Chemistry of the Anionically Activated Aromatic CF_3 Group

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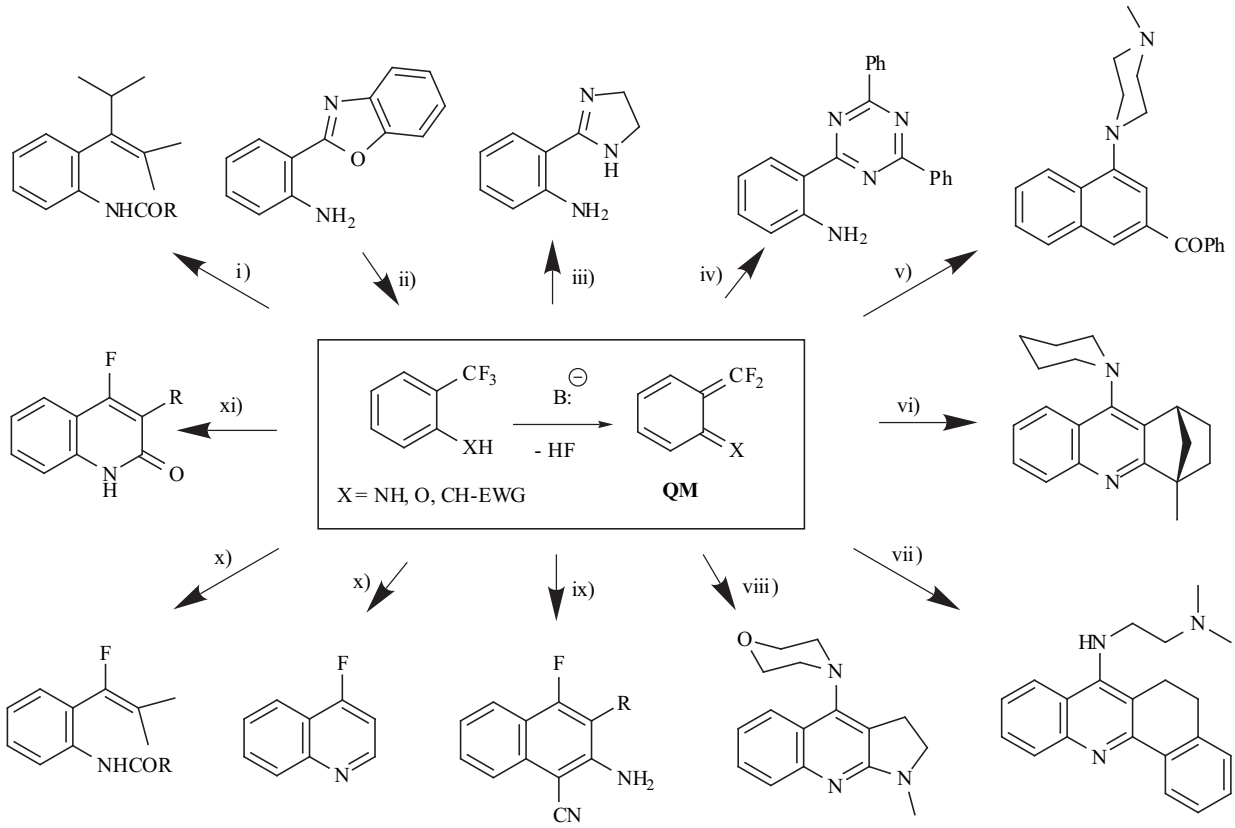
Abstract: Various chemistries could be accessed from the aromatic substrates containing CF_3 functionality that is conjugated with the ionizable NH, OH or CH groups. The suggested mechanism involves formation of the quinone methide intermediate. It is generally accepted that these reactive species can be viewed as either C_1 or C_3X (X = N or CH_2) synthone. Their reactions *in situ* with diverse electrophiles yield an array of [6,6]-fused or 5-membered aromatic heterocycles.

Keywords: Trifluoromethyl group, quinone methide, fluorinated aromatics.

INTRODUCTION

The anionically activated trifluoromethyl (CF_3) group has attracted considerable interest due to its synthetic utility. A variety of aromatic and heteroaromatic molecules could be accessed from the commercially available substrates containing CF_3 functionality that is conjugated with the ionizable NH, OH or CH groups (Scheme **1**) [1,2].



Scheme 1.

These include 2-(substituted 1-alkenyl) anilines (i), 2-substituted benzothiazoles and benzoxazoles (ii), 4(5)-dihydro-1*H*-imidazole (iii), triazines (iv), and isoxazoles, 1,3-disubstituted naphthalenes (v), 2,4-di- or 2,3,4-trisubstituted quinolines (vi), 7-(substituted amino)-5,6-dihydrobenz[c] acridines (vii). Both synthetic details and scope of relevant transformations prior to 1996 have been reviewed [1]. This review covers subsequent developments in the filed up to the end of 2006. It has been suggested [1] that all of the above transformations are likely to proceed *via* the initial abstraction of the acidic proton from the XH moiety, followed by the elimination of F^-, to afford the quinone methide intermediate **QM**. Furthermore, these highly reactive species **QM** can be viewed as either C_1 or C_3X (X = N or CH_2) synthone in reactions with electrophiles yielding i) [6,6]-fused or ii) 5-membered heterocycles (Scheme **1**). In several instances, the reaction provided easy access to the analogues of known physiologically active compounds (*ex.* viii) [3] and fluorinated species in good yields (*ex.* ix-xi) [4-6]. Notably, it is an alternative to the low-yielding syntheses of fluorinated aromatics from diaza compounds, including Sandmeyer and Finger reactions [7].

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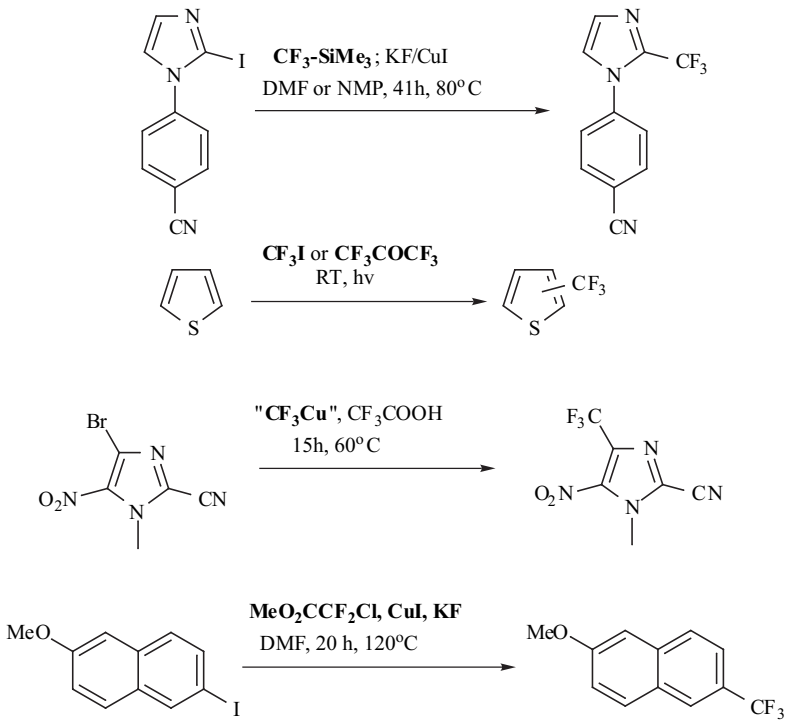
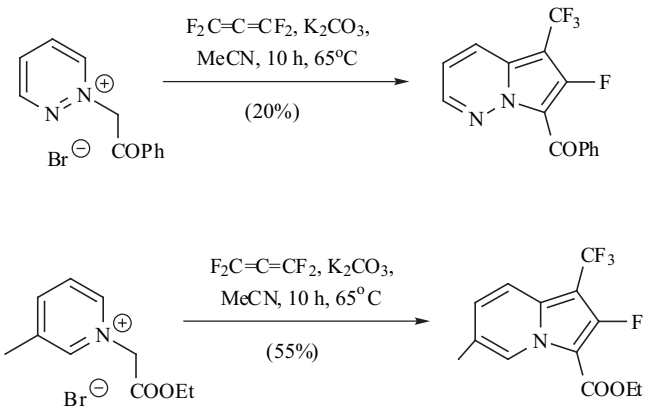


Scheme 2.

SYNTHESIS OF CF_3 AROMATICS

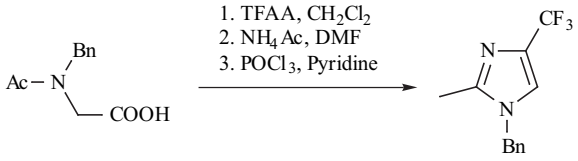
The scope of synthetic strategies to access aromatics containing CF_3-group could be divided into two main categories. These are i) introduction of the CF_3 moiety into the existing aromatic system and ii) assembly from the trifluoromethylated alicyclic components. Introduction of the CF_3 group into 5- or 6-membered aromatics is normally achieved *via* sequences involving generation of a "radical CF_3" species from CF_3-$SiMe_3$ [8], CF_3I [9], CF_3COCF_3 [9], CF3COONa [10], $MeO_2CCF_2SO_2F$ [11], MeO_2CCF_2Cl/KF [12] and metal (I) halogenides (for example, CuI [13,14] or CdI [15,16]). Modification of this protocol including CF_3-$SiMe_3$/$Me_2N_2S{=}NMe_2^+$ $Me_3SiF_2^-$ system has been reported [17]. Representative examples are summarized below (Scheme **2**).

Heterocyclization to yield aromatic CF_3 derivatives from alicyclic components is useful alternative to the direct introduction of the CF_3 moiety into an aromatic system. For example, tetrafluoroallene $F_2C{=}C{=}CF_2$ was reacted with zwitterionic pyridinium species generated *in situ* to afford the respective trifluoromethyl indolizines [18] (Scheme **3**).



Scheme 3.

Reaction of trifluoroacetic anhydride (TFAA) with protected *N*-acylated α-amino acids followed by the treatment of the resulting aromatic intermediates (oxazoles) with NH_4OAc was used in the synthesis of polysubstituted trifluoromethyl imidazoles (Scheme **4**) [19].



Scheme 4.

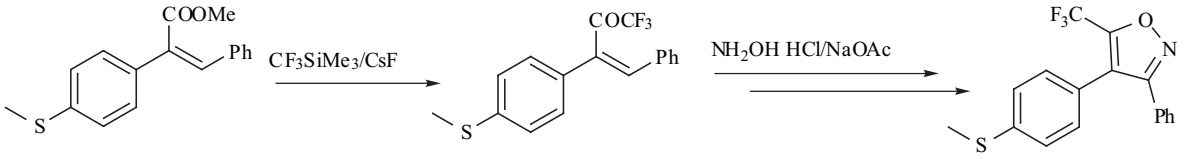
Synthesis of α,β-unsaturated trifluoromethyl ketones and their derivatives from the respective carbonyl precursors followed by the heterocyclization step offered a convenient path towards 5- and 6-membered heterocyclic derivatives substituted with CF_3 function (Scheme **5**) [20].

Similar reaction involving vinilogous trifluoromethyl ketone derivatives was used in the synthesis of polysubstituted 4-trifluoromethyl derivatives of pyrimidine [21].

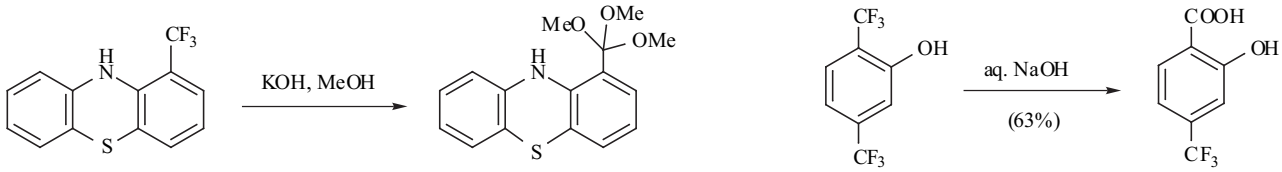
REACTIVITY

Anionically Activated Aromatic CF_3 group as a C_1 Synthone

Base-promoted hydrolysis of the anionically activated aromatic CF_3 group to yield the respective carbonyl compounds is well documented. Two representative examples of this conversion are shown below (Scheme **6**) [22,23]. Notably, reaction of 2,5-*bis*-trifluoromethyl phenol with *aq*. NaOH regiospecifically furnished the respective *ortho*-carboxylic acid in a 63% yield.

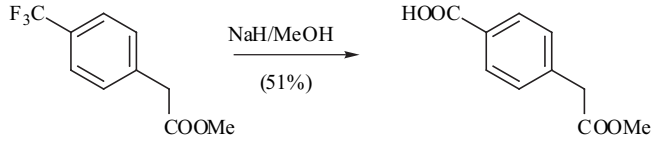


Scheme 5.

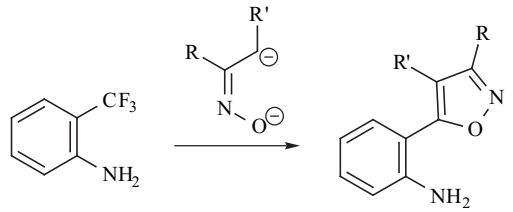


Scheme 6.

Similarly, NaH-mediated hydrolysis of the ionizable *para*-CF_3-substituted aromatics to afford carboxylic acid has been reported (Scheme **7**) [24].



Scheme 7.



Scheme 8.

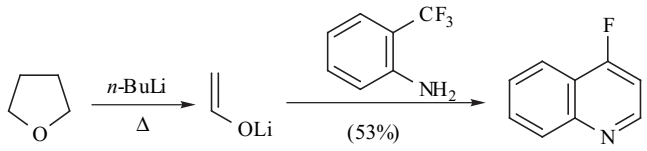
Reaction of dianions derived from oximes with *para*- and *ortho*-CF_3 anilines yielded isoxazoles (Scheme **8**) [25,26].

Anionically Activated Aromatic CF_3 group as a C_3X Synthone

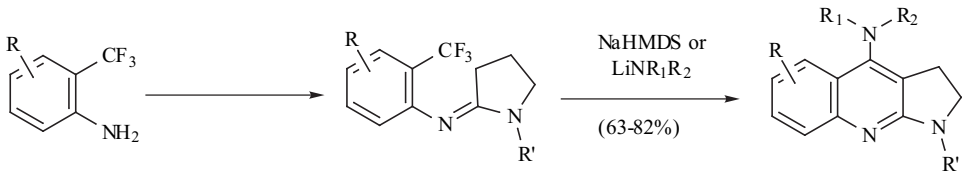
A one-pot reaction of (2-trifluoromethyl)aniline with enolate of acetaldehyde derived from THF and *n*-BuLi afforded 4-fluoroquinoline (Scheme **9**) [5]. This protocol was used recently to access polysubstituted 4-fluoroquinolines [27].

Amidines derived from *ortho*-trifluoromethyl anilines and cyclic lactams were cyclized under basic conditions to yield aza analogues of Tacrine™ (Scheme **10**) [3].

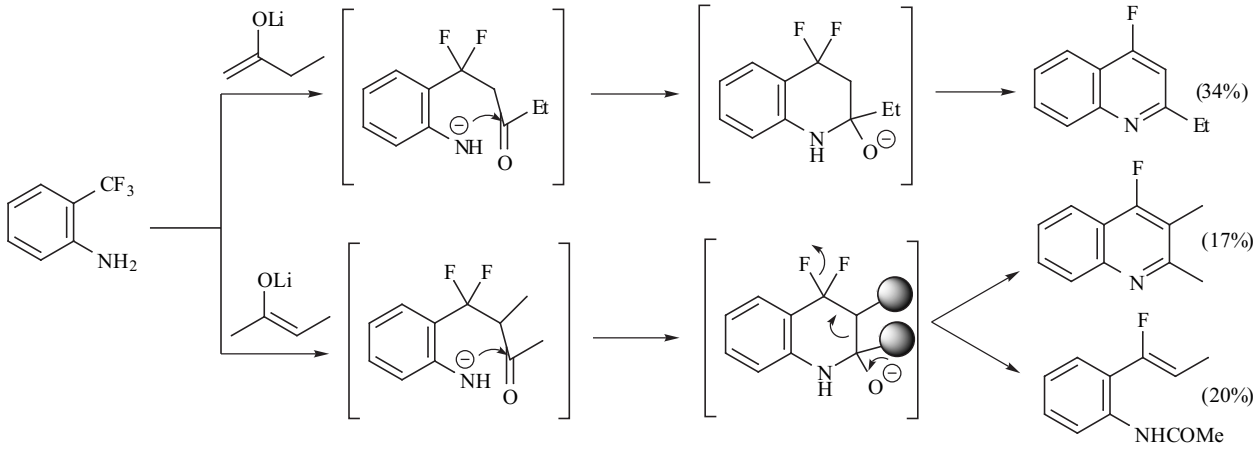
Similar reaction with a mixture of enolates derived from 2-butanone yielded three fluorinated products in a 2:1:1 ratio, as shown below (Scheme **11**). This outcome was explained by the steric strain caused by two adjacent Me groups in the intermediate tetrahydroquinoline. Consistent with this



Scheme 9.



Scheme 10.



Scheme 11.

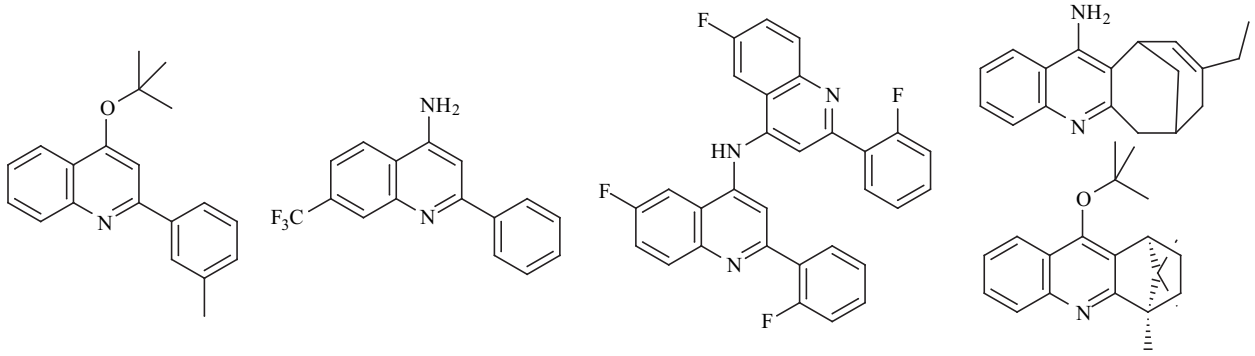
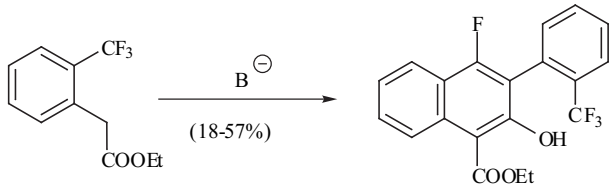


Fig. (1).

observation, enolates with increased steric bulk afforded fluoro olefins exclusively [5].

A base-promoted cyclization of Schiff bases derived from the substituted (2-trifluoromethyl)anilines was used to access either 4-O*t*Bu (base - KO-*t*Bu) [28] or 4-amino (base - NaHMDS) [29] quinolines. These protocols were extended to the synthesis of physiologically-active compounds including antagonists of immunostimulatory CpG-oligodeoxynucleotides [27], acetyl-choline esterase inhibitors *syn*-huprines [29,30] and quinolines derived from camphor, as exemplified in Fig. (**1**) [31].

A facile one-pot synthesis of polysubstituted naphthalenes has been described. The reaction protocol was based on the serendipitous observation that under basic conditions (2-trifluoromethylphenyl)ethylacetate undergwent dimerization to yield polysubstituted 1-fluoronaphthalene (18-57% yields) (Scheme **12**) [32].



Scheme 12.

Reaction of the same starting material with a series of benzonitriles under optimized conditions furnished a diverse array of naphthalenes (37-68% yields) along with the product of dimerization (20-35% yields). Attempts to reduce the amount of this self-condensation product were unsuccessful (Scheme **13**) [4].

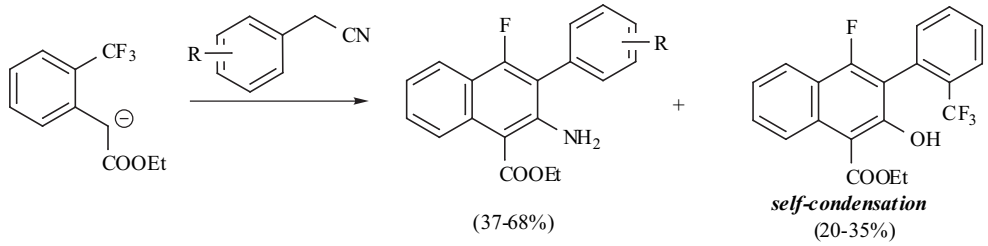
The issue was addressed by using immobilized (2-trifluoromethyl)phenyl acetic acid as a reaction component. Base-induced condensation reaction with benzonitriles followed by treatment of the resin with TFA afforded targeted naphthalenes in good yields and purities (Scheme **14**) [4].

The reaction of *N*-benzylated heterocycles available from the respective NH-precursors and (2-trifluoromethyl)benzyl chloride with LDA afforded fused fluoro isoquinolines (38-57%, Scheme **15**) [33].

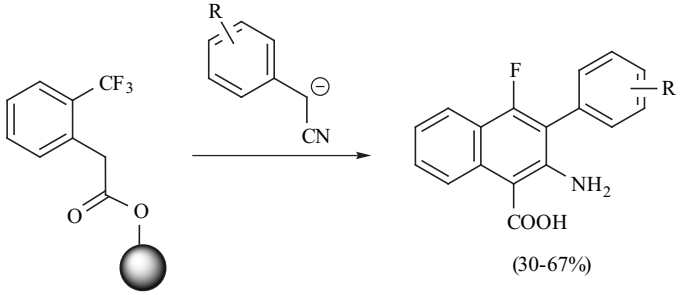
In contrast, similar reactions mediated by KHMDS resulted in nitriles instead of the anticipated fluoro isoquinolines. Possible rationale for this outcome has been suggested (Scheme **16**) [33].

CF_3 AS A LEAVING GROUP

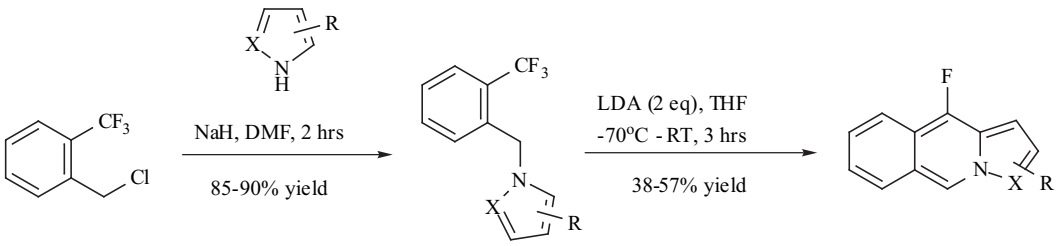
Several reports describe CF_3 as a leaving group under basic conditions. For example, the attempted synthesis of fluoro



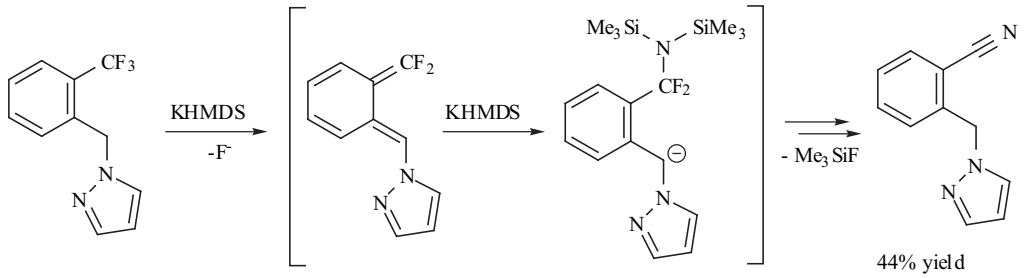
Scheme 13.



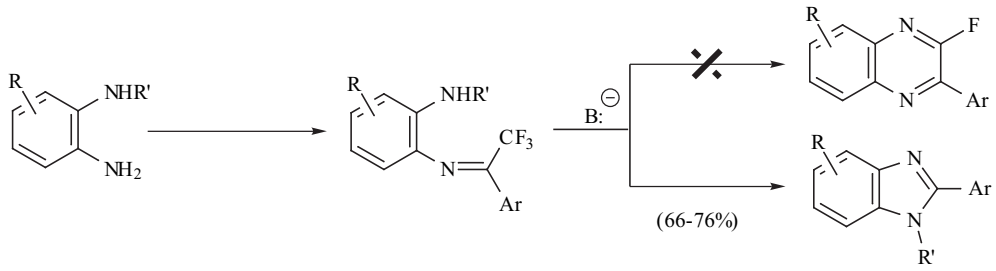
Scheme 14.



Scheme 15.



Scheme 16.



Scheme 17.

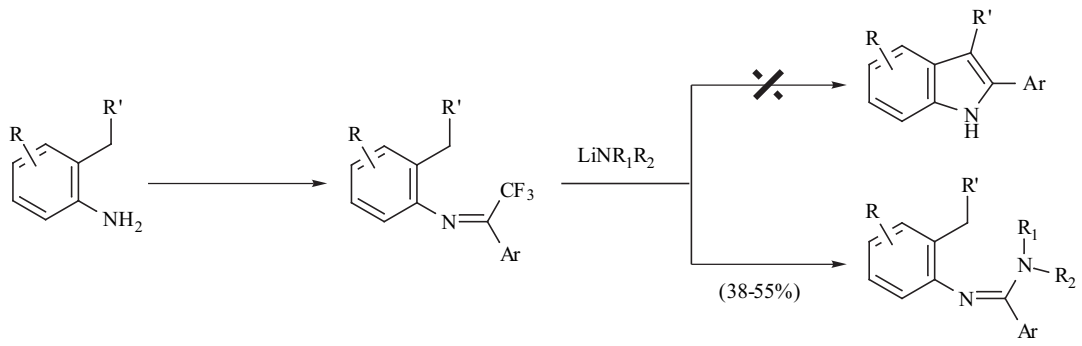
quinoxalines from the respective aromatic CF_3-imines yielded benzimidazoles, products of a formal nucleophilic displacement of the CF_3 group (62-76% yields). A number of bases including KO-*t*Bu, LDA and Li(piperidide) mediated this transformation (Scheme **17**) [34].

Under similar reaction conditions, imines derived from toluidines and trifluoromethyl aryl ketones yielded amidines, instead of the anticipated indoles (38-55% yields, Scheme **18**) [34].

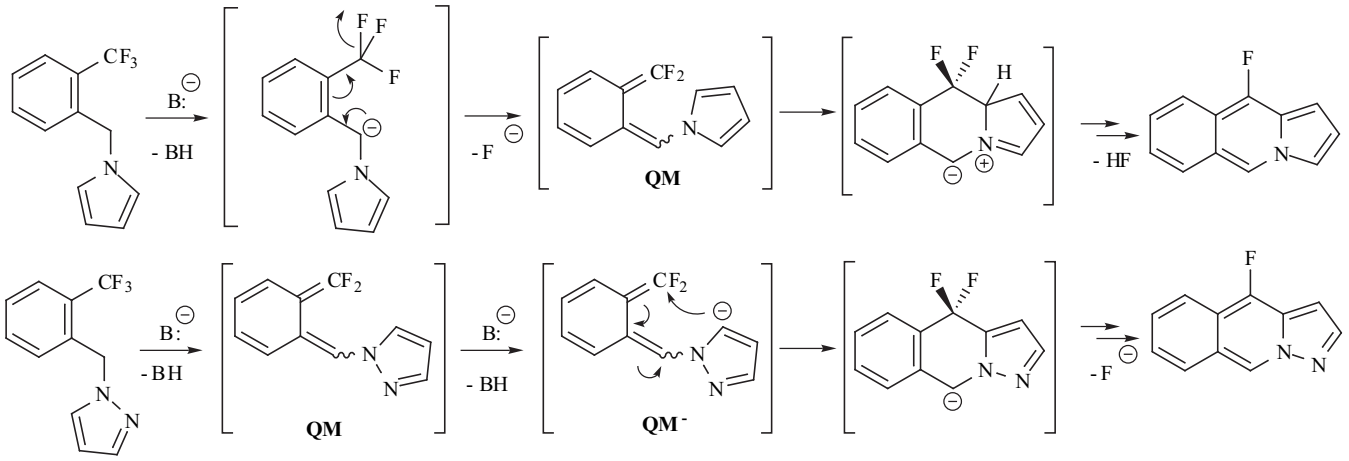
Mechanistic Considerations

As stated in the Introduction, the described base-promoted conversions of the aromatic CF_3 compounds could be rationalized in terms of formation of a highly reactive quinine methide intermediate **QM**. An example of the detailed mechanism for the conversion of *N*-benzylated heterocycles into a respective fluoro isoquinolines is summarized below (Scheme **19**) [33].

The initial abstraction of the acidic methylene proton from the CH_2 group of the *N*-benzylated heterocycle followed by the elimination of F^- is postulated to yield **QM**. These species are likely to cyclize to afford, after elimination of another HF molecule and aromatization, the observed fluorinated isoquinoline**.** Alternatively, second equivalent of LDA could further abstract acidic C5 proton from the intermediate **QM**, as shown for the pyrazole derivative, to yield anionic species **QM**. These undergo intramolecular cyclization and elimination of F^-



Scheme 18.



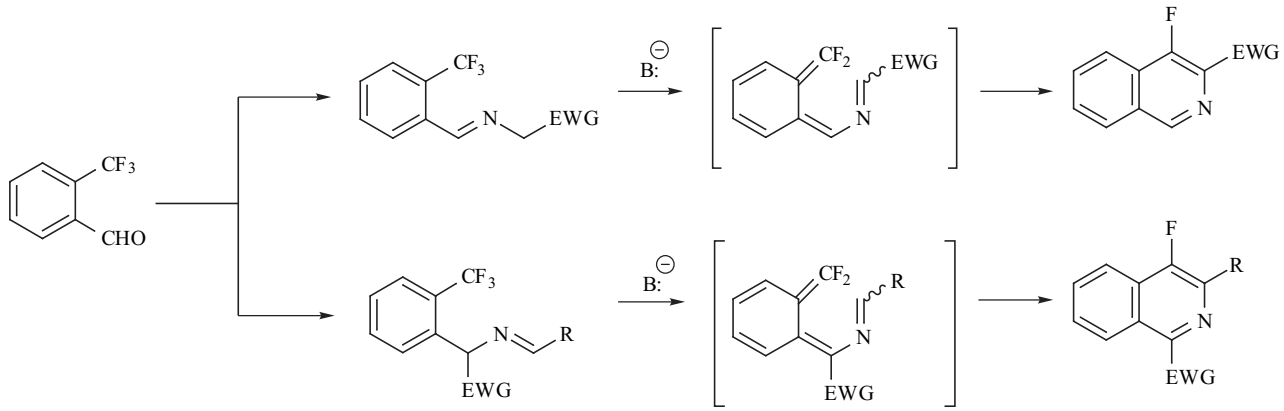
Scheme 19.

to yield the observed product**.** The postulated intermediacy of the quinone methide intermediate **QM** was in agreement with the lack of formation of fluoro isoquinoline derivatives in an attempted reaction of *ortho*-trifluoromethyl benzylated derivatives of 2,5-dimethylpyrrole and 5-methylpyrazole with LDA [33].

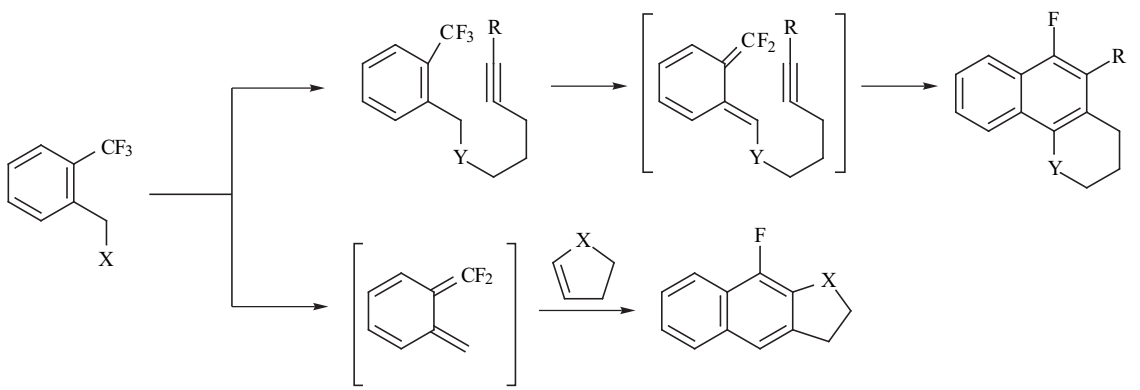
CONCLUSION

Despite of the considerable progress made to date, the synthetic potential of the anionically activated aromatic CF_3 group is still largely unexplored. We plan to further expand the utility of this transformation to the synthesis of heterocyclic systems including fluorinated aromatics. Ongoing project directed towards the synthesis of 3-fluoro isoquinoliones from *ortho*-trifluoromethyl benzaldehyde derivatives is exemplified below (Scheme **20**).

In addition, a series of experiments are in the queue to determine the nature of reactive intermediates in these conversions. Specifically, we are to attempt trapping of the quinine methide species *via* both intra- and intermolecular cycloaddition reactions (Scheme **21**).



Scheme 20.



Scheme 21.

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