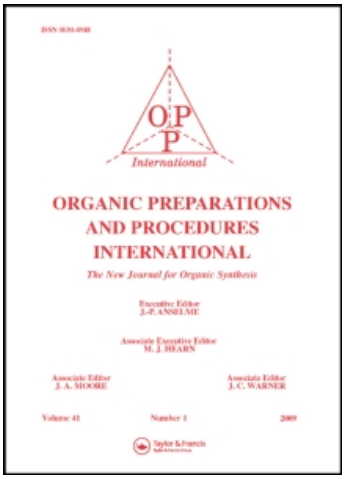

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THE TRIFLUOROMETHYL GROUP IN ORGANIC SYNTHESIS. A REVIEW

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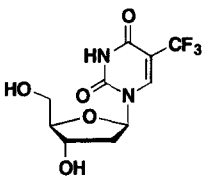
This review is dedicated to my parents, Nina and Sergei Kiselyov.

INTRODUCTION

The last two decades have witnessed a tremendous growth of interest in fluoroorganic compounds.[1] Numerous treatises on this subject covered various aspects of the chemistry and biochemistry of fluorinated compounds, including the synthesis of chiral and bioactive fluoroorganic compounds,[2] the biomedical aspects of fluorine chemistry,[3] the synthesis of organofluorine compounds,[4,5] fluorinated heterocycles,[6,7] and fluorinated natural products.[8] The aim of this review is to summarize the data on the recent developments in synthesis and chemical transformations of compounds containing the trifluoromethyl group.[9]

Compounds containing the CF_3 function represent a broad array of biological and chemical activities. Trifluridine (**1**) as well as perfluorinated purine and pyrimidine derivatives are active antiviral agents.[10] Numerous compounds containing a CF_3 group possess anti-inflammatory, antiparasitic and central nervous system activities.[10,11] For example, fluoxetine (**2**) is a highly selective serotonin reuptake inhibitor.[12]



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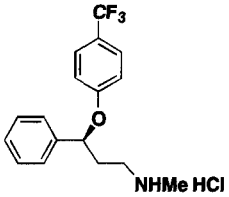

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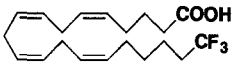

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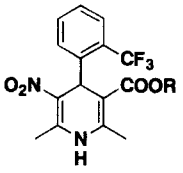

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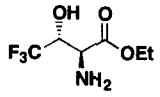

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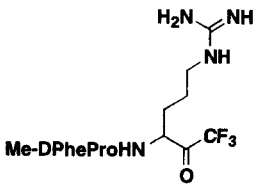

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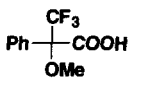

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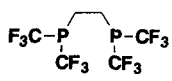

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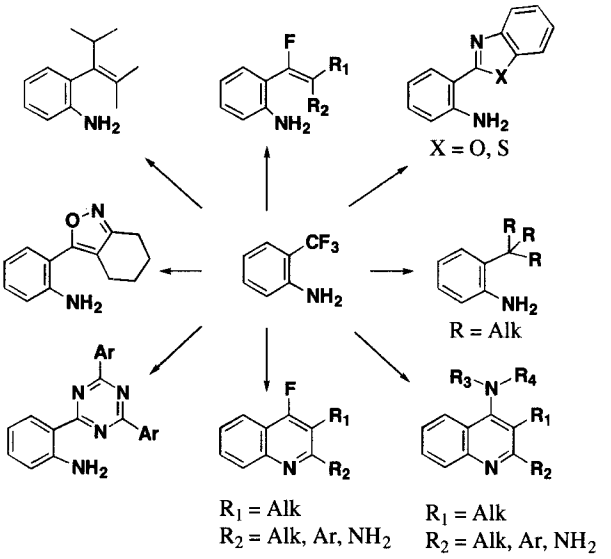
Various fluorinated derivatives of arachidonic acid and leukotriene B_4 (such as **3**) are active toward human neutrophils.[13,14] Application of trifluoromethylgeraniol as a potential insect juvenile hormone substituent was reported.[15] Derivatives of 1,4-dihydropyridine containing the CF_3 moiety (**4**) are

antagonists of L-type Ca^{2+} channels.[16] 13-(Trifluoromethyl) retinal is an active chromophore in bacteriorhodopsin.[17] Interest in "artificial blood" stimulated intensive research in the area of perfluorochemicals, including trifluoromethylated compounds.[3,18] A potent inhibitor of human neutrophil elastase containing a pentafluoroethyl group was introduced recently.[19] Various amino acids containing the CF_3 moiety have been prepared[20] (the fluorinated analog of *D*-threonine (**5**) is given as an example). Trifluoromethylated ketone tripeptide analogs of thrombin (**6**) were prepared and shown to be potent agents for the treatment for thrombosis.[21]

Trifluoromethyl compounds are useful reagents for organic synthesis. Thus, the application of trifluoromethyl hypofluorite (CF_3OF) for the fluorination of various organic substrates is well documented.[22] Trifluoromethyl compounds (Mosher's acid (**7**), and 2,2,2,-trifluoro-1-(9-anthryl)ethanol) are widely used for the determination of enantiomeric purity of organic compounds.[23] Studies on the cations destabilized by the CF_3 group have been reported.[24] Novel chelating tertiary phosphine ligands containing the CF_3 moiety (**8**) have been synthesized.[25] A broad array of aromatic, heteroaromatic, and aliphatic compounds have been obtained using novel chemistries of anionically activated CF_3 groups (*vide infra).*



A series of DNA triple-helix specific intercalators containing a quinoline nucleus were prepared from trifluoromethylated aromatic precursors using similar methodologies.[26]

I. SYNTHESIS OF ALIPHATIC TRIFLUOROMETHYL COMPOUNDS

Several procedures for the perfluoroalkylation of aliphatic compounds were recently introduced. Direct coupling of alkenyl, allyl, or alkynylstannanes with perfluoroalkyl iodides in the presence of catalytic amounts of $Pd(PPh_3)_4$ furnished perfluoroalkylated (*E*)-alkenes and alkynes[27] in 11-

100% yield (typical yields were 52-70%) (*Eq. 1*).

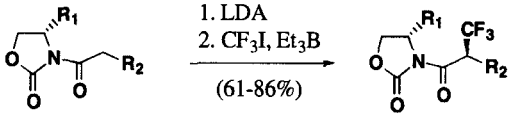
$$\mathbf{R\text{-}SnR'_3} + \mathbf{R_fI} \xrightarrow[11\text{-}100\%]{\text{Pd(0)}} \mathbf{R\text{-}R_f} \quad (1)$$

R = Alkenyl, Allyl, Alkynyl;
R_f= CF_3, n-C_4F_9, n-C_6F_{13};
R'= Alk

The addition of perfluoroalkyl iodides to olefins in the presence of $Pd(PPh_3)_4$ at room temperature or in the presence of benzoyl peroxide at 110° afforded the corresponding adducts in 71-88% yield.[28] In a similar way, perfluoroalkyl copper reagents[29] reacted with propargyl halides or tosylates to furnish perfluoroalkyl allenes regiospecifically.[30] The reaction was conducted in DMF or DMSO at 0°. A variation of this procedure was reported by Burton.[31]

Thermal addition of perfluoroalkyl iodides to monosubstituted perfluoroalkyl acetylenes led to 1,2-*bis*(perfluoro-alkyl)iodoethylenes.[32] Dehydroiodination of these intermediates with NaOH in the presence of a phase-transfer catalyst[33] afforded the desired acetylenes in 50-65% yield. Trifluoromethyl-selenation (telluration) of olefins was performed under radical conditions using the $NaBH_4/(PhSe)_2/CF_3I$ system. The mechanism of this reaction was suggested to involve a single-electron transfer from $PhSe^-$ anion to CF_3I.[34] Application of ultrasound irradiation promoted trifluoromethylation of various unsaturated compounds including olefins, acetylenes, dienes, halogenides, optically active enamines, and carbonyl compounds with the system Zn (powder)/CF_3I.[35]

Trifluoromethylation of silyl enol ethers with the system CF_3I/Et_3B furnished the corresponding trifluoromethylated silyl enol ethers.[36] A stereoselective preparation of peptidyl trifluoromethyl ketones using trifluoromethyl zinc iodide, generated *in situ* from Zn dust and CF_3I in DMF was described.[37] Another method of introduction of the trifluoromethyl (perfluoroalkyl) moiety into an organic substrate is the trifluoromethylation of lithium enolates with CF_3I. For example, trifluoromethylation of lithium enolates of chiral *N*-acyloxazolidinones in the presence of triethylborane was reported to proceed with good diastereomeric excess (62-86% de)[38] (*Eq.* 2). Dialkylamides were



(2)

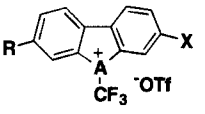
R_1 = *i*-Pr, Bn
R_2 = Me, Bn, *n*-Bu, *t*-Bu

conveniently trifluoromethylated with the system $P(NEt_2)_3/CF_3Br$[39] in the presence of BCl_3 to give the corresponding α-trifluoromethyl enamines.

The silane, CF_3SiMe_3 (Ruppert's reagent[40]) attracted particular attention as a valuable reagent for the trifluoromethylation of carbonyl compounds,[41] or the Cu-mediated coupling with halocompounds.[42] Application of Ruppert's reagent for the synthesis of trifluoromethyl-aziridines (41-86% yield) was reported by Laurent and co-authors.[43] Yagupolski and co-authors introduced an efficient procedure for the trifluoromethylation of arenesulfonyl fluorides into aryl trifluoromethyl

sulfones using a system made up of the Ruppert's reagent and $(Me_2N)_3S^+Me_3SiF_2^-$.[44]

A convenient procedure for trifluoromethylation of enolate anions was devised by Umemoto and Adachi.[45] A series of electrophilic trifluoromethylating agents (**9**), varying in reactivity were prepared. Treatment of lithium or potassium enolates of carbonyl compounds, or trimethylsilyl enol



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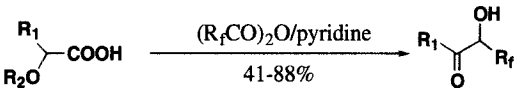
A = S, Se
R = H, NO_2
X = H, NO_2

ethers with these agents in the presence of boron reagents (added to moderate the reactivity of enolate anions by complexation) afforded trifluoromethylated materials in 40-92% yield. Proper selection of the boron compound eliminated the introduction of two CF_3 groups. Notable regioselectivity of the trifluoromethylation reaction was achieved for potassium enolates. The application of optically active borepins for this reaction afforded optically active trifluoromethylated products (12-45% ee). Treatment of methyl chlorodifluoroacetate with aliphatic halides in the presence of an equimolar amount of KF, CuI, and CdI_2 in HMPA yielded trifluoromethylated compounds (68-81% yield).[46]

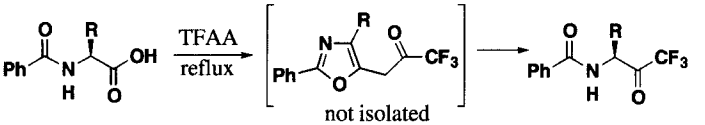
Starting materials which already contain the necessary perfluoroalkyl moiety are useful building blocks for the synthesis of trifluoromethyl compounds. Reaction of α-hydroxy acids with trifluoroacetic (TFAA) or perfluoroacetic anhydride in the presence of pyridine yields α-hydroxylated acyloins (*Eq.* 3) in 41-88% yield.[47] It was assumed that the meso-ionic 1,3-dioxolium-4-olates-6 are



(3)

R_1 = Ph, $PhCH_2$, $Me(CH_2)_5$
R_2 = H, COMe, COPh
R_f = CF_3, C_2F_5, C_3F_7

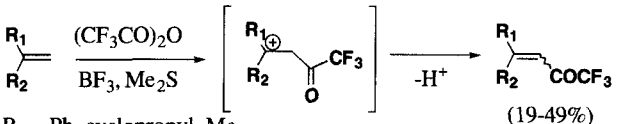
intermediates in this reaction.[48] Similar reaction of carboxylic acid chlorides with TFAA in pyridine provided facile entry to trifluoromethyl ketones (40-81%).[49,50] Several related approaches to peptidyl trifluoromethyl ketones are known. In a modified Dakin-West reaction,[51] TFAA reacted with acid to afford the desired product *via* the intermediate formation of oxazoles (*Eq.* 4). Reaction of CF_3CHO



(4)

with nitroalkanes (Henry reaction),[52] and substituted acetic acids followed by a Curtius rearrangement[53] are alternative approaches to peptidyl trifluoromethyl ketones. A series of new trifluoropyruvic, and lactic thioamides were prepared from ethyl trifluoroacetoacetate.[54]

Extensive research by Nenajdenko and Balenkova revealed a facile pathway to a series of perfluoroacylated olefins *via* direct electrophilic perfluoroacylation of olefins with the system trifluoroalkylacetic anhydride/BF_3/Me_2S (*Eq.* 5).[55]



(5)

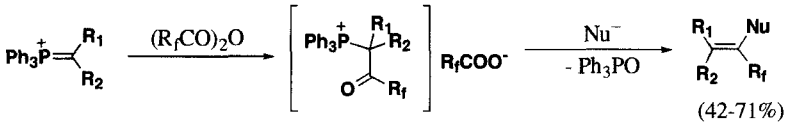
(19-49%)

R_1 = Ph, cyclopropyl, Me
R_2 = H, Ph, cyclopropyl, Me

Recently, a novel trifluoromethylated reagent, $PhC(CF_3)(CN)NH_2$, was developed for the ^{19}F NMR determination of the optical purity of chiral acids.[56] The synthetic approach to this compound involves the application of trifluoroacetamide as a starting material. Trifluoroalkanamides, which are valuable precursors for trifluoroalkylamines,[57] were conveniently prepared in 82-98% yield from secondary amines and TFAA. An electrochemical version of this procedure was reported.[58] Studies on the 2,2-*bis*(trifluoromethyl)ethylene-1,1-dicarbonitrile chemistry by Huisgen revealed that this electron-deficient olefin easily reacts with isobutenyl and methallyl ethers, thioethers, and various alkenes to give the trifluoromethylated products.[59]

Condensation reactions of perfluoroalkyl organometallic reagents with aldehydes or ketones afforded the corresponding perfluoroalkyl substituted carbinols.[60,61] A convenient transformation of the resultant carbinols into trifluoromethyl ketones with Dess-Martin reagent was described.[62]

The Wittig reaction is a powerful tool for the introduction of the perfluoroalkyl moiety into organic molecules. One-pot syntheses of CF_3 containing tetrasubstituted olefins,[63] perfluoroalkylated enolates, vinyl esters, β-hydroxy ketones, vinyl ethers and ketones,[64] 4-trifluoromethyl-2,4-dienyl carboxylates,[65] trifluoromethylated α,β-unsaturated esters,[66] *trans*-perfluoroalkylated vinylcyclopropanes,[67] perfluoroalkylated α,β-unsaturated acids,[68] and perfluoroalkylated α,β-unsaturated nitriles[69] were introduced. A representative example of perfluoroalkyl olefin synthesis is given in *Scheme* 1.



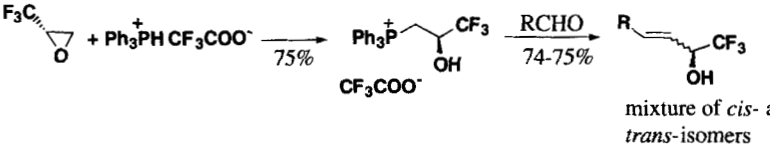
(42-71%)

R_1 = allyl, $PhCH_2$, *n*-Bu, *n*-Pr, Me; R_2 = Me, cyclopentyl, cyclohexyl
R_f = CF_3, C_2F_5, *n*-C_3F_7; Nu^- = Ph, *n*-Bu

Scheme 1

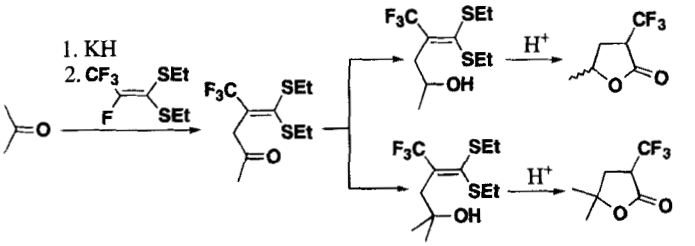
The stereochemistry of the desired olefins was easily controlled by the reaction conditions. Treatment of β-oxido ylides with AcOH gave *Z*-olefins, whereas hydrolysis with 5% HCl (aq.) afforded predominantly *E*-isomers. Recently, a somewhat similar procedure was reported for the synthesis of trifluoromethyl vinyl sulfides[70] (48-94% yield). (*S*)-Trifluoropropene oxide is a convenient building block for the synthesis of trifluoromethylated compounds.[71] Treatment of this

compound with PPh_3 in the presence of CF_3COOH yields the corresponding β-hydroxyalkyl phosphonium salt . Wittig reaction of various aldehydes with this salt affords optically active α-trifluoromethylated allylic alcohols (46-89% yield, *Eq.* 6).



(6)

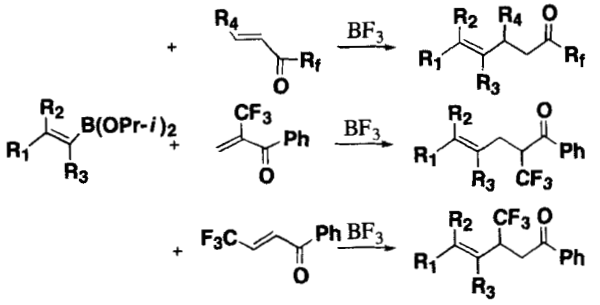
Perfluorinated ketene dithioacetals are efficient building blocks for the synthesis of α-trifluoromethylated γ-lactones (*Scheme* 2). This three-step procedure includes the intermediate formation



Scheme 2

of an unsaturated trifluoromethyl ketone followed by its conversion to the corresponding alcohols with either $NaBH_4$ or MeLi. Both alcohols were converted into the target trifluoromethylated lactones.[72] 1-Alkyl-3-trifluoromethyl propargyl alcohols are useful precursors for trifluoromethylated *cis*- and *trans*- olefins.[73]

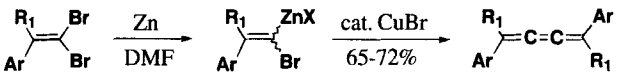
1,4-Addition reactions of organometallic reagents to perfluoroalkyl α,β-unsaturated ketones is an efficient method for the synthesis of perfluoroalkyl ketones. For example, the BF_3 mediated addition of alkenyldialkoxyboranes to perfluoroalkylated unsaturated ketones furnishes the corresponding γ,δ-unsaturated ketones (77-99% yield) stereoselectively (*Scheme* 3).[74]



Scheme 3

Synthesis of perfluoroalkylated 1,2,3-butatrienes[75] involves the dimerization reaction of the α-bromovinylzinc reagent in the presence of CuBr (*Eq.* 7). The preparation of perfluoro-3,4-dihalo-

2,5-dimethylhexa-2,4-dienes based on this protocol was reported recently.[76] Electrolysis is a useful

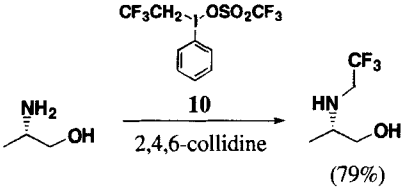


(7)

$R_1 = CF_3, C_2F_5, n\text{-}C_3F_7$
$Ar = C_6H_5, C_6F_5$

method for the synthesis of perfluoroalkylated compounds.[77] For example, the Pummerer rearrangement of trifluoromethylated species conducted under the conditions of anodic acetoxylation was much superior to the conventional Pummerer reaction.[78]

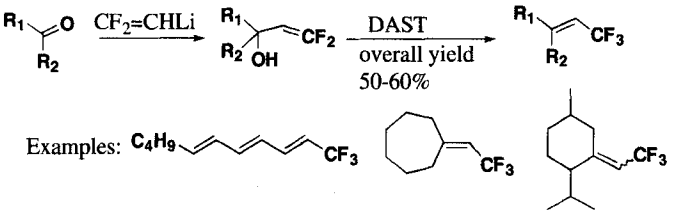
The synthesis of trifluoromethylated carbocycles by Bu_3SnH induced regioselective radical cyclization has been introduced.[79] The procedure was also extended to the tandem cyclization, mediated by an olefinic bond containing a CF_3 substituent, to yield the trifluoromethylated bicyclic compounds (25-81% yield). *N*-Trifluoroethylation of a series of aminoalcohols with Umemoto's iodinane **10** (*Eq.* 8; 76-88% yield) has been reported.[80]



(8)

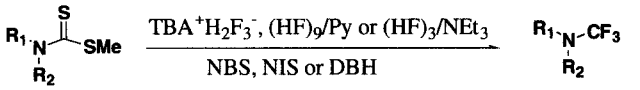
The mechanism of the reaction was suggested to involve the displacement of the triflate group in **10** with the nucleophile, followed by the decomposition of the intermediate into iodobenzene, triflic acid, and the desired product. Trifluoroethylation of aromatic substrates with 1-chloro-2,2,2-trifluoroethyl phenyl sulfide in the presence of $ZnCl_2$, or $SnCl_4$ furnished 1-aryl-2,2,2-trifluoroethyl phenyl sulfide in 37-83% yield.[81]

An efficient conversion of *gem*-difluoroalkenes into trifluoromethylated products with DAST [(diethylamino)sulfur trifluoride] has been reported[82] (*Eq.* 9). Alternatively, oxidative desulfurization-fluorination of organosulfur compounds has been employed for the replacement of C-S bonds



(9)

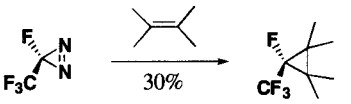
with C-F bonds (*Eq.* 10).[83] The synthesis of trifluoromethylamines from methyl dithiocarbamates,[84] and trifluoromethyl ethers from xanthates[85] are examples of this strategy.



R_1 = Ar, R_2 = CH_2Ph (62-99%) (10)

An essentially similar conversion of the carboxyl function into CF_3 takes place under treatment with SF_4.[86]

Trifluoromethylated diazirines are convenient precursors for tetrafluoroethylidenes.[87] Thermolysis of diazirines in the presence of olefins leads to the corresponding cyclopropanes containing the CF_3 moiety (30% yield, *Eq.* 11).[88,89]



(11)

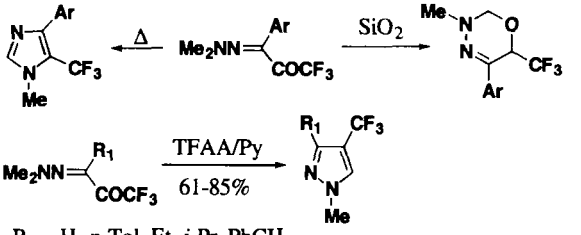
II. SYNTHESIS OF TRIFLUOROMETHYLATED AROMATIC COMPOUNDS

Recently, several reviews dealing with advances in the synthesis of trifluoroaromatic compounds were published.[6,7,9]

A number of procedures exist for the direct introduction of the CF_3 moiety into aromatic substrates, one of the most widely used being trifluoromethylation with the CF_3 radical. This reactive particle was generated *via* (i) the photochemical approach,[6] (ii) the thermal approach,[90] (iii) electrochemically,[91] and (iv) chemically by metal mediated reactions,[92] from XeF_2/CF_3COOH,[93] *bis*(trifluoromethyl)peroxide,[94] sodium trifluoromethane sulfinate,[95] $Hg(CF_3)_2$,[96] or $Te(CF_3)_2$,[97] $CF_3SO_3CF_3$,[98] $Br(Cl)CF_2CO_2K/KF/CuI$,[99] and CF_3COONa/t-BuOOH/Cu(II) systems.[100] Standard procedures for the perfluoroalkylation of aromatic substrates catalyzed by Ru(II) complexes[101] are not applicable for the introduction of the CF_3 moiety due to the instability of the CF_3M complexes,[36] however, the system Mg/CF_3I in DMF was reported to be efficient for the trifluoromethylation of pyrrole.[102] Perhaps the most useful reagent system for the direct introduction of the CF_3 moiety into aromatic substrates is CF_3I/Cu/DMF or DMSO.[103] For efficient coupling to occur the aromatic halides (iodides or bromides) are required.[104] The mechanistic aspects, and the nature of this reaction were discussed.[105] Similar trifluoromethylations of aromatic and heteroaromatic amines by the system CF_3I/Zn/DMF were described recently.[106] The observed regioselectivity of this reaction was rationalized in terms of the electrophilic interaction of the CF_3 radical with the aromatic ring at the sites with the greatest electron density. The system of Ruppert's reagent/Cu(I) and (trialkylsilyl)(trifluoromethyl)diazenes were also efficiently applied for the trifluoromethylation of aromatics.[37,107,108]

Similar to the synthesis of aliphatic trifluoromethylated compounds, the CF_3 moiety can be introduced into aromatic compounds by conversion of preexisting COOH, CCl_3 or $C(SR)_3$ groups with SF_4,[109] DAST,[110] $AgBF_4$,[111] or the NBS/HF-pyridine system.[112]

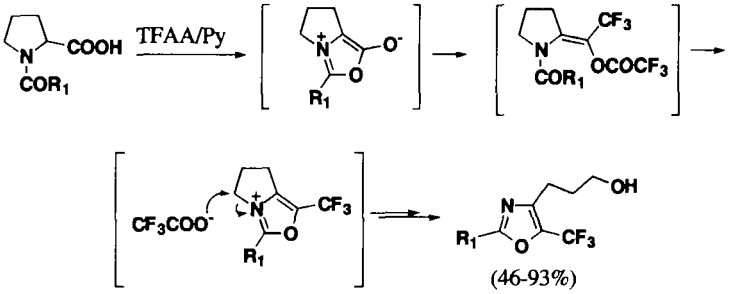
Heterocyclization of aliphatic compounds containing the CF_3 moiety is another major approach to the synthesis of trifluoromethylated aromatic compounds. The most frequently used substrates for the construction of trifluoromethylated aromatic compounds are trifluoromethylated Wittig reagents,[113] trifluoroacetylated hydrazones[114] (*Scheme* 4), *N*-aryl-2,2,2-trifluoroacetimidoyl



R_1 = H, *p*-Tol, Et, *i*-Pr, $PhCH_2$

Scheme 4

iodide,[115] the TFAA/pyridine/DMAP[116] system (*Scheme* 5), the $CF_3CF_2I/Na_2S_2O_4$ system,[117] hexafluoroacetone,[118] trifluoroacetyl acetylenes, and trifluoroacetonitrile.[119]



R_1 = t-Bu, Ph, 4-$MeOC_6H_4$, 4-ClC_6H_4, PhCH=CMe, 2,4,6-$Me_3C_6H_2$

Scheme 5

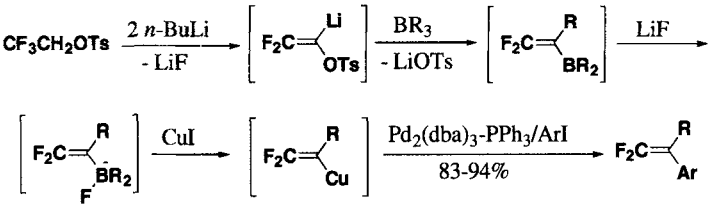
A procedure for the trifluoromethylation of C_{60} with trifluoroacetyl peroxide was reported.[120] Several new procedures for the trifluoroacetylation of aromatic compounds were devised recently.[121]

Introduction of the CF_3 moiety into aromatic substrates can be achieved *via* various cycloaddition or cyclocondensation reactions. This subject was thoroughly covered in the review by Burger *et. al.*[6] Recent representative examples of this strategy include the Diels-Alder reaction of trifluoromethylated acetylenes with various dienes.[122]

III. REACTIONS OF ALIPHATIC TRIFLUOROMETHYL COMPOUNDS

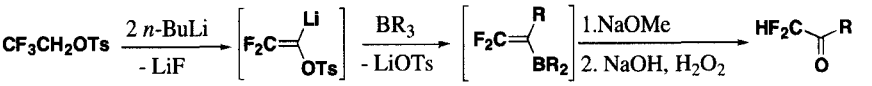
Until recently, the trifluoromethyl group was considered to be a relatively inert moiety.[123] Research in the last decade, however, led to the discovery of many useful transformations involving CF_3.[124] Ichikawa and co-workers found the CF_3 residue to be an excellent source of the CF_2 function-

ality for the synthesis of terminal difluoroolefins (*Scheme* 6).[1b,4,125]



Scheme 6

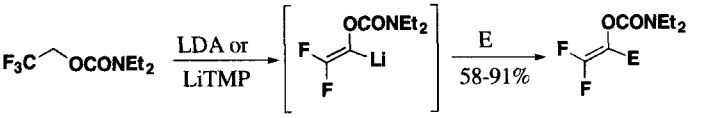
Synthetic strategies developed by this group allow easy and efficient access to 1,1-difluoro-1-alkenes,[126-129] 2,2-difluorovinyl carbonyl compounds,[130] and difluoromethyl ketones (*Scheme* 7).[131]



(27-81%)

Scheme 7

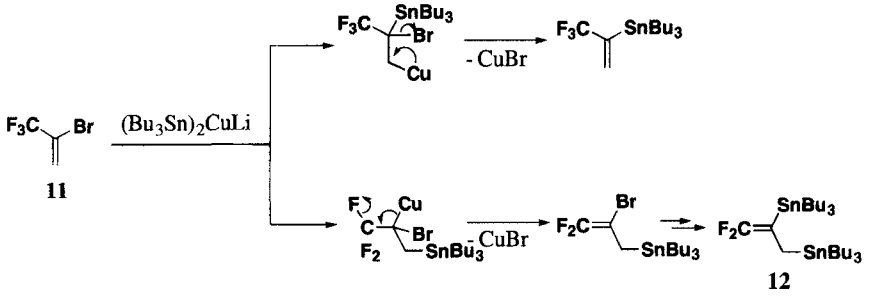
A similar protocol was used by Percy and co-workers for the synthesis of difluoroallylic alcohols.[132,133] Snieckus and co-workers elaborated the synthesis of fluoroolefins based on generation *in situ* of α-lithio difluorovinyl carbamate followed by its trapping with various electrophilic agents (*Eq.* 12).[134] A further modification of this procedure was reported recently.[135] Reaction of **11** with the



(12)

E = TMS, SePh, Me, CH_2TMS

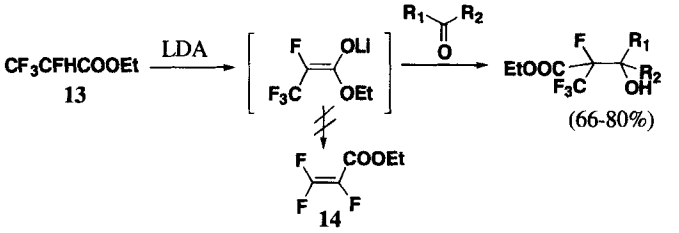
cuprate reagent furnished **12** in 76% yield (*Scheme* 8). It was suggested that the reaction proceeds *via* the initial nucleophilic attack of the cuprate reagent on the C1 of **11** followed by the elimination of



Scheme 8

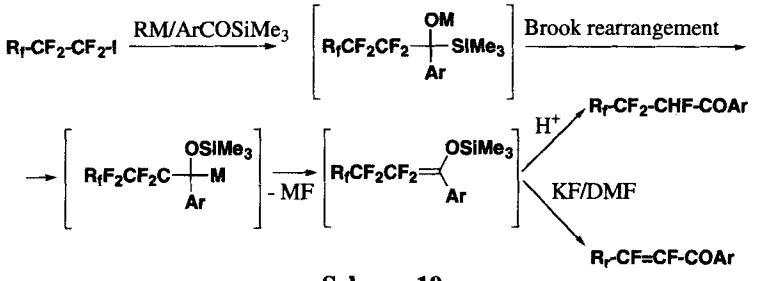
CuBr from the resulting intermediate. Reaction of 2,2,2-trifluoroethyl sulfides with alkyl- or phenyllithium followed by the acidic hydrolysis of the resultant monofluoroketene hemiacetal led to α-monofluoro-alkanoic acids (70-90% yield).[136]

Treatment of $CF_3C(O)SiPh_3$ with organolithium reagents provided a facile entry to 2,2-difluoro enol silyl ethers (88-95% yield).[137] The suggested mechanism involves a nucleophilic addition of organolithium reagent to the carbonyl group followed by the migration of the silyl moiety to the negatively charged O-atom (Brook rearrangement), and β-elimination of F^- from the resultant carbanion to give the observed product. Application of vinylmagnesium bromide for this reaction allowed the entry to 1,1-difluoro-2-triphenylsiloxybuta-3-diene, a convenient buiding block for he synthesis of fluorinated carbocycles.[138] A further expansion of this protocol by Watanabe and co-workers led to the preparation of 2-difluoromethylene-4-pentenoic acid.[139] It should be noted that under similar conditions, tetrafluoropropionate **13** did not afford the expected product of defluorination **14**. Instead, conducting the experiment in the presence of electrophile yielded a series of coupling products (*Scheme* 9).[140]



Scheme 9

Portella and co-workers found that the reaction of perfluoroalkyliodides with acylsilanes in the presence of MeLi or EtMgBr furnishes perfluoroalkenyl ketones (*Scheme* 10).[141,142] The reaction is believed to proceed *via* the initial conversion of R_fI into the perfluoro-organometallic reagent

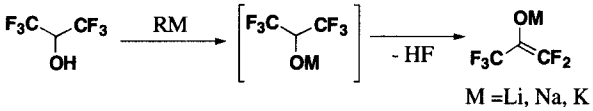


Scheme 10

followed by its reaction with aroylsilane. The Brook rearrangement of the resultant intermediate is followed by MF elimination and formation of an enoxysilane, which is further attacked by F^- to give the observed product. Similar syntheses of perfluoroketene dithioacetals from perfluoroaldehyde hydrates *via* their thioacetal derivatives was suggested to involve the KOH induced elimination of HF

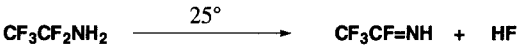
as the first step.[143] Reaction of aliphatic primary amines with alkyl α-H-perfluoroesters furnished β-iminoesters. The reaction is considered to involve the initial elimination of HF from the starting esters followed by the addition of amine to the resulting difluoroolefin, and formation of the product after elimination of a second molecule of HF.[144] Similar procedure for the synthesis of β-enamino perfluoroesters and α-H-perfluoro β-ketoesters has been reported.[145]

α-CF_3 enolates undergo defluorination to give the corresponding difluoro derivatives (*Eq.* 13).[146] Treatment of α-methoxy trifluoroethyl sulfide with 2 eq. of BuLi affords monofluoroketene hemithioacetal (70% yield), which is further converted into α-fluorohexanoic acid.[147] Nakai and co-



(13)

workers found that metal F-propenolates can be easily obtained from 1,1,1,3,3,3-hexafluoro-2-propanol by treatment with 2 equiv. of BuLi (NaH/BuLi or KH/BuLi for Na and K enolates). The resulting fluorinated species are useful building blocks for the synthesis of fluorinated materials.[148] The instability of the *N*-perfluoroalkylamines is attributed to the proximity of hydrogen to fluorine, which facilitates the loss of HF and the formation of the corresponding *F*-nitrilimines (*Eq.* 14)[149]. α-Chloro-α'-trifluoromethyl ketones react with formamidine to yield 5-substituted 4-fluoro-6-chloromethyl pyrimidines (23-35% yield).[150]

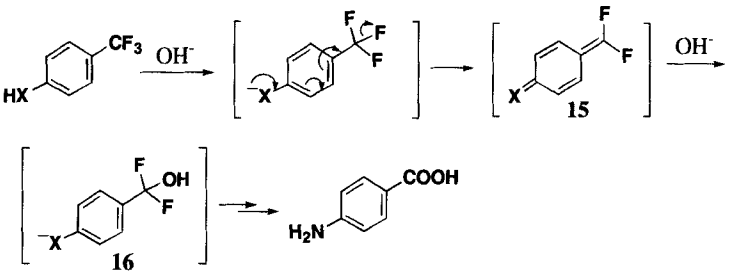


(14)

IV. REACTIONS OF AROMATIC TRIFLUOROMETHYL COMPOUNDS

A review of the literature on the chemistry of the aromatic trifluoroalkyl group prior to 1992 was published recently.[151] Repetition of the material presented there will be avoided whenever possible.

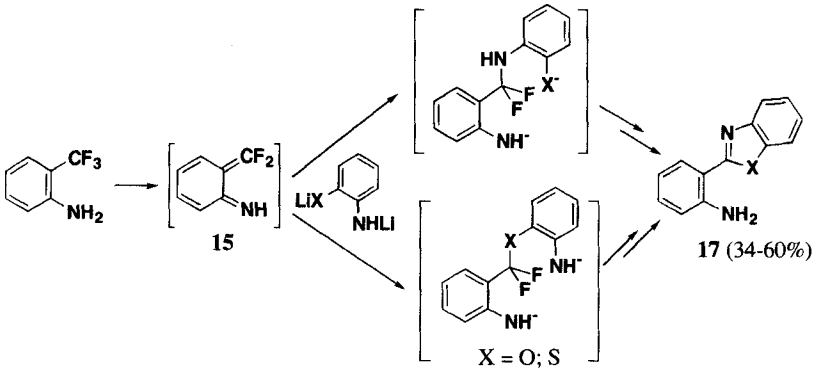
Jones[152] and Belcher[153] discovered that the trifluoromethyl group conjugated with an *ortho*- or *para*-hydroxyl or amino function can be converted into COOH under conditions of basic hydrolysis. It was also found that the corresponding *meta* isomer was resistant to hydrolysis. The generally accepted mechanism for these transformations involves the initial deprotonation of the ionizable group with base followed by the elimination of the F^- anion, and formation of the highly reactive key intermediate **15**. Subsequent attack on the CF_2 residue with the second equivalent of base/nucleophile leads to the rearomatization of the intermediate **15**, and the formation of the anion which is capable of elimination of the second, and ultimately the third F^- anion to afford the observed product (*Scheme* 11).[154] The similar reactivity of the *ortho*-isomer, and resistance of the *meta*-isomer to basic hydrolysis can be explained in terms of this mechanism. A similar mechanism was suggested for the reaction of 4-(trifluoromethyl)aniline with sodium amide which affords a carbonitrile. Kobayashi and Kumadaki described transformations of a trifluoromethyl group into carboxylic acid and carbonitrile



Scheme 11

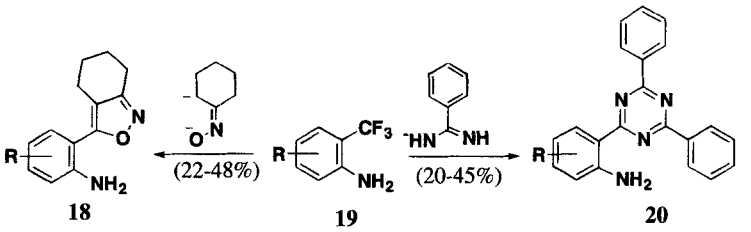
functions in a series of trifluoromethyl substituted heteroaromatic compounds. Additional examples of the facile hydrolysis of the trifluoromethyl group are believed to involve formation of transient intermediate products structurally related to **15**.[154] The trifluoromethyl substituent was found to be a more versatile synthon for various functional groups than the trichloromethyl group. Synthetically useful are efficient transformations of 2-(trifluoromethyl)imidazoles, 4(5)-(trifluoromethyl)-imidazoles, and 5-amino-4-(trifluoromethyl)thiazoles into the corresponding carboxylate, carbonitrile and/or amidine derivatives. Anionically activated dehydrofluorination of a trifluoromethyl substituent at a pyridine ring was recently presented.[154]

para-Trifluoromethyl substituted anilines and quinoline analogs react with dianions derived from 2-mercapto- and 2-hydroxyaniline to afford 2-substituted benzothiazole and benzoxazole respectively.[155] The reaction is believed to proceed *via* the formation of the key intermediate **15** (*Scheme* 12).



Scheme 12

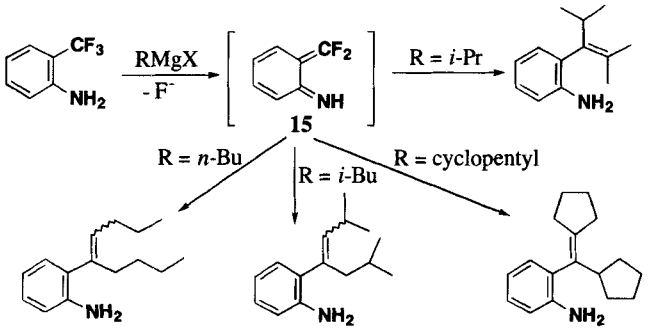
Subsequent attack on **15** by dianions followed by a series of F^- elimination steps yields the observed products **17**. In a similar manner, reaction of trifluoromethyl-substituted anilines **19** with dianions derived from oximes of 3-pentanone, and cyclohexanone furnishes the corresponding isoxazoles **18** in 22-48% yield. Reaction of **19** with a monoanion derived from benzamidine affords triazines **20** (20-45% yield, *Scheme* 13).[156] Treatment of 2- and 4-(trifluoromethyl)anilines with lithium 2-aminoethylamide and lithium 3-aminopropylamide yields 2-(aminophenyl)-4,5-dihydro-1*H*-imidazole or 2-(aminophenyl)-1,4,5,6-tetrahydro-pyrimidines.[157]



18 19 20

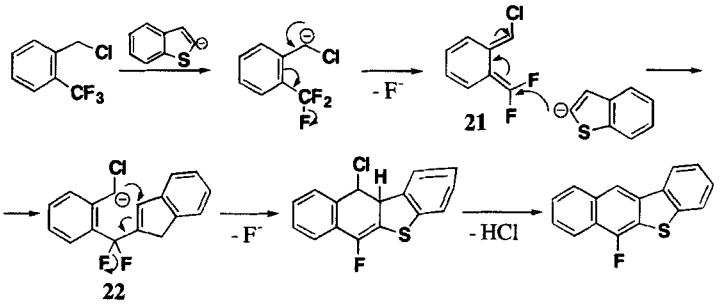
Scheme 13

The CF_3 group represents a C1 building block in the synthesis of 2-(substituted 1-alkenyl)anilines from 2-(trifluoromethyl)aniline and alkyl Grignard reagents[158] (*Scheme* 14). The reaction provides a facile entry to sterically congested olefins (49-75% yields). Numerous reports are



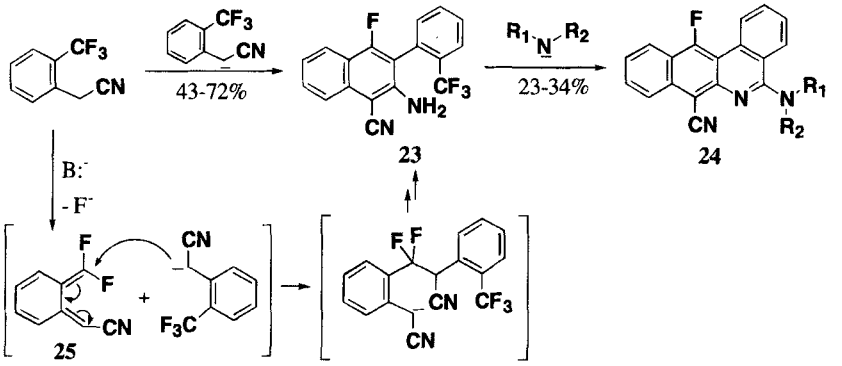
Scheme 14

available on the application of the CF_3 group for the synthesis of substituted quinolines and naphthalenes. Cyclization of 1-(2-substituted-1-propenyl)-2-(trifluoromethyl)-benzenes with lithium 4-methylpiperazide furnishes various 3-substituted 1-(dialkylamino)-naphthalenes.[159] In a related procedure the reaction of 2-(trifluoromethyl)benzyl chloride with various aryllithium reagents afforded 6-fluorobenzo[b] naphtho [2,3-d]heterocycles (a representative example of the reaction with 2-benzo[b]thienyl-lithium anion is given in *Scheme* 15).[160] It was suggested that the reaction involves the intermediate **21**. The lithium aromatics undergo addition to **21** to give an intermediate anion **22**,



Scheme 15

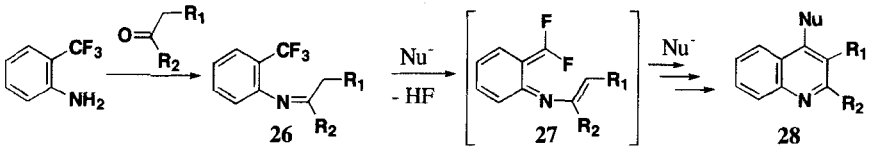
which after elimination of F^-, and HCl affords the observed product. (2-Trifluoromethyl)phenylacetonitrile undergoes a facile self-condensation under treatment with various bases to give the naphthalene **23** (55-78% yield, *Scheme* 16).



Scheme 16

Further reaction of this product with lithium dialkylamides leads to the product of cyclization **24** (43-55%). Amide-anions generated from primary amines are not efficient for this cyclization.[161] A mechanism, involving the initial formation of the intermediate **25**, was offered to account for the observed transformations.

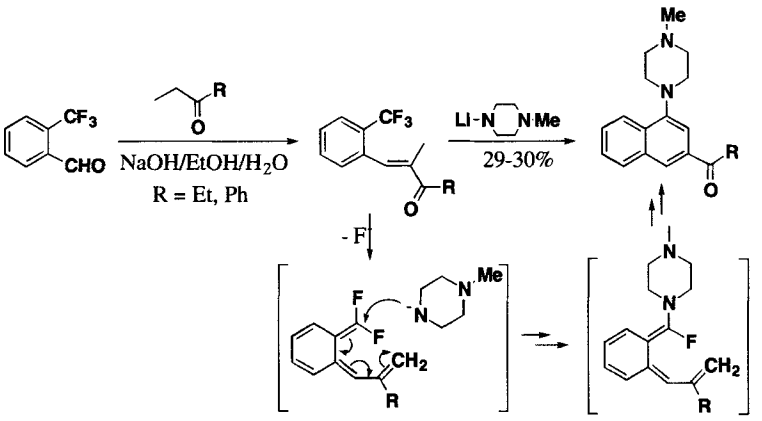
A versatile synthesis of substituted quinolines from 2-(trifluoromethyl) aniline is another example of the application of the CF_3 group in organic synthesis. The cyclization of aralkylketimines of the general formula **26** derived from 2-(trifluoromethyl) aniline, and the corresponding ketone mediated by amide anions or *t*-BuOK results in 2-arylquinolines **28** (*Scheme* 17). Different



R_1 = H, Alk; R_2 = Ar, Hetar, Alkenyl
Nu = NHR, NRR'

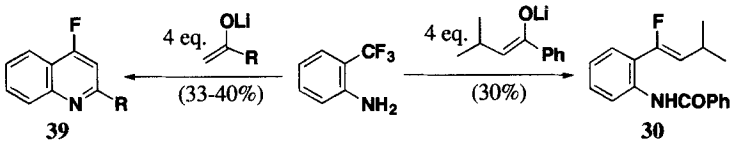
Scheme 17

substituents were introduced into the 4 position of the quinoline ring by changing the base for the cyclization.[162] The reaction is believed to proceed *via* the intermediate formation of **27**, followed by a series of F^- elimination steps induced by the addition of a nucleophile to **27**. This approach was also useful for the synthesis of dihydroacridines,[163] and quinazolines.[164] Reaction of 1-(1-propenyl)-2-trifluoromethyl)benzene derivatives with lithium dialkylamides provides a new synthetic route to 3-substituted 1-(dialkylamino)naphthalenes (*Scheme* 18).



Scheme 18

It was shown recently that the CF_3 group is a versatile source for the C-F moiety in the synthesis of 4-fluoroquinolines.[165] Reaction of 2-(trifluoromethyl)aniline with lithium enolates derived from methyl ketones led to 2-substituted 4-fluoroquinolines **29** (*Scheme* 19). More sterically hindered lithium enolates afforded *(Z)-N*-[2-(1-fluoroalkenyl)phenyl] carboxamides **30**. Enolates

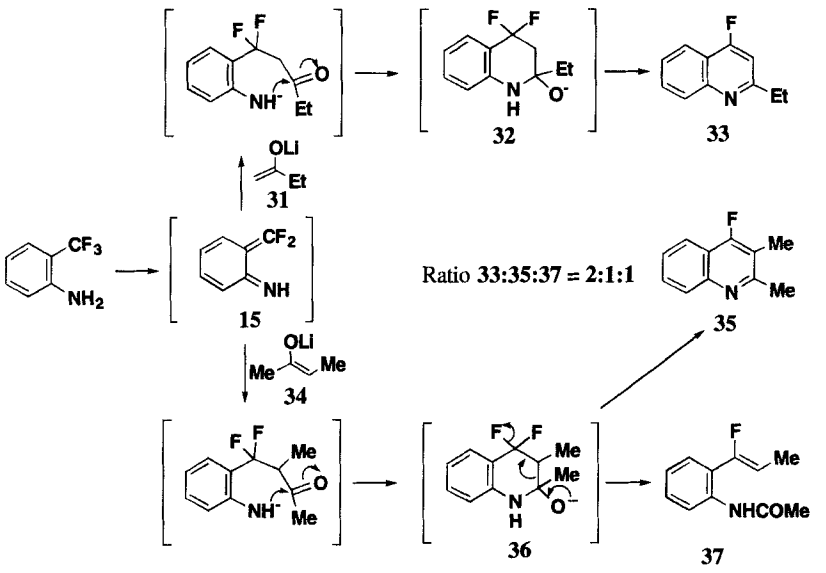


R = Me, *t*-Bu, Adamantyl, Ferrocenyl, 2-Naphthyl

Scheme 19

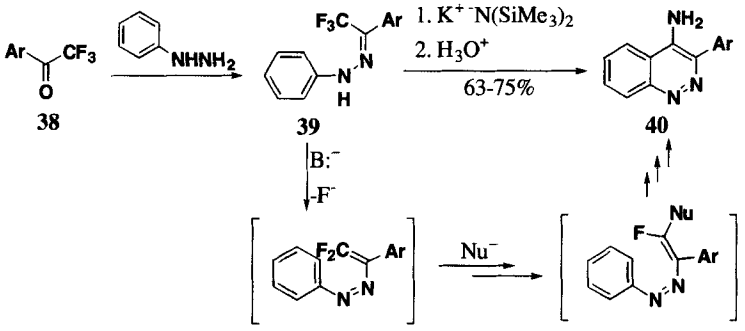
derived from 2-butanone afforded three products **33**, **35**, and **37** corresponding to the reaction of 2-(trifluoromethyl)aniline with two enolate anions. Remarkably, enolate **31** afforded only fluorinated quinoline, whereas enolate **34** furnished a mixture of the fluorinated quinoline, and 2-(1-fluoroalkenyl)phenylcarboxamide. The reaction was also expanded to the synthesis of fluorinated phenanthroline. The reaction is believed to involve the initial formation of the intermediate **15**, followed by the nucleophilic attack of enolate on the CF_2 moiety (*Scheme* 20). The resultant tetrahydroquinolines **32** and **36** either aromatize to give 4-fluoroquinolines or undergo ring-opening reaction to afford the olefin. It was suggested that the steric strain in **36** may be a reason for the existence of this alternative pathway for the reaction. This procedure was further applied to the synthesis of 2-amino-4-fluoroquinolines (41-53% yield).[160]

A novel synthesis of 3-aryl-4-aminocinnolines **40**, (52-75% yield) based on the base-induced cyclization of the corresponding hydrazones **39**, has been reported. The starting hydrazones were conveniently prepared from trifluoromethyl aryl ketones **38** and various arylhydrazones (*Scheme* 21).[166] Interestingly, the attempts to prepare fluorinated quinoxalines **42** from **43** using similar reaction conditions were unsuccessful. Treatment of **43** with various bases afforded **44** as a single product



Scheme 20

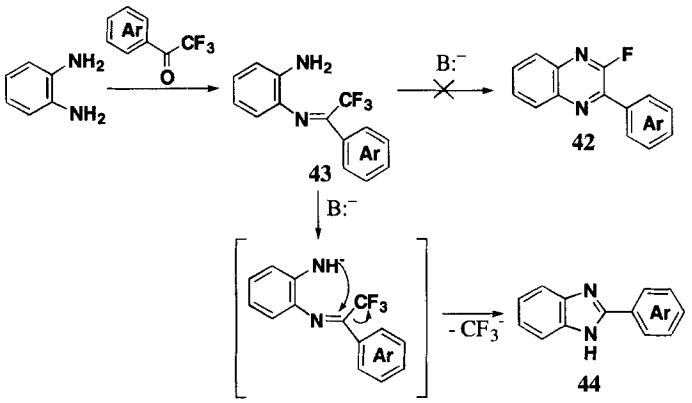
(45-73% yield, *Scheme* 22). We believe that the ionization of the amino group with base followed by the nucleophilic attack of electron-deficient carbon atom with NH^-, and elimination of CF_3 is a possible mechanism for this transformation.[167]



Scheme 21

V. CONCLUSION AND PERSPECTIVES

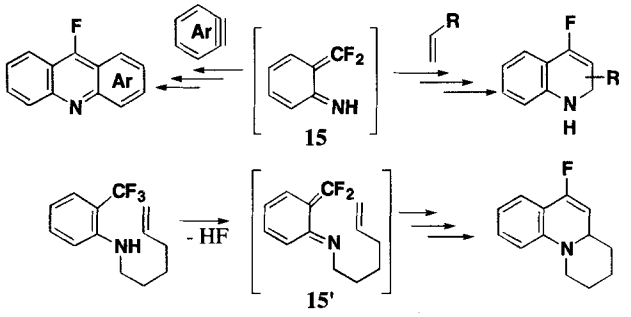
Trifluoromethyl group is a useful buiding block in organic chemistry. The presence of a negative charge in the position α to the CF_3 group results in the elimination of F^-, and the formation of intermediate terminal difluoroolefins. Numerous treatises report the application of this approach for the synthesis of fluorinated materials. Of a special interest is the preparation of heterocycles from



Scheme 22

trifluoromethylated aromatic compounds based on the chemistry of anionically activated CF_3 group. It is believed that the first step in these transformations is the elimination of HF from the starting trifluoromethylated compound, and formation of a highly reactive intermediate (for example, **15**). Series of naphthalenes, anthracenes, quinolines, acridines, and cinnolines were prepared using this methodology, and majority of these transformations are efficient one-pot procedures. Fluorine, or amino substituents can be introduced into the resulting aromatic compounds by careful selection of base for the reaction. Anionically activated CF_3 group also works as a CHO group equivalent when treated with organometallics, or dianions derived from aminophenol or aminothiophenol.

Currently, we are trying to further expand the use of trifluoromethylated aromatic compounds for the synthesis of fluorinated polyaromatic hydrocarbons. Trapping of the intermediate **15**, or **15'** by intra, or intermolecular cyclization reactions (*Scheme* 23) is another challenging area which is under investigation in our group.



Scheme 23

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