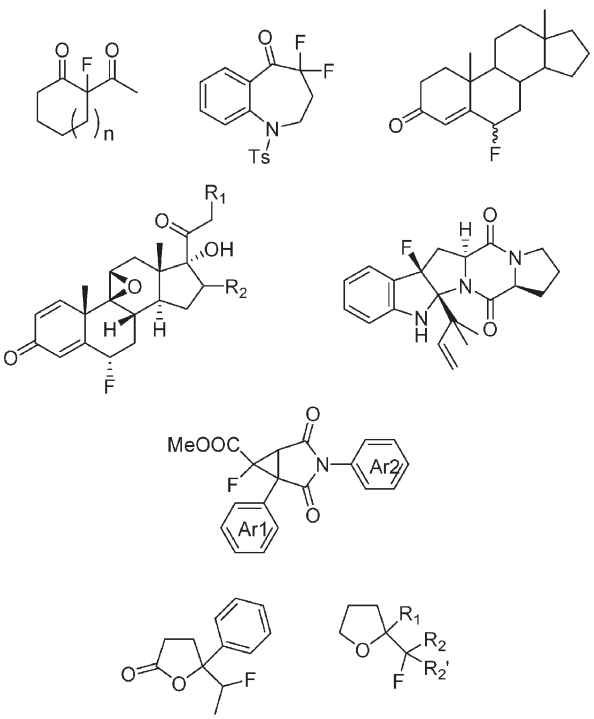
Fluorination reactions

In the past decade, several improvements to the fluorinating potential of *N*-fluoropyridinium salts have been performed. These are mainly directed towards i) eliminating "side" reactions involving inclusion of the pyridine ring into final products and ii) enhancing yield/specificity of a fluorination step. However, trends suggest that although *N*-fluoropyridinium salts are still useful, they are gradually replaced by more effective and specific agents based on the diazabicyclooctane moiety. For example, the relative fluorinating power of Selectfluor™ (1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) in a reaction with $EtCOCHMeCO_2Bn$ was determined to be 100 fold faster than that for **1b**.[13]

Perhaps the most widely used "second generation" fluorinating agents based on the *N*-fluoropyridinium moiety include i) *N*,*N*′-Difluoro-2,2′-bipyridinium bis(tetrafluoroborate) (MEC-31) and related bis-pyridine derivatives;[14] ii) zwitterionic *N*-fluoropyridinium sulfates[7] and iii) 2,6-disubstituted *N*-fluoropyridinium salts.[15]

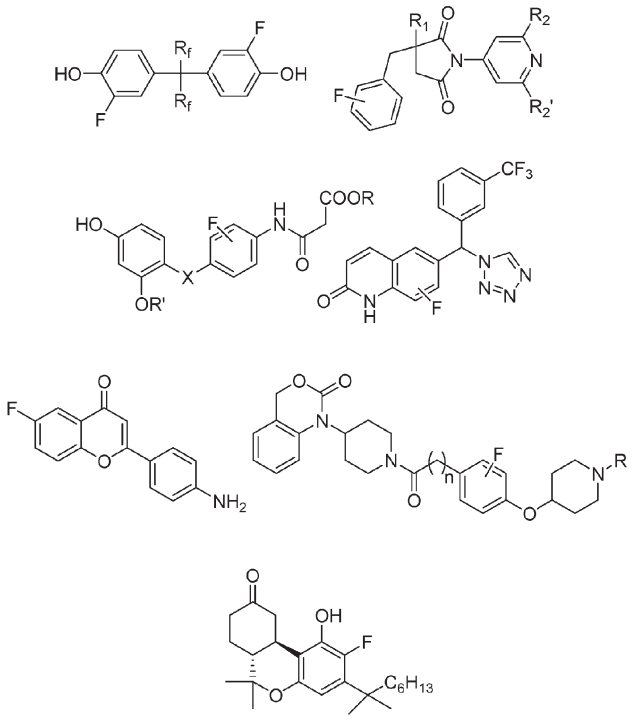
MEC-31 is a highly reactive electrophilic fluorinating agent with the highest effective fluorine content (103.3 g kg^{-1}) in its class. The fluorinating capability for these species decreased in the order 2,2′- ≫ 2,4′- > 3,3′- ≈ 4,4′-isomer ≫ **1**. Notably, both *N*-F moieties in a molecule are effective for fluorination. This fluorination occurs in a step-by-step manner. The reactivity differences between the first and second fluorinations are insignificant. In the model study, fluorination of 2-naphthol in liquid supercritical CO_2 with MEC-31 in the presence of catalytic NaOTf yielded 1-fluoro-β-naphthol in 99% yield.[14] Application of *N*-fluoro-5-(trifluoromethyl)-pyridinium 2-sulfonate under reflux for the same conversion has been described (85% yield).[7]

N-Fluoro-2,6-dichloropyridinium salts along with several alternative agents were effective "fluorine-transfer" reagents in the preparation of *N*-fluoroammonium salts of the *Cinchona* alkaloids.[16] The latter were subsequently employed in the construction of stereogenic fluorinated carbon centers with good yield and *ee* as high as 81%.



Further elaborations on fluorination of steroids with **1** have been described. For example, **1** were used in the synthesis of 17α-hydroxy-4-halogenated equilenin derivatives.[17] Fluorination-cyclization cascade triggered by **1c** was used in a stereospecific synthesis of gypsetin and brevianamide E isosteres from the derivatives of tryptophan.[18] Fluorination of

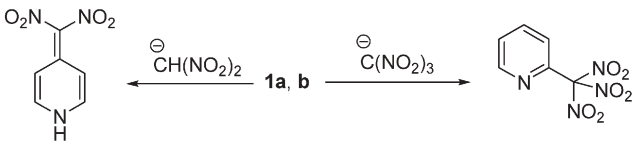
CH-acids based on cyclopropane with **1c** afforded mixtures of the respective *exo* and *endo* 6-fluoro isomers.[19] Reaction of **1** with alkenylcarboxylic acids with **1** yielded fluorinated lactones in good yields and diastereospecificity (*ca.* 85%).[20] Selected examples of products resulting from the reactions of **1** with diverse organic substrates are presented (see previous page).



Application of **1** to the synthesis of physiologically active fluorinated substances has been reported. Selected examples include synthesis of factor Xa inhibitors,[21] tubulysin,[22] and carboxypeptidase U inhibitors.[23] Additional examples of electrophilic fluorination of activated aromatics are summarized (see above).

Reactions mediated by *N*-fluoropyridinium salts

1. Nucleophilic aromatic *cine-ltele*-substitution. Our interest in *N*-fluoropyridinium salts took us away from the "traditional" fluorination routine, initially not by choice. In our hands, reactions of both **1a** and **1b** with $CH(NO_2)_2^-$ yielded a 4-substituted dinitromethyl pyridine derivative, instead of the expected fluoro dinitromethane. Similar regiospecificity was observed for $^-CH(NO_2)COOEt$. Interestingly, reaction of **1b** with $C(NO_2)_3^-$ resulted in the exclusive formation of the respective 2-pyridyl derivative. A similar substitution pattern was observed for the reaction of **1b** with $^-CH_2NO_2$, however the desired product of nitromethane addition to pyridine was isolated only in 21% yield. Products of carbanion fluorination, again were not detected in the reaction mixtures.[4]

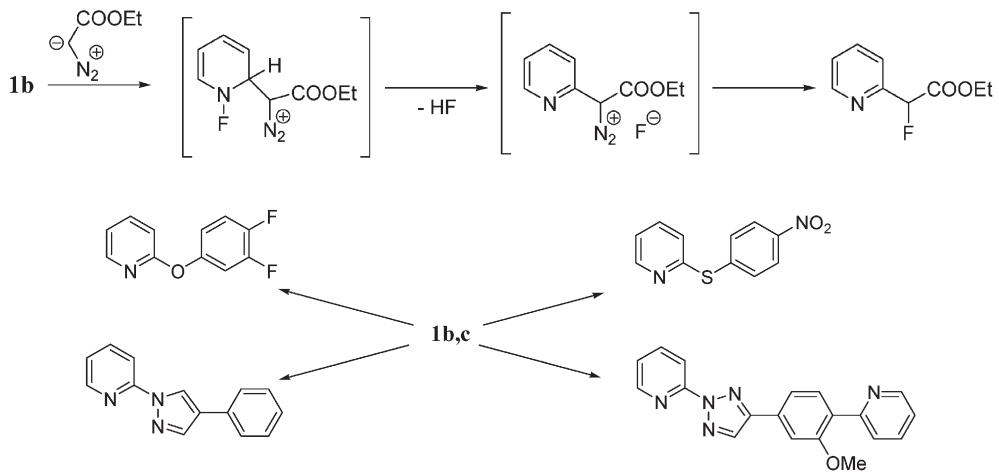


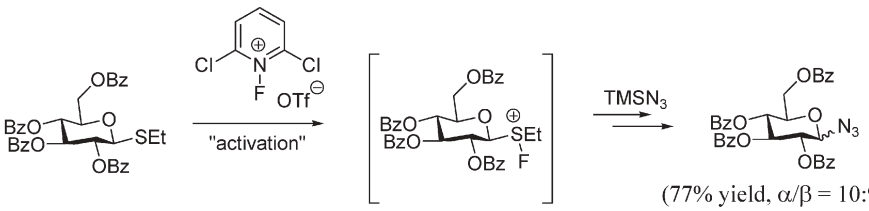
A synthetic potential of these "side-reactions" led us to believe that the *N*-fluoropyridinium cation could serve as a "hetarylating" agent for a series of nucleophiles. For example, reaction of **1b** with anions derived from stabilized diaza derivatives yielded the respective α-fluoroacetyl derivatives of pyridine. The proposed reaction mechanism involves a *cine*-substitution step followed by the nucleophilic displacement of diaza group with F^-.[4]

We have shown that diverse phenolates and anions derived from NH heterocycles react with **1b** in a similar fashion to yield the respective 2-substituted pyridines.[24] A recent application of this protocol to the synthesis of mGluR5 inhibitors based on the 2-triazolopyridine core has been reported.[25]

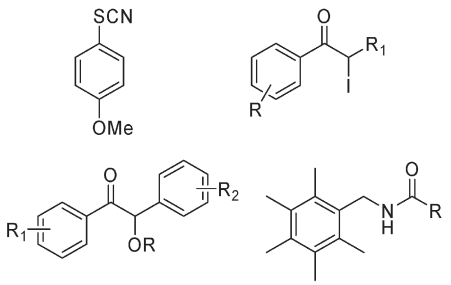
2. Homolytic reactions of *N*-fluoropyridinium salts. Electrophilic equivalents of Cl^+, Br^+, SCN^+, and NO_2^+ were generated from the respective salt NaX and **1** or Selectfluor™ in MeCN at RT. The reaction of the generated electrophiles with electron-rich aromatics such as phenol, aniline, toluene, 4-methoxyacetophenone, and 1,4-dimethoxybenzene give mixtures of the respective regioisomeric chloro, bromo, thiocyanato and nitro compounds in high yield.[26]

N-Fluoropyridinium triflates including **1c** were described as "activating" agents in transforming thioglycoside into *O*-glycoside, glycosyl azide and sulfoxide. The electronic nature of the substituents on the pyridine ring could reportedly control their ability to activate thioglycosides.[27]



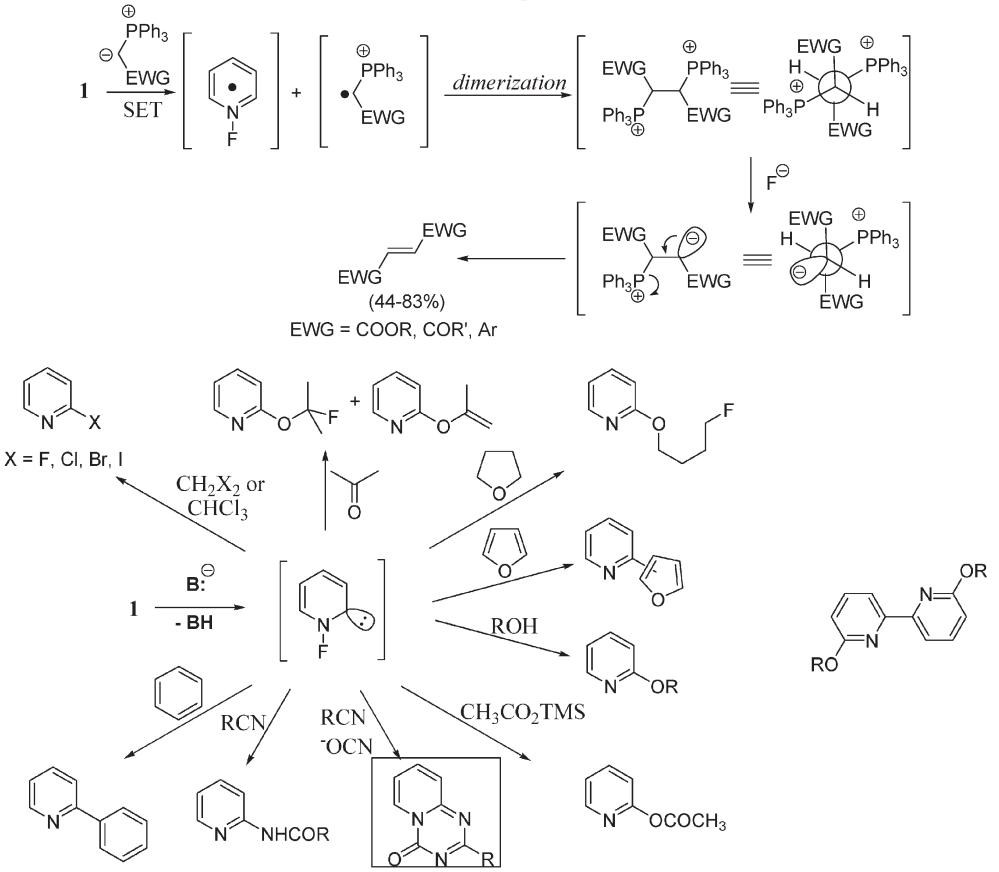


Direct introduction of alkoxy-, amino-, azido- or halogeno-functional groups in the benzylic position of hexamethylbenzene was mediated by **1** in the presence of alcohols, carboxylic acids, cyanides or trimethylsilyl derivatives as sources of an external nucleophile.[28] Under neat conditions, reactions of *trans*-stilbene with fluorinated alcohols in the presence of MEC-31, gave the respective α-keto ethers and benzil in moderate to good yields.[29] Selected examples of the described products are summarized below.



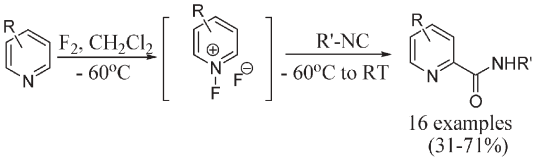
Interaction of **1b** with sulfur anions stabilized with electron-withdrawing groups furnished the expected 2-substituted pyridines in moderate to good yields.[24] Under the same conditions, non-stabilized sulfur anions, thiols and sulfides afforded products of dimerization and dithioacetals. The reaction pathway correlated well with the electronic character of the sulfur nucleophile. Furthermore, hydrolysis of dithioacetals including 1,3-dithianes and 1,3-dithiolanes mediated by *N*-fluoropyridinium salts furnished the parent carbonyl compounds (72–86% isolated yields).[4] Reaction of **1** with Wittig reagents containing electron-withdrawing groups (EWG) in wet THF afforded *trans*-olefins (47–83% isolated yields).[30] An SET mechanism was suggested for this as well as for other reactions of **1** with good electron donors including selected carbanions, sulfur and phosphorus nucleophiles. Additional mechanistic considerations on the SET reactions of **1** are available.[4]

3. Carbene-mediated reactions of *N*-fluoropyridinium salts. Fluoride **1a** was reported to decompose violently at temperatures >-2 °C to yield 2-fluoropyridine as the main product.[2] Similarly, reaction of **1c** with a base in CH_2Cl_2 gave 2-chloropyridine as the major product along with 2-pyridyl triflate and 2-fluoropyridine, regardless of the nature of the base. These base-initiated reactions were also shown to take place similarly in other halogenated alkanes, ethers, nitrile,



aromatics, ketone, vinyl ethers, alcohols and TMS acetate as solvents to give pyridine derivatives substituted with a solvent molecule at the 2-position. The outcome was explained by a singlet carbene produced through proton abstraction of *N*-substituted pyridinium salts (see below). The *ab initio* MO calculations revealed the structure and properties of the labile deprotonated *N*-fluoropyridinium cation and supported the carbene intermediate reaction mechanism rather than a pyridyl cation mechanism.[31] Recently, similar reactions of MEC-31 with base in ROH as solvents to yield the respective6,6′-alkoxy- and 6,6′-perfluoralkoxy bis-pyridines was reported.[32]

To further elaborate on this chemistry, we decided to utilize *N*-fluoropyridinium fluorides, including **1a** as a convenient "one-pot" source of the postulated carbene species. We reasoned that with proper selection of reagents and conditions one could harness their high reactivity to lead to additional useful chemistries unrelated to fluorination. An earlier application of this strategy to the synthesis of 2-susbstituted pyridines by the reaction of **1a** with trimethylsilyl derivatives was reported by us.[4] Reactions of **1a** with isonitriles yielded the respective 2-pyridilcarboxamides in good yields (31–71%).[33]



Reactions with cyclohexyl- and *p*-nitrophenyl isocyanides were most practical as they both i) afforded the highest yields and ii) allowed for the easy isolation of the desired products by crystallization. Both weak electron donating- and withdrawing groups in pyridine enhanced yields of the desired products. Consistent with this reactivity pattern was the formation of the respective 2-quinoline (shown below) and 1-isoquinoline derivatives upon treatment of quinoline and isoquinoline with a F_2/RNC system as described above (47% and 41% yields respectively).

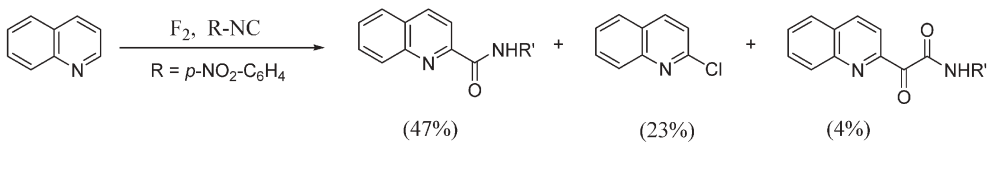
The postulated intermediacy of the carbene was in agreement with the lack of formation of the respective carboxamide derivative in an attempted reaction of 2,6-dimethylpyridine under the described conditions.

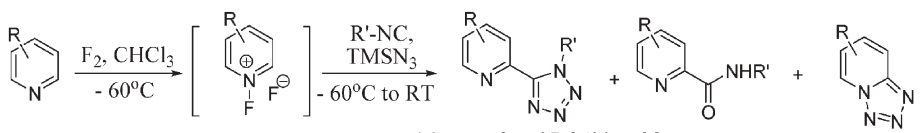
To further expand the synthetic potential of **1a**, we attempted a three-component reaction of the postulated carbene intermediate. This idea was based on an earlier observation that the reaction of **1** with a $^{-}$OCN/RCN system furnished pyridotriazines (*vide supra*).[4] One-pot reactions of *N*-fluoropyridinium fluorides generated *in situ* with isonitriles in the presence of $TMSN_3$ yielded tetrazol-5-yl pyridines in 37–84% yields.[34] Small amounts of 2-picolinamides (8–27% yields) and tetrazolo[1,5-*a*]pyridines (7–10% yields) were also isolated from the reaction mixtures.

The outcome of this conversion was explained by the reaction of the carbene intermediate with isonitrile to afford the respective isonitrilium ylid. This ylid undergoes subsequent reaction with *in situ* generated azide anion to yield the observed products. In a similar fashion, *N*-fluoropyridinium fluorides afforded respective 2-acetamidopyridines when reacted with MeCN. This reaction thus provides a practical alternative to the Chichibabin amination. Mechanisms for both conversions described above are shown.[4]

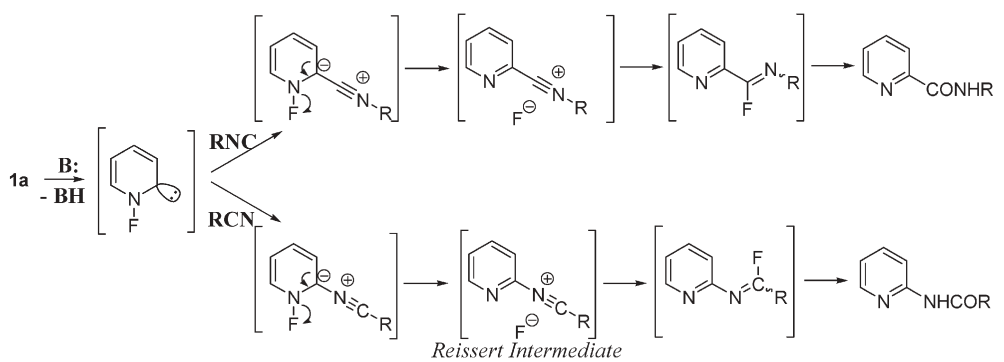
A one-pot reaction of **1c** with isonitriles in RCN media in the presence of $NaBH(OAc)_3$ used as both a base and a reducing agent yielded imidazo[1,2-*a*]pyridin-3-amines in 44–73% yields.[35]

Currently, we are in the process of expanding the synthetic utility of these three-component reactions. A series of 1,3-dipoles, including *in situ* generated nitrile oxides,





16 examples, 37-84% yield



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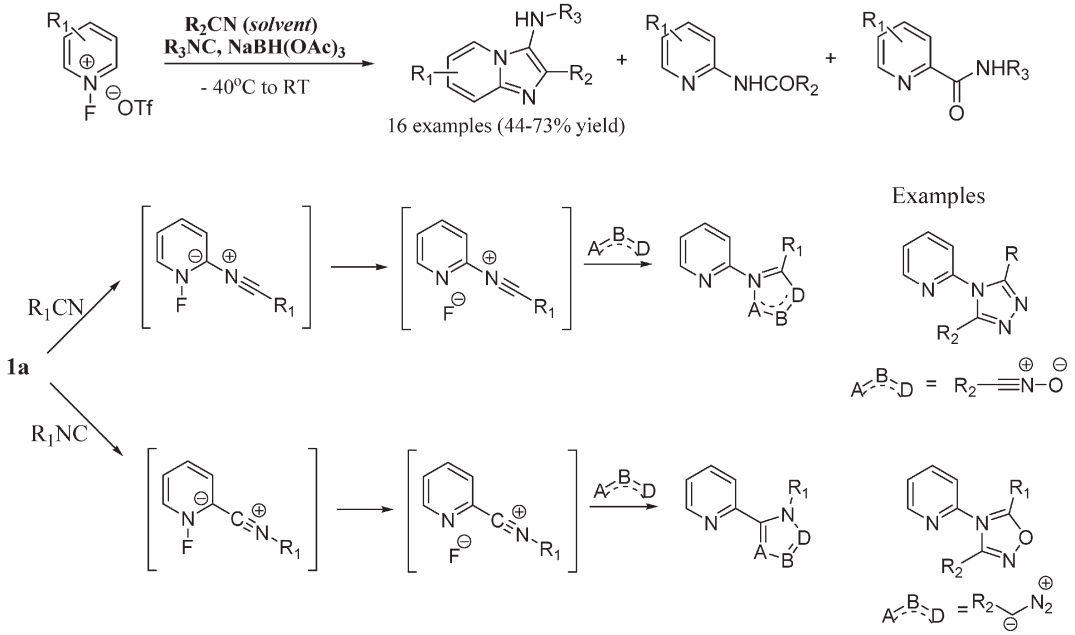
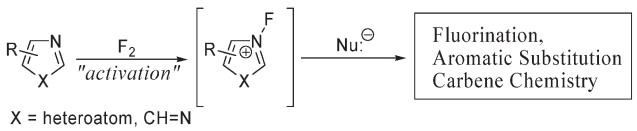


diazomethane derivatives, *etc.* are to be reacted with the system **1a**/nitrile or **1a**/isonitrile. Based on our earlier observations, we expect to arrive at 2-pyridine derivatives modified with five-membered heterocycles.

Perspectives

Despite of the considerable success in developing chemistries of the *N*-fluoropyridinium salts, the potential of **1** as hetarylating agents is largely unexplored. One of the key challenges to be addressed is the general approach to fluorine-mediated activation of heteroaromatics containing a pyridine-type nitrogen towards nucleophilic attack.



Mixtures of molecular F_2 with inert gas are safe to handle. This, along with the availability of diverse heterocyclic substrates and simplicity of the experimental protocol (a quick ''go/no go'' answer based on the observation of the respective *N*-fluoroaromatic species) are attractive features of the strategy. It was proven to be successful for quinoline, isoquinoline and several additional aromatic systems.[4] However, the careful balance of reagents' nature, ratio and reaction conditions is still a challenge, especially considering the high reactivity of both the F_2 gas and the intermediate N–F species.

Numerous mechanistic questions remain to be answered, especially those concerning the unequivocal evidence for the existence of carbene *vs* cation intermediate in the base-induced transformations of **1**. Although mounting evidence suggests that the former pathway is prevailing, there are facts testifying for the importance of the latter under specific reaction conditions.[4] In addition, detailed computational analysis and classification of reactivity for salts **1** is past due. It would be of use to identify key descriptors defining a reaction pathway(s) based on the nature of both **1** and nucleophile.

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