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Chemistry of fluoroalkyl cyanides

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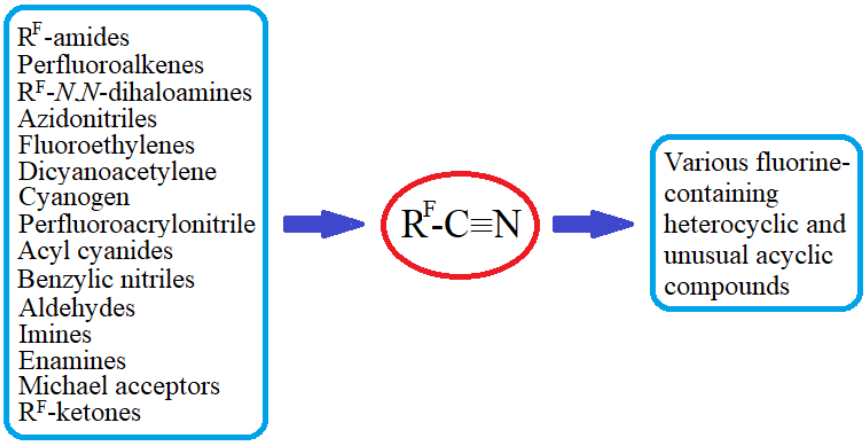
Abstract

This review is devoted to the chemistry of fluoroalkyl cyanides (R^F-nitriles): their synthesis and chemical properties. Syntheses of non-functionalized R^F-nitriles (FCH_2CN, F_2CHCN, CF_3CN, C_2F_5CN, FCH_2CH_2CN, etc.) and dinitriles (NCCHFCN, $NCCF_2CN$, $NCCF_2CF_2CN$, etc.) are considered. The synthesis of functionalized R^F-nitriles such as F_2NCF_2CN, $F_2NCClFCN$, Cl_2CFCN, Br_2CFCN, $(O_2N)_2CFCN$, $O_2NCF_2CH_2CH_2CN$, and dinitriles, such as $O(CF_2CN)_2$, $NCCF_2N{=}NCF_2CN$, is also considered. R^F-Nitriles are attractive electrophilic, enophilic, and dienophilic building-blocks: they were used in the synthesis of various fluorine-containing heterocyclic compounds, such as R^F-bearing pyridines, 1,3,5-triazines, tetrazoles, and others. R^F-nitriles were also used in the synthesis of unusual acyclic compounds, such as fluoroalkylated *N*,*N*-difluoroamines, $F_2NCF_2CF_2N{=}SF_2$, R^F-imino esters, and others.



Keywords: Fluoroalkyl cyanides, fluoroalkyl nitriles, fluorination, cycloaddition, fluoroalkylated *N*,*N*-dihaloamines

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1. Introduction

Fluorinated organic compounds attract much interest due to their unique physicochemical properties, biological activities, and because they are of great importance in medicine.[1-4] An electron-withdrawing R^F group bonded to a carbon atom that belongs to a double or triple bond, or a conjugated system, significantly increases the electrophilic, dienophilic and dienic (in the case of a conjugated system) properties of the molecule.[5,6] Fluoroalkyl cyanides (R^F-cyanides, R^F-nitriles) are a group of unique compounds, where a fluoroalkyl group is bonded to the highly polarized C≡N group. This fact dramatically increases the electrophilic as well as dienophilic properties of the C≡N group.

R^F-cyanides (R^FCN) can be divided into two groups: non-functionalized R^F-cyanides and functionalized R^F-cyanides. In non-functionalized R^F-cyanides, the R^F group contains only atoms of sp^3 hybridized carbon, as well as atoms of fluorine and, optionally, hydrogen. In functionalized R^F-cyanides, the R^F group besides sp^3-C, F, and, optionally, H, contains at least one non-fluorine heteroatom or an sp^2(sp)-C (a double/triple bond). Those non-functionalized R^F-cyanides, which don't have a hydrogen atom in their R^F groups, are perfluoroalkyl cyanides.

Trifluoroacetonitrile, CF_3CN, the parent perfluoroalkyl cyanide, is a symmetric top molecule. The measured dipole moment μ = 1.262 ± 0.010 D (measurements were made in a Stark-modulated microwave spectrometer).[7] The enthalpy of formation of CF_3CN is -118.9 kcal/mol.[8] The vibrational spectrum of this compound was originally assigned by Edgell and Potter.[9] The lowest frequency vibrational mode of this molecule was measured at 192 cm^{-1} and is assumed to be the -C-C≡N bond. Owing to the large dipole moment and the large thermal population, the spectra are intense and it is relatively easy to observe spectra in the excited vibrational state v_8 = 2. Physical properties of trifluoroacetonitrile such as critical temperature (311.11 K), critical pressure (524.75 lbf^{-2}), and critical density (0.470 g cm^{-3}) were measured.[10] Thermodynamic properties of trifluoroacetonitrile from 12 K to its boiling point (-67.68 °C) were explored.[11]

High resolution IR spectra over a range of temperatures from -80 to 250 °C of gaseous CF_3CN were published in 1970.[12]

The rotational spectra of the ground state and some excited states of CF_3CN have been studied by several authors.[13–18] The nuclear quadrupole hyperfine structure observed in the ground vibrational state has been the subject of Fourier transform work by Cox *et al.*[19]

The rotational spectra of CF_3CN for transitions at J'' = 16, 18-21, and 32 (100–200 GHz) were recorded at -78 °C (P ~0.01 torr).[20] These spectra are complex, similar to the spectra of $CF_3C{\equiv}CH$ in the v_{10} = 2 state,[21] having a superposition of three series for each J'' corresponding to l = 0 and l = ± 2 (kl > 0 or k < 0).[20]

The effect of electrode surface roughness on the breakdown characteristics of C_3F_7CN/CO_2 gas mixtures was explored: these mixtures are considered as a potential alternative for replacing SF_6 in high voltage power equipment.[22]

The proton affinities of R^F-nitriles such as CF_3CN (695 kJ/mol), CF_3CF_2CN (699 kJ/mol) and $CF_3(CF_2)_2CN$ (700 kJ/mol) were estimated.[23]

R^F-nitriles are able to form complexes with atoms and molecules, and adducts with anions. Thus, the rotational spectrum of the weakly bound (van der Waals) complex CF_3CN–argon has been observed and assigned.[24] The structure of this complex is T-shaped with a center of mass separation of 3.73 Å.[24] Centrifugal distortion analysis yields a weak bond stretching force constant of 1.92 Nm^{-1}.[24] The CF_3CN–H_2O complex has been studied by pulsed-nozzle Fourier transform microwave spectroscopy.[25] The rotational constants, centrifugal distortion constants, and the ^{14}N nuclear quadrupole coupling constants have been determined. The complex is T-shaped, with the oxygen atom of the water located 3.135 Å from the carbon atom of CF_3 of

the CF_3CN molecule.[25] Fluoride adducts of R^F-nitriles may be generated by bimolecular ion-molecule reactions. Calculated standard free energies (ΔG^o, kcal/mol) are: 21.9 for $CF_3C(F)=N^-$, 23.1 for $C_2F_5C(F)=N^-$, and 23.6 for $CF_3CF_2CF_2C(F)=N^-$.[26]

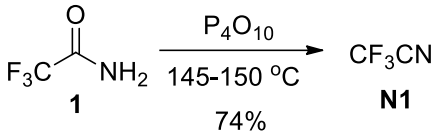
α-Functionalized R^F-nitriles are attractive intermediates in organic synthesis. α-Nitro groups significantly increase the reactivity of α-fluorinated nitriles. Thus, O_2NCF_2CN adds the CH_3 radical to the C≡N group four times as fast as CF_3CN, and $(O_2N)_2CFCN$ is more reactive than O_2NCF_2CN.[27]

The preparation of non-functionalized and functionalized R^F-nitriles involves a wide variety of synthetic methods. R^F-nitriles are excellent electrophilic, dienic, and dienophilic building-blocks: they were used in the synthesis of various fluorine-containing heterocyclic compounds, as well as unusual highly reactive acyclic compounds. Fluoroalkyl cyanides are important reagents for medicinal chemistry.

2. Synthesis of Fluoroalkyl Cyanides

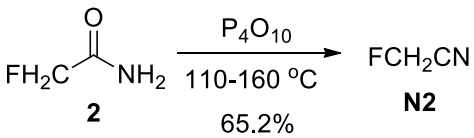
2.1. Dehydration of R^F-amides

In 1922, Swarts described the preparation of trifluoroacetonitrile (**N1**) by dehydration of trifluoroacetamide (**1**) with phosphorus anhydride at 145-150 °C.[28] In 1943, Gilman and Jones used essentially the same method for the preparation of trifluoroacetonitrile (74%), collected the product as a colorless liquid in a dry-ice-acetone trap (Scheme 1). The compound boiled at -63.9 °C (743 mm Hg).[29] Similarly, difluoroacetonitrile, F_2CHCN, was prepared from difluoroacetamide and P_4O_{10}. This nitrile was isolated as a liquid that boils at 22 °C.[30]



Scheme 1. Preparation of trifluoroacetonitrile (**N1**) from trifluoroacetamide (**1**) and P_4O_{10}.

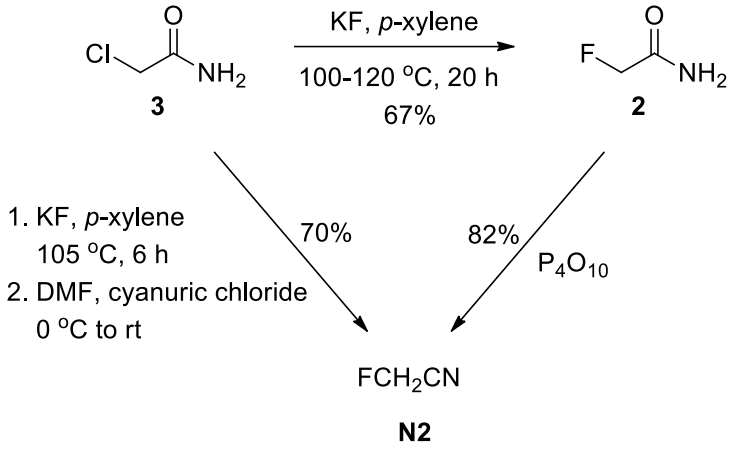
The first synthesis of fluoroacetonitrile (**N2**) was published by Swarts in 1922 who claimed that it was necessary to distil the amide with phosphoric anhydride under reduced pressure and to collect the distillate at -50 °C.[31] In 1949, Buckle *et al.* used a similar approach to the synthesis of fluoroacetonitrile (65.2%) from fluoroacetamide (**2**) (Scheme 2), for its toxicity testing.[32] The toxicity of fluoroacetonitrile on inhalation proved to be lower than that of methyl fluoroacetate because the nitrile is not hydrolyzed *in vivo* to the toxic fluoroacetic acid.[32-34]



Scheme 2. Preparation of fluoroacetonitrile (**N2**) from fluoroacetamide (**2**) and P_4O_{10}.

It was reported that fluoroacetonitrile (**N2**) can by synthesized from chloroacetamide (**3**) either via two separate procedures (a Finkelstein halogen exchange reaction with the formation of intermediate

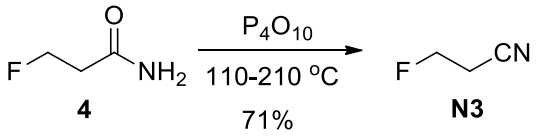
fluoroacetamide (**2**) (67%) and a dehydration reaction that gives **N2** in 82% yield) or via one-pot approach (70%) (Scheme 3).[35]



Scheme 3. Synthesis of fluoroacetonitrile (**N2**) from chloroacetamide (**3**).

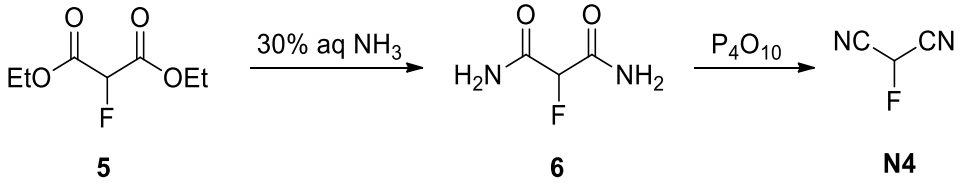
Chlorofluoroacetonitrile, ClFCHCN,[36] dichlorofluoroacetonitrile, Cl_2FCCN, and dibromofluoroacetonitrile, Br_2FCCN[37] were also prepared through the dehydration of the corresponding amides with P_4O_{10}.

3-Fluoropropionitrile (**N3**) (71%) was synthesized by heating amide **4** with P_4O_{10} at 110-210 °C (Scheme 4).[34]



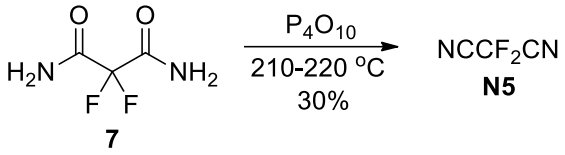
Scheme 4. Preparation of 3-fluoropropionitrile (**N3**) from 3-fluoropropioamide (**4**) and P_4O_{10}.

Different attempts have been undertaken to synthesize fluoromalononitrile through halogen-halogen exchange reaction by treating monobromomalononitrile with fluorinating agents.[38] Neither the variation of the fluorinating agent nor the alternation of the solvent, such as MeCN, DMSO, diglyme, and *N*-methylpyrrolidone have led to the desired compound, however, dehydration of fluoromalonamide (**6**) (prepared from ester **5**) with P_4O_{10} allowed preparation of fluoromalononitrile (**N4**) (Scheme 5).[38] Fluoromalononitrile (**N4**) is of particular interest due to the anticipated competing effects of substituents in its molecule: the π-conjugative interaction between the cyano groups and the strongly electron-withdrawing fluorine atom.[39]



Scheme 5. Preparation of fluoromalononitrile (**N4**) from fluoromalonamide (**6**) and P_4O_{10}.

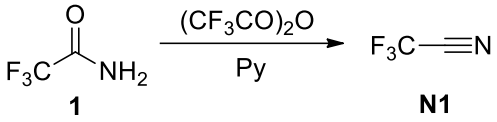
Dehydration of difluoromalonamide (**7**) with P_4O_{10} at 210-220 °C gave difluoromalononitrile (**N5**) in 30% yield (Scheme 6).[40]



Scheme 6. Preparation of difluoromalononitrile (**N5**) from difluoromalonamide (**7**) and P_4O_{10}.

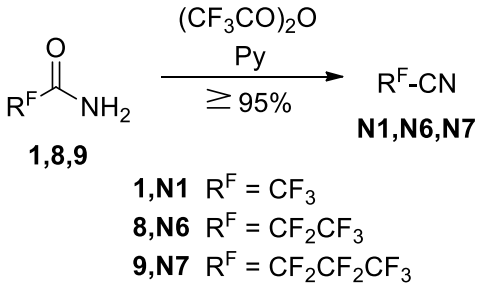
Similarly, tetrafluorosuccinonitrile, $NCCF_2CF_2CN$ (9%),[40] hexafluoroglutaronitrile, $NCCF_2CF_2CF_2CN$,[40] and octafluoroadiponitrile, $NCCF_2CF_2CF_2CF_2CN$ (64%) were prepared from the corresponding fluorinated diamides and P_4O_{10}.[41]

The dehydration of trifluoroacetamide (**1**) under mild conditions (trifluoroacetic anhydride/pyridine) generates CF_3CN, which is transferred directly into the reactive medium.[42] To effect the dehydration, $(CF_3CO)_2O$ was dissolved in pyridine and cooled to room temperature prior to its addition to a solution of trifluoroacetamide. This exothermic premixing prevents the formation of volatile impurities contaminating the newly formed CF_3CN.[42] The solution of CF_3CN was added through a dropping funnel to a solution of CF_3CONH_2 (Scheme 7).[42]



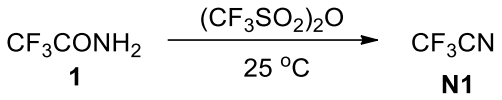
Scheme 7. Preparation of trifluoroacetonitrile (**N1**) from trifluoroacetamide (**1**) and $(CF_3CO)_2O$.

The high-yield syntheses of CF_3CN **N1**, C_2F_5CN **N6**, and heptafluorobutyronitrile (**N7**) under mild reaction conditions using readily available trifluoroacetamide (**1**), pentafluoropropionamide (**8**), heptafluorobutanamide (**9**), and trifluoroacetic anhydride were described (Scheme 8).[43]



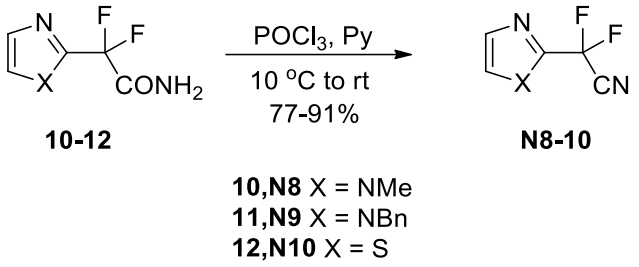
Scheme 8. Dehydration of R^F-amides with $(CF_3CO)_2O$/Py.

Many other dehydrating agents can be used to transform R^F-amides into R^F-nitriles. Thus, trifluoromethanesulfonic anhydride was used to transform trifluoroacetamide (**1**) into trifluoroacetonitrile (**N1**) at 25 °C (Scheme 9).[44]



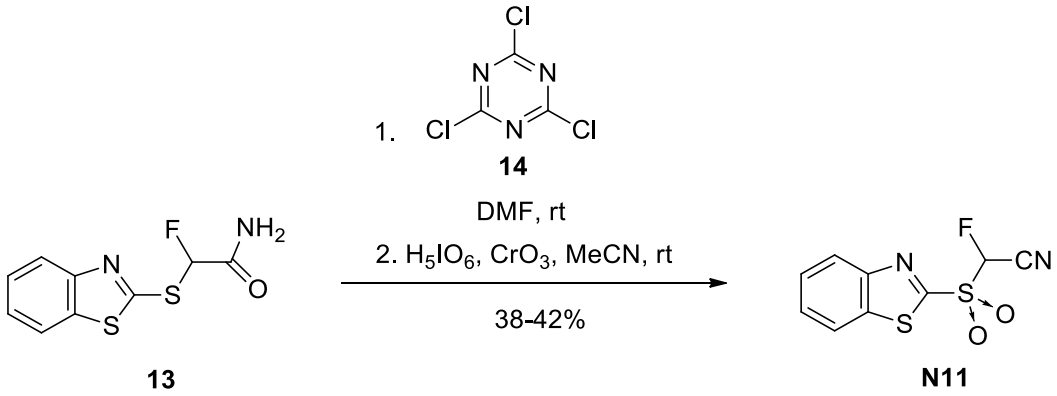
Scheme 9. Dehydration of trifluoroacetamide (**1**) with $(CF_3SO_2)_2O$.

Difluoroamides **10-12** were transformed into the corresponding nitriles **N8-10** in 77–91% yield upon treatment with $POCl_3$ in pyridine at 10 °C to rt (Scheme 10).[45]



Scheme 10. Synthesis of α-functionalized α,α-difluoronitriles **N8-10**

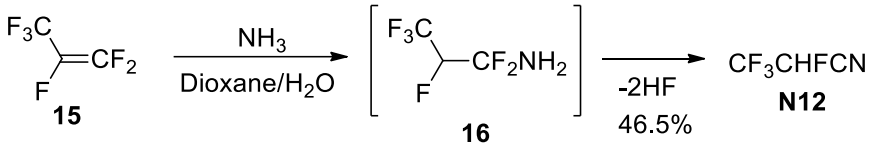
Reaction of α-fluoroamide **13** with cyanuric chloride (**14**) afforded monofluorinated nitrile **N11**: the crude reaction mixture was subjected to oxidation with H_5IO_6/CrO_3 without prior purification, to give the desired **N11** in isolated yields ranging from 38 to 42% (Scheme 11).[46]



Scheme 11. Dehydration of amide **13** with cyanuric chloride (**14**).

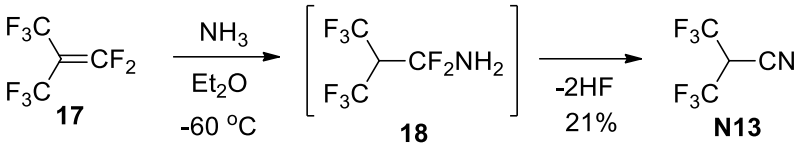
2.2. Hydroamination of perfluoroalkenes

R^F-nitriles can be prepared through hydroamination of perfluoroalkenes. Thus, treatment of perfluoropropylene (**15**) with ammonia in aqueous dioxane resulted in the formation of α-hydroperfluoropropionitrile (**N12**) as the result of dehydrofluorination of intermediate amine **16** (Scheme 12).[47]



Scheme 12. Hydroamination of perfluoropropylene (**15**).

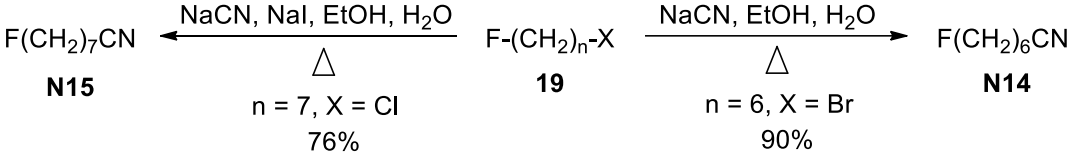
Similarly, 3,3,3-trifluoro-2-(trifluoromethyl)propanenitrile (**N13**) was synthesized from perfluoroisobutylene (**17**) and NH_3 via the HF elimination from intermediate amine **18** (Scheme 13).[47]



Scheme 13. Hydroamination of perfluoroisobutylene (**17**).

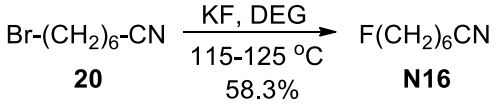
2.3. Nucleophilic substitution of alkyl halides

Terminally monofluorinated nitriles, 7-fluoroheptanenitrile (**N14**) (90%) and 8-fluorooctanenitrile (**N15**) (76%) were synthesized from the corresponding fluorohaloalkanes **19** and NaCN (Scheme 14).[34]



Scheme 14. Synthesis of terminally monofluorinated nitriles **N14** and **N15** via nucleophilic substitution.

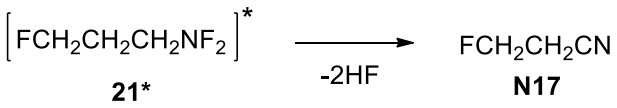
The reaction of 7-bromoheptanenitrile (**20**) with anhydrous KF in DEG gave 7-fluoroheptanenitrile (**N16**) in 58.3% yield (Scheme 15).[34]



Scheme 15. Synthesis of 7-fluoroheptanenitrile (**N16**).

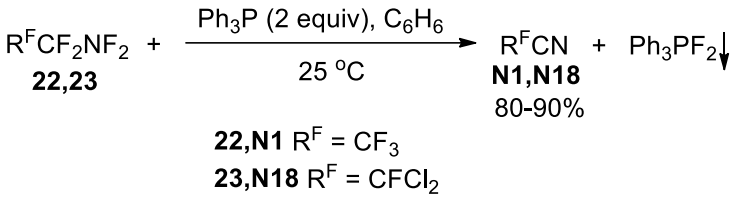
2.4. Synthesis from *N*,*N*-dihaloamines

Irradiation (253.7 nm) of cyclopropane with tetrafluorohydrazine, N_2F_4, resulted in a complex mixture including $F(CH_2)_3NF_2$ (**21**) and $F(CH_2)_2CN$ (**N17**), and the last is the result of dehydrofluorination of 1-difluoramino-3-fluoropropane (**21**) in its excited state $[F(CH_2)_3NF_2]^*$ **21*** (Scheme 16).[48]



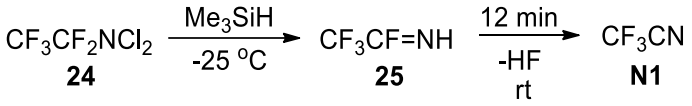
Scheme 16. Formation of 3-fluoropropanenitrile from $F(CH_2)_3NF_2$ **21** in its excited state $[F(CH_2)_3NF_2]^*$ **20***.

It was found that triphenylphosphine reacts smoothly with R^F-*N*,*N*-difluoroamines **22** and **23** in a 2:1 stoichiometry to afford the corresponding R^F-nitriles **N1** and **N18** in 80-90% yield. The reaction is rapid, free of side products (Scheme 17).[49]



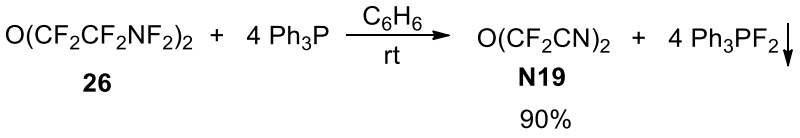
Scheme 17. Synthesis of R^F-nitriles **N1,N18** from R^F-*N*,*N*-difluoroamines **22**,**23**.

The reaction of *N*,*N*-dichloro(pentafluoroethyl)amine (**24**) with Me_3SiH at -25 °C resulted in the formation of unstable imidoyl fluoride **25**.[50] Decomposition of **25** to trifluoroacetonitrile (**N1**) is complete after about 12 min at ambient temperature (Scheme 18).[50]



Scheme 18. Preparation of trifluoroacetonitrile (**N1**) from *N*,*N*-dichloro(pentafluoroethyl)amine (**24**)**.**

The reaction of α,ω-bisdifluoriamine (**26**) with Ph_3P in benzene at room temperature afforded R^F-dinitrile of formula $O(CF_2CN)_2$ **N19** in 90% yield (Scheme 19).[49]



Scheme 19. Synthesis of $O(CF_2CN)_2$.

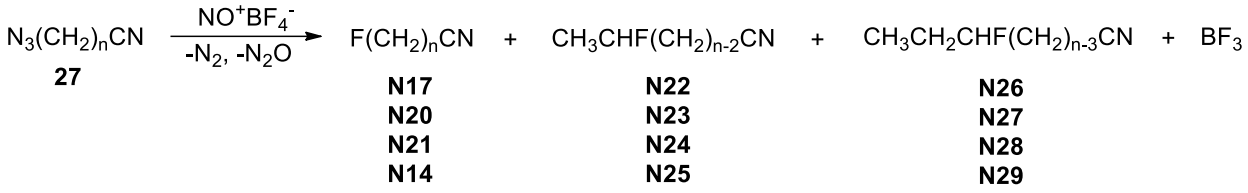
2.5. Synthesis from azidonitriles

It was shown that azidonitriles **27** react with $NO^+BF_4^-$ to produce R^F-nitriles **N17,N14,N20-29** in nearly quantitative yields.[51] Results from the reactions of a series of azidonitriles **27** with $NO^+BF_4^-$ in $CDCl_3$ are given in Table 1. The nature of the reaction and the extent of rearrangement serve to classify this fluoride transfer process as involving carbenium ion intermediates.[51] However, since fluoride substitution does not occur in similar reactions of $NO^+BF_4^-$ with monofunctional alkyl azides, the authors of the research suggested that fluoride transfer cannot be represented simply as an intermolecular reaction of the tetrafluoroborate anion with a carbenium ion. The nitrile group is involved in the fluoride transfer process in the suggested mechanism.[51]

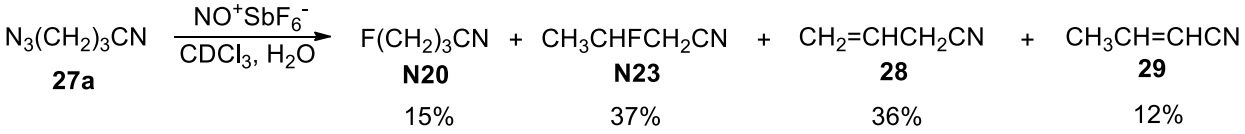
Some amounts of H_2O (1-2 equiv) added to the nitrosonium salt prior to the azidonitrile produced an observable increase in the rate of gas evolution but did not measurably affect the reaction products.[51]

Treatment of 4-azidobutanenitrile (**27a**) with nitrosonium hexafluoroantimonate, $NO^+SbF_6^-$, in deuterochloroform containing 1.0 equiv of H_2O resulted in the product distribution given below (Scheme 20).[51]

Table 1. Product yields from reactions of azidonitriles **27** with $NO^+BF_4^-$ in $CDCl_3$ at 25 °C[51]



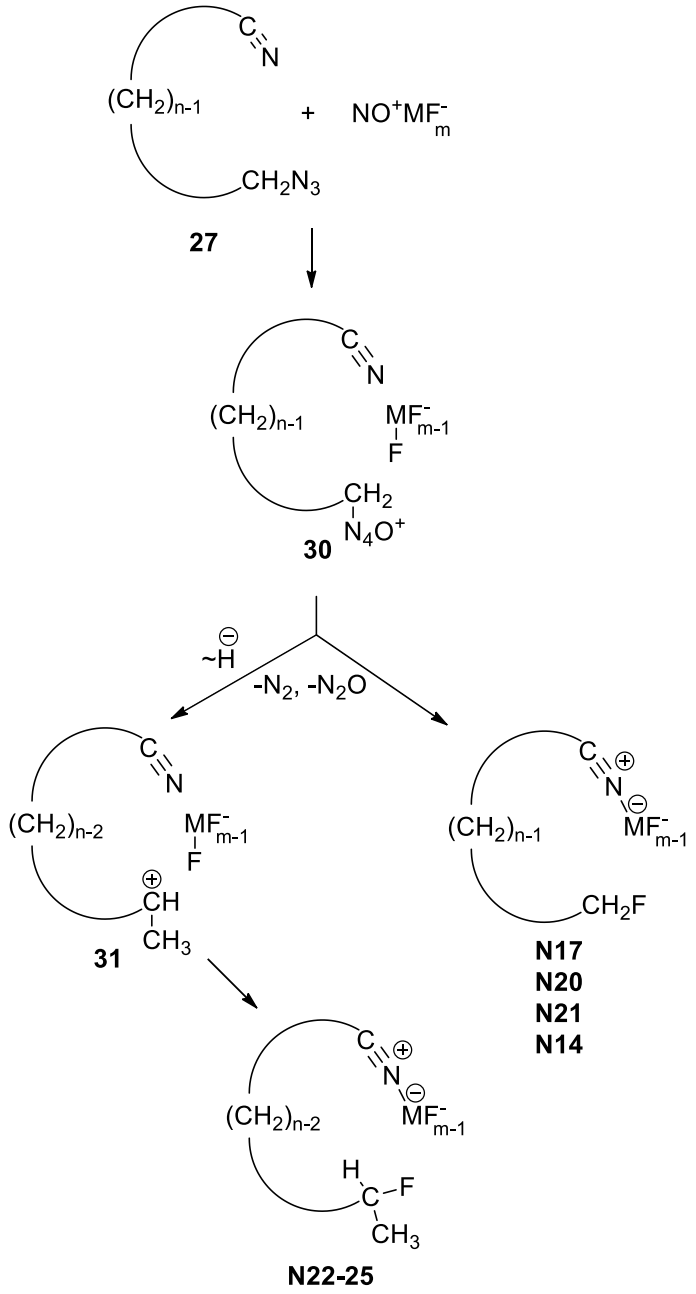
Entry	n	R^F-nitriles	Yield, %		
			$F(CH_2)_nCN$	$CH_3CHF(CH_2)_{n-2}CN$	$CH_3CH_2CHF(CH_2)_{n-3}CN$
1	2	**N17,N22,N26**	100	-	-
2	3	**N20,N23,N27**	40	60	-
3	4	**N21,N24,N28**	22	78	-
4	6	**N14,N25,N29**	30	45	25



Scheme 20. Product distribution after treatment of 4-azidobutanenitrile (**27a**) with $NO^+SbF_6^-$

4-Azidobutanenitrile (**27a**) reacted three-times slower with $NO^+BF_4^-$ to give **N20** (32%), **N23** (61%), 3-butenenitrile (**28**) (6%), and 2-butenenitrile (**29**) (1%). Nitrosonium hexafluorophosphate, $NO^+PF_6^-$, was slightly more reactive than $NO^+BF_4^-$ towards 4-azidobutanenitrile yielding **N20** (18%), **N25** (72%), **28** (7%), and **29** (3%).[51]

It was noted[51] that these results suggest that fluoride transfer from complex fluoride anions occurs through association of the developing Lewis acid with the basic nitrile group, as described in Scheme 21. The reactivities of nitrosonium salts with azidonitriles follow the order of Lewis acidities of the developing Lewis acids (SbF_5>PF_5>BF_3), and indicate a requirement for association of these developing acids with the nitrile group during nitrosation.[51] Water acts to complex with the developed Lewis acid, decreasing the degree of association of the Lewis acid with unreacted azidonitrile **27**.[51]

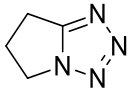


Scheme 21. Mechanism of formation of monofluoronitriles **N17,N20,N21,N14** and **N22-25**.

Extensions of this nitrosative fluoride substitution process were reported.[52] Nitrosative decomposition of azidonitriles **27** under the action of either $NO^+BF_4^-$, or $NO^+PF_6^-$, or $NO^+SbF_6^-$, gave mixtures fluoroalkyl cyanides and nonfluorinated substances.[52]

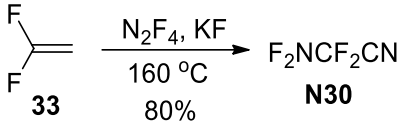
Thus, reactions of these nitrosonium salts with 4-azidobutanenitrile (**27a**) at 25 °C produced mixtures of $F(CH_2)_3CN$ **N21**, CH_3CHFCH_2CN **N24**, $CH_2=CHCH_2CN$ **28**, $CH_3CH=CHCN$ **29**, and trimethylenetetrazole (**32**) (Table 2).[52]

Table 2. Product yields from nitrosative decomposition of 4-azidobutanenitrile (**27a**)[52]

Reactant	Yield, %				
	$F(CH_2)_3CN$ **N21**	CH_3CHFCH_2CN **N24**	$CH_2=CHCH_2CN$ **28**	$CH_3CH=CHCN$ **29**	 **32**
$NO^+BF_4^-$	26	37	5	4	28
$NO^+PF_6^-$	15	61	< 1	< 1	24
$NO^+SbF_6^-$	4	10	10	8	68
$NO^+BF_4^-$ + H_2O	38	61	1	< 1	< 1
$NO^+PF_6^-$ + H_2O	18	72	7	3	< 1
$NO^+SbF_6^-$ + H_2O	15	37	36	12	< 1
BF_3 + $NO^+BF_4^-$	22	16	< 1	< 1	62
SbF_5 + $NO^+SbF_6^-$	< 1	< 1	< 1	< 1	100

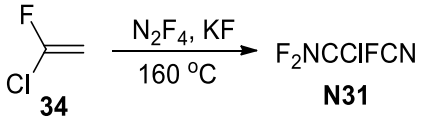
2.6. Reactions of alkenes and alkynes with N_2F_4

α-Functionalized R^F-nitriles are a large group of synthetically attractive building-blocks. (Difluoroamino)difluoroacetonitrile, compound **N30**, was synthesized in 80% yield through the reaction of 1,1-difluoroethylene (**33**) and tetrafluorohydrazine in the presence of KF (Scheme 22).[53]



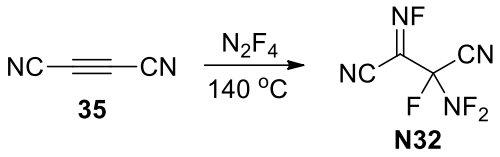
Scheme 22. Synthesis of (difluoroamino)difluoroacetonitrile (**N30**) from 1,1-difluoroetylene (**33**) and N_2F_4.

Similarly, $F_2NCClFCN$ **N31** was synthesized from 1-chloro-1-fluoroethylene (**34**) and N_2F_4 (Scheme 23).[54]



Scheme 23. Synthesis of $F_2NCClFCN$ **N31**.

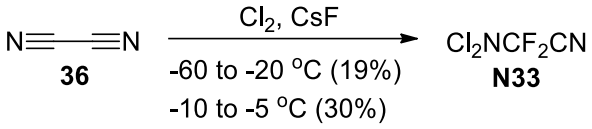
Treatment of dicyanoacetylene (**35**) with N_2F_4 at 140 °C gave functionalized α-fluorodinitrile **N32** (Scheme 24).[55]



Scheme 24. Synthesis of functionalized α-fluorodinitrile **N32**.

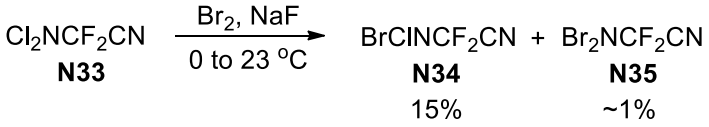
2.7. Halogenation of nitriles

Cesium fluoride promoted chlorination of cyanogen (**36**) with Cl_2 (1.2 equiv) at -60 to -20 °C gave Cl_2NCF_2CN **N33** in 19% yield.[56] Harsher conditions (-10 to -5 °C) and excess Cl_2 (1.5 equiv) increased the yield to 30% (Scheme 25). The catalytic effect of fluorides is based on the formation of the intermediate fluoride adducts (in this case, $N{\equiv}C\text{-}C(F){=}N^-$).[56]



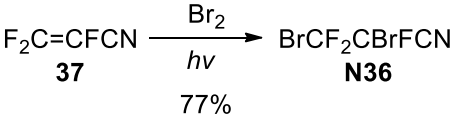
Scheme 25. Cesium fluoride promoted chlorination of cyanogen (**36**) with Cl_2.

Reaction of Cl_2NCF_2CN **N33** with Br_2 at 0 to 23 °C in the presence of NaF afforded difluoronitriles $BrClNCF_2CN$ **N34** (15%) and Br_2NCF_2CN **N35** (~1%) (Scheme 26).[56]



Scheme 26. Bromination of Cl_2NCF_2CN **N33** in the presence of NaF.

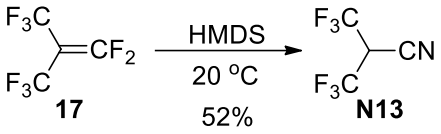
Bromination of perfluoroacrylonitrile (**37**) with Br_2 yielded 2,3-dibromo-2,3,3-trifluoropropanenitrile (**N36**) in 77% yield. Irradiation from an infrared lamp was required to start the reaction (Scheme 27).[57]



Scheme 27. Bromination of perfluoroacrylonitrile with Br_2.

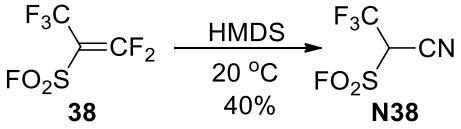
2.8. Reaction of fluoroalkenes with HMDS

2*H*-hexafluoroisobutyronitrile (**N13**) was obtained in 52% yield by the reaction of HMDS with a large excess of perfluoroisobutylene (**17**) at 20 °C (Scheme 28).[58]



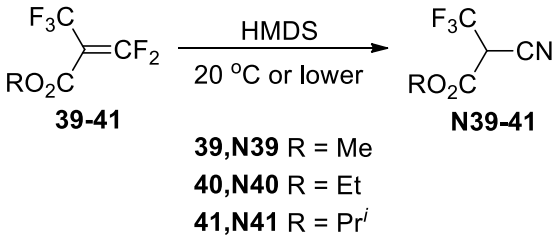
Scheme 28. Synthesis of 2*H*-hexafluoroisobutyronitrile (**N13**).

Similarly, α-functionalized β-trifluorinated nitrile **N38** was synthesized in 40% yield from the corresponding fluoroalkene **38** (Scheme 29).[58]



Scheme 29. Synthesis of α-functionalized β-trifluorinated nitrile **N38**.

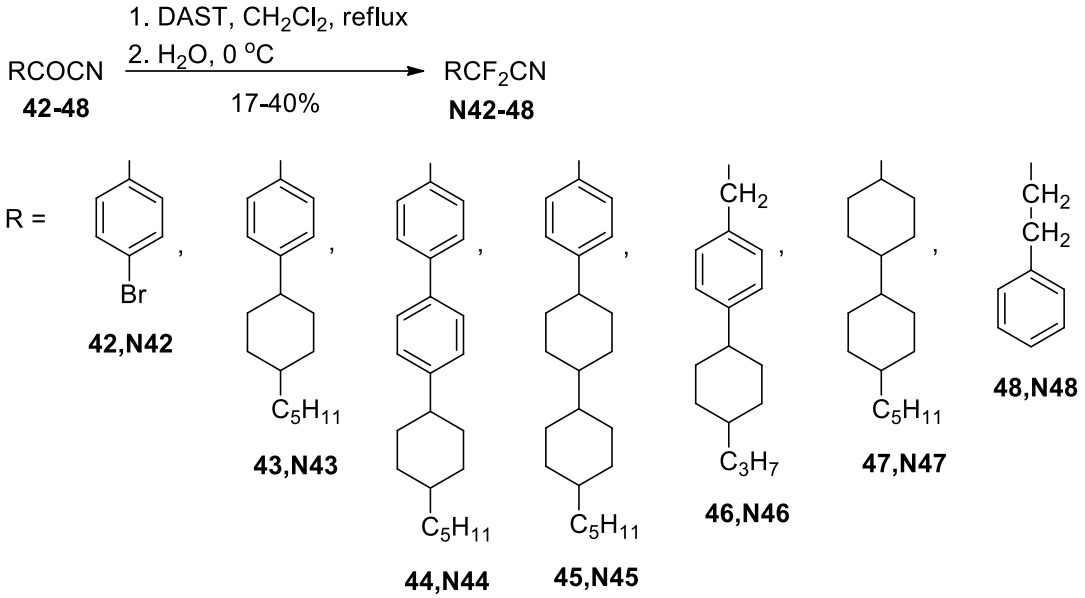
The same approach was used for the preparation of esters of 2-cyano-3,3,3-trifluoropropionic acid **N39-41**, which were synthesized in high yields from esters of perfluoromethacrylic acid **39-41** by reaction with HMDS (Scheme 30).[58]



Scheme 30. Synthesis of β-trifluorinated nitriles **N39-41**.

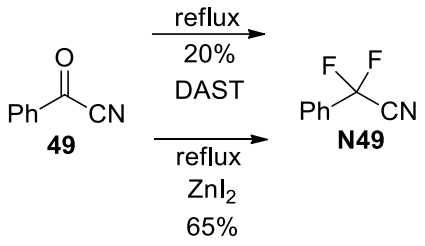
2.9. Reaction of acyl cyanides with DAST

Reactions of acyl cyanides with DAST without a catalyst give α-difluorinated nitriles in low yields.[59,60] Thus, treatment of acyl cyanides **42-48** with DAST gave α,α-difluoronitriles **N42-48** in low yields (17-40%) (Scheme 31).[59]



Scheme 31. Reaction of acyl cyanides **42-48** with DAST.

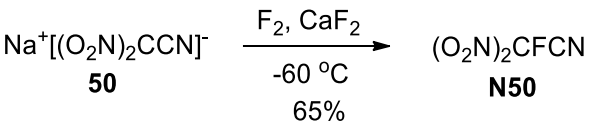
The reaction of benzoyl cyanide (**49**) with DAST gave 2-phenyl-2,2-difluoroacetonitrile (**N49**) in 20% yield. The same reaction conducted in the presence of ZnI_2 as a catalyst resulted in **N49** in 65% yield (Scheme 32).[60]



Scheme 32. Synthesis of 2-phenyl-2,2-difluoroacetonitrile (**N49**).

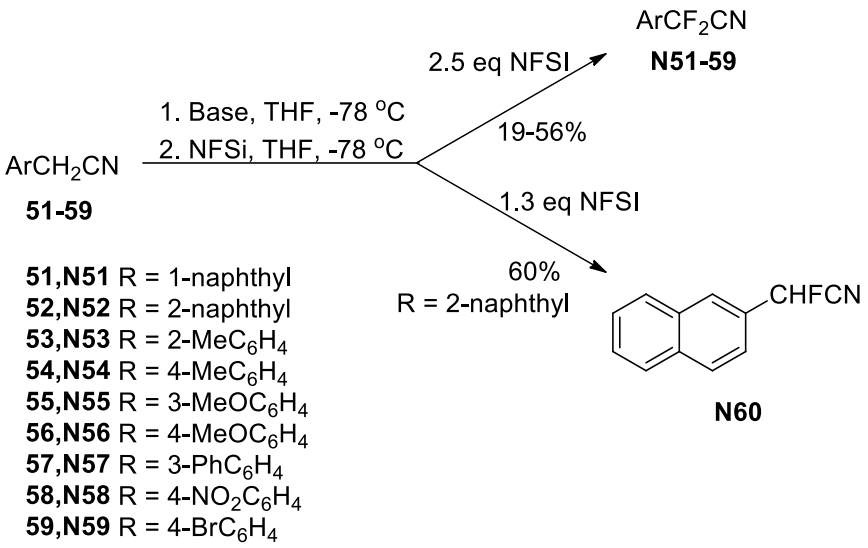
2.10. Fluorination of active methylene nitriles

Direct fluorination of sodio-dinitroacetonitrile (**50**) with F_2 in the presence of CaF_2 allows preparation of fluorodinitroacetonitrile (**N50**), which was isolated in 65% yield (Scheme 33).[61]



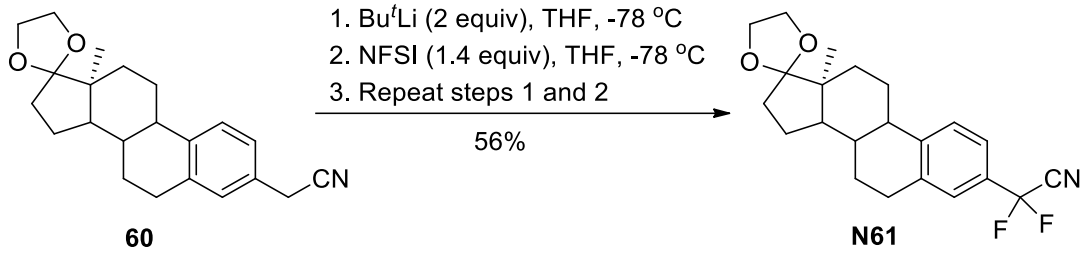
Scheme 33. Synthesis of fluorodinitroacetonitrile (**N50**).

Electrophilic fluorination of benzylic nitriles **51-59** with NFSI (2.5 equiv) gave α,α-difluoronitriles **N51-59** in 19-60% yield.[62] In the case of 1.3 equiv of NFSI, monofluorinated nitrile **N60** was obtained in 60% yield (Scheme 34).[62]



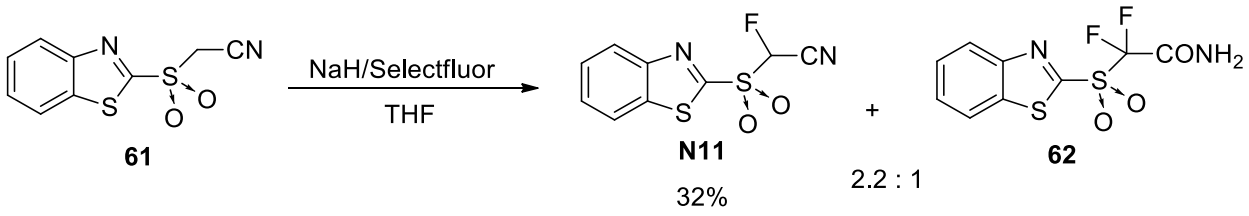
Scheme 34. Synthesis of α-fluorinated nitriles **N51-60**.

Similarly, the precursor of estrone-3-sulfate analogues, difluoronitrile **N61**, was synthesized from benzylic nitrile **60** in 56% yield (Scheme 35).[63]



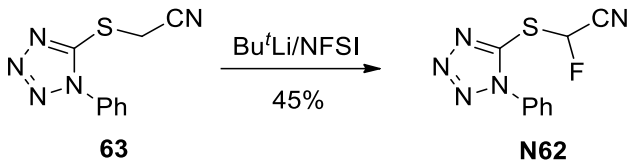
Scheme 35. Synthesis of α,α-difluoronitrile **N61**.

α-Fluorination of active methylene nitrile **61** with NaH/Selectfluor in THF resulted in a mixture of monofluoro derivative **N11** (32%), and difluoroamide by-product **62** (2.2:1 ratio, respectively), along with starting material (Scheme 36).[46] Most likely, the formation of amide **62** is the result of the hydrolysis of the corresponding α,α-difluoronirile, after the reaction mixture was quenched with aqueous NH_4Cl.[46]



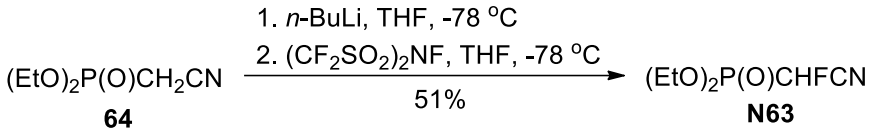
Scheme 36. Synthesis of α-monofluorinated nitrile **N11** from nitrile **61**.

Monofluorinated nitrile **N62** was synthesized in 45% yield from nitrile **63** and Bu^{t}Li/NFSI (Scheme 37).[46]



Scheme 37. Synthesis of α-fluoronitrile **N62**.

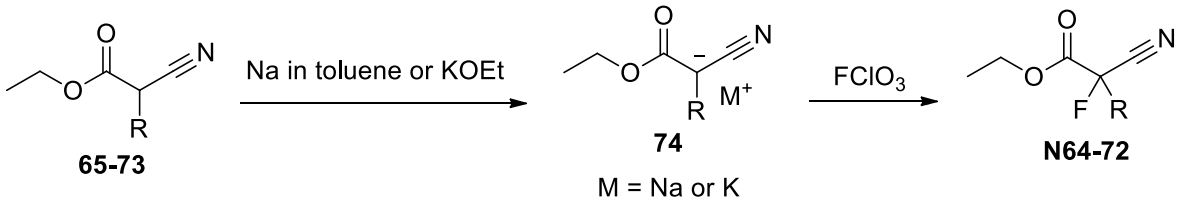
Fluorination of diethyl cyanomethanephosphonate (**64**) with $(CF_3SO_2)_2NF$ at -78 °C in THF in the presence of *n*-butyllithium afforded an α-functionalized α-fluoronitrile, diethyl cyanofluoromethanephosphonate (**N63**), in 51% yield (Scheme 38).[64]



Scheme 38. Synthesis of α-functionalized α-fluoronitrile **N63**.

Fluorination of ethyl α-cyanoalkanoates **65-73** with perchloryl fluoride, $FClO_3$, gives ethyl α-cyano-α-fluoroalkanoates **N64-72** via intermediate salts **72**. The synthesized **N64-72** and their yields are shown in Table 3.[65]

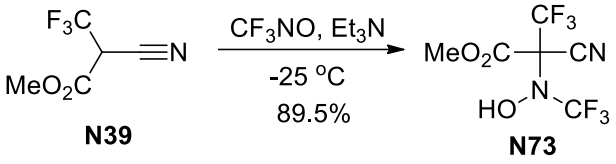
Table 3. Fluorination of alkylated ethyl α-fluorocyanoacetate derivatives **65-73** with $FClO_3$[65]



Entry	R	Substrate	Product	Yield, %
1	Me	**65**	**N64**	35
2	Et	**66**	**N65**	80
3	Pr	**67**	**N66**	48
4	Pr^i	**68**	**N67**	80
5	Bu	**69**	**N68**	47
6	Bu^i	**70**	**N69**	78
7	Bu^s	**71**	**N70**	46
8	Bn	**72**	**N71**	49
9	$EtOC(O)CH_2CH_2$	**73**	**N72**	71

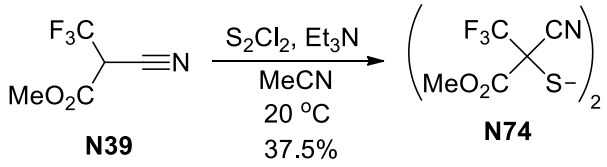
2.11. Reactions of active methylene CF_3-nitriles with electrophiles

Reaction of **N39** with trifluoronitrosomethane at -25 °C in the presence of a catalytic amount of Et_3N gave α-trifluoromethylated hydroxylaminonitrile **N73** in 89.5% (Scheme 39).[58]



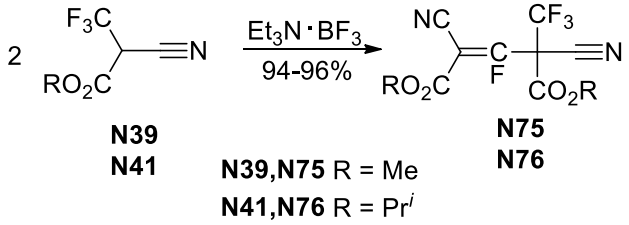
Scheme 39. Synthesis of α-trifluoromethylated hydroxylaminonitrile **N73**.

Reaction of **N39** with S_2Cl_2 in MeCN at 20 °C in the presence of Et_3N yielded another α-CF_3-nitrile, bis-(α-carbomethoxy-α-cyanotrifluoroethyl)disulfide (**N74**) in 37.5% yield (Scheme 40).[58]



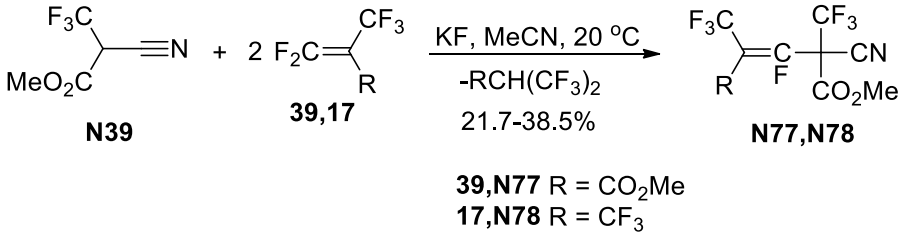
Scheme 40. Synthesis of bis-(α-carbomethoxy-α-cyanotrifluoroethyl)disulfide (**N74**).

R^F-nitriles **N39** and **N41**, in the presence of a mild dehydrofluorinating reagent $Et_3N{\cdot}BF_3$, at -10 °C quantitatively convert into CF_3-dinitriles **N75** and **N76,** respectively (Scheme 41).[58]



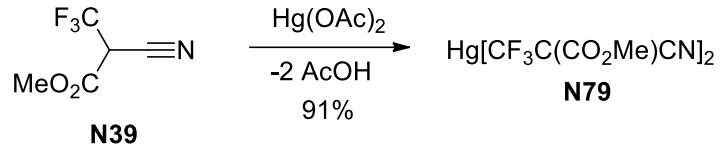
Scheme 41. Synthesis of CF_3-dinitriles **N75** and **N76**.

Reaction of α-CF_3-nitrile **N39** with fluorinated alkenes **39** and **17** in the presence of KF in MeCN at 20 °C afforded fluorinated nitriles **N77** and **N78**, respectively, in 21.7-38.5% yield (Scheme 42).[58]



Scheme 42. Synthesis of fluorinated nitriles **N77** and **N78**.

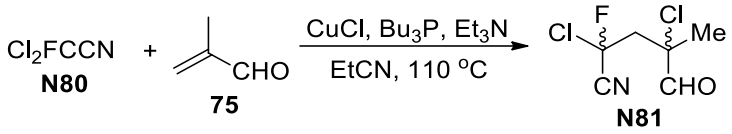
Mercurated CF_3-nitrile **N79** (91%) was prepared from **N39** and mercuric acetate (Scheme 43).[58]



Scheme 43. Synthesis of mercurated CF_3-nitrile **N79**.

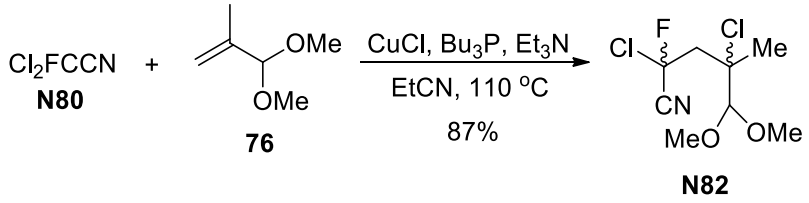
2.12. Addition of dichlorofluoroacetonitrile to alkenes

The addition of dichlorofluoroacetonitrile (**N80**) to methacrolein (**75**) in propionitrile at 110 °C in the presence of CuCl as catalyst and tributylphosphine/triethylamine as cocatalysts resulted in the formation of functionalized α-fluoronitrile **N81** as a mixture of diastereomers (Scheme 44).[37]



Scheme 44. Synthesis of γ-formylated α-fluoronitrile **N81**.

The addition of dichlorofluoroacetonitrile (**N80**) to methacrolein dimethyl acetal (**76**) resulted in a functionalized α-fluoronitrile, 2,4-dichloro-2-fluoro-4-methyl-5,5-dimethoxypentmenitrile (**N82**), which was obtained as a mixture of diastereomers in 87% yield (Scheme 45).[37]

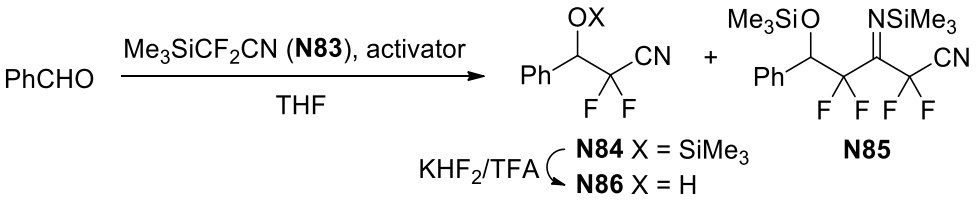


Scheme 45. Synthesis of α-fluoronitrile **N82**.

2.13. Fluoroalkylation of aldehydes, imines, and enamines

Fluoroalkylation of benzaldehyde with difluoro(trimethylsilyl)acetonitrile (**N83**) (its preparation is considered in paragraph 2.16, Scheme 51) in the presence of an activator gave difluoronitrile **N84** as the major product and some amounts of **N85** as the by-product, which is likely produced from the nucleophilic addition of **N83** to primary product **N84** (Table 4).[66] After desilylative workup with KHF_2/CF_3CO_2H and column chromatography, the final product, α,α-difluoro-β-hydroxynitrile **N86** was isolated in 82% yield (entry 9). The use of LiOAc as an activator gave **N84** with 93-95% conversion and a minimum amount of by-product **N85**.[66]

Table 4. Fluoroalkylation of benzaldehyde with difluoro(trimethylsilyl)acetonitrile (**N83**)[66]

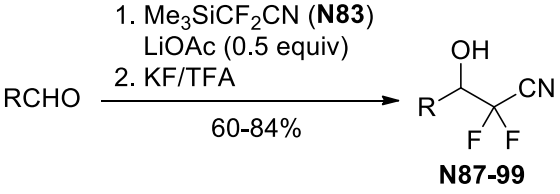


Entry	Activator	**N83**, equiv	Conditions	Conversion, %	**N84**:**N85** ratio
1	CsF, 10%	1.3	0 °C, 1 h	80	11:1
2	TBAT, 10%	1.3	0 °C, 1 h	87	15:1
3	Bu_4NOAc, 10%	1.3	0 °C, 1 h	73	14:1
4	NaOAc, 10%	1.3	0 °C, 1 h	18	>30:1
5	NaOAc, 10%	1.3	rt, 24 h	96	14:1
6	KOAc, 10%	1.3	rt, 18 h	>98	6:1
7[a]	KOAc, 10%	1.3	0 °C, 2 h	84	5:1
8	LiOAc, 10%	1.3	rt, 24 h	78	>30:1
9	LiOAc, 50%	2.0	rt, 18 h	93 (82[b])	>30:1
10	LiOAc, 50%	1.05	50 °C, 3 h	95 (85[b])	>30:1

[a]DMF as solvent. [b]Isolated yield of **N86**.

The results of the fluoroalkylation of various aldehydes with difluoro(trimethylsilyl)acetonitrile (**N83**) in the presence of LiOAc are shown in Table 5.[66]

Table 5. Reaction of aldehydes with Me_3SiCF_2CN **N83**[66]



Method A: **N83** (2.0 equiv), rt, 18 h
Method B: **N83** (1.05 equiv), 50 °C, 3 h

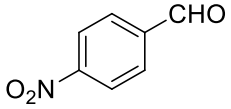
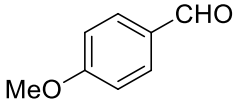
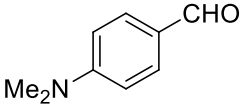
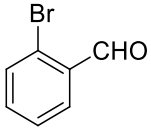
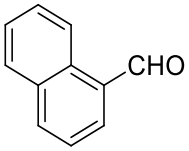
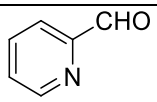
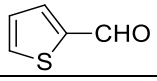
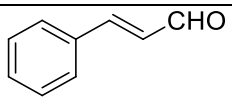
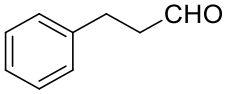
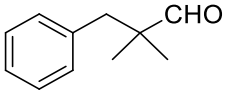
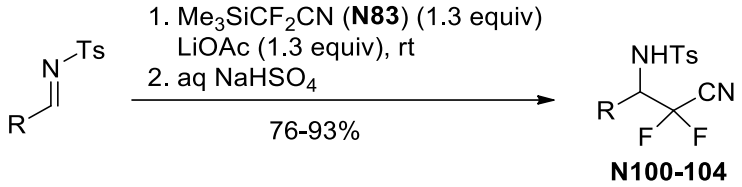
Entry	Aldehyde	Method	Product	Yield of product, %
1		A	**N87**	70
2		B	**N88**	77
3		A	**N89**	75
4		B	**N90**	60

Table 5. Continued

Entry	Aldehyde	Method	Product	Yield of product, %
5		B	**N91**	84
6		B	**N92**	72
7		B	**N93**	73
8		A	**N94**	72
9		A	**N95**	72
10		A	**N96**	72
11		B	**N97**	70
12		A	**N98**	65
13		B	**N99**	66

Fluoroalkylation of *N*-tosylimines with **N83** in the presence of LiOAc allows preparation of α,α-difluorinated β-tosylaminonitriles **N100-104**, which were isolated in 76-93% yield (Table 6).[66]

Table 6. Preparation of α,α-difluorinated β-tosylaminonitriles **N100-104**[66]



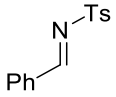
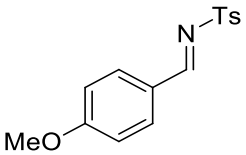
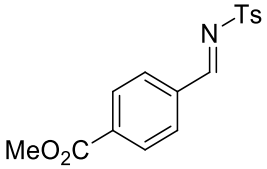
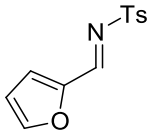
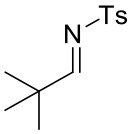
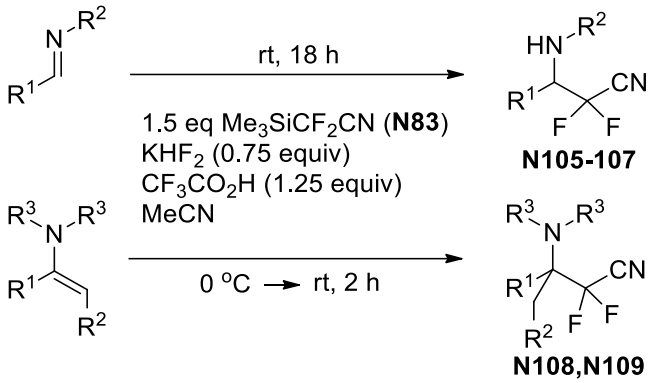
Entry	Imine	Time, h	Product	Yield of product, %
1		18	**N100**	93
2		48	**N101**	78
3		18	**N102**	91

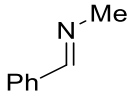
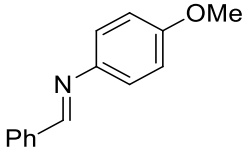
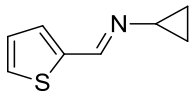
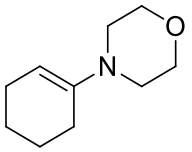
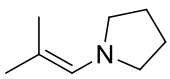
Table 6. Continued

Entry	Imine	Time, h	**Product**	Yield of product, %
4		18	**N103**	82
5		48	**N104**	76

Fluoroalkylation of unactivated imines and enamines with **N83** under acidic conditions in MeCN was explored, and *N*-monosubstituted (**N105-107**) and *N*,*N*-disubstituted (**N108** and **N109**) α,α-difluorinated β-aminonitriles were isolated in 66-95% yield (Table 7).[66]

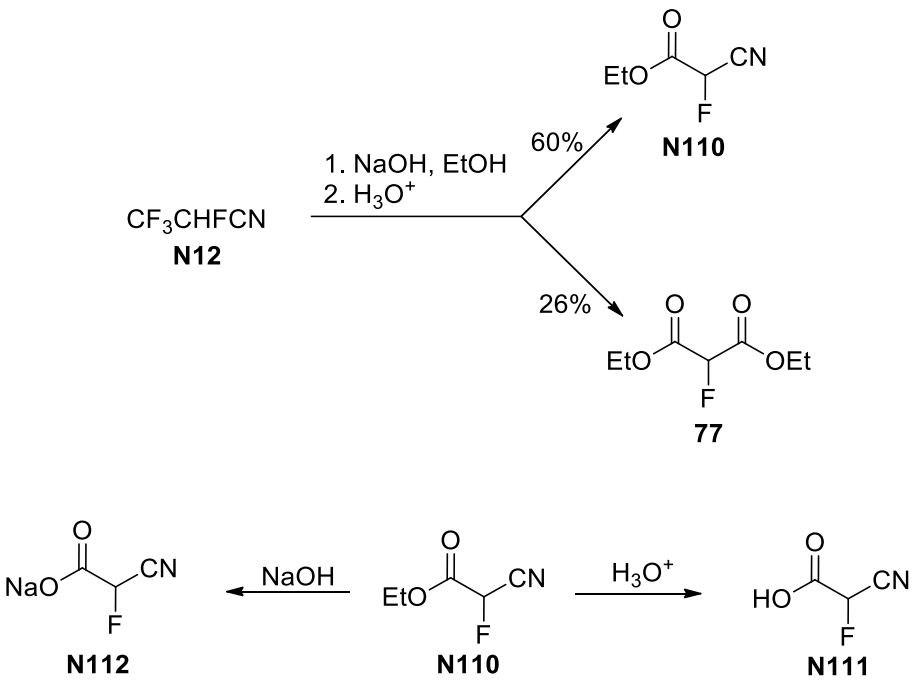
Table 7. Preparation of *N*-monosubstituted (**N105-107**) and *N*,*N*-disubstituted (**N108** and **N109**) α,α-difluorinated β-aminonitriles[66]



Entry	Substrate	Product	Yield of product, %
1		**N105**	66
2		**N106**	68
3		**N107**	78
4		**N108**	95
5		**N109**	82

2.14. Syntheses of ethyl α-fluorocyanoacetate and its derivatives

Treatment of α-hydroperfluoropropionitrile (**N12**) with NaOH in EtOH and then HCl resulted in a mixture of ethyl α-fluorocyanoacetate (**N110**) (60%) and ethyl fluoromalonate (**77**) (26%) as the result of the formation of perfluoroacrylonitrile as the key reactive intermediate.[67] Ester **N110** can be either hydrolyzed to α-fluorocyanoacetic acid (**N111**) or saponified to sodium α-fluorocyanoacetate (**N112**) (Scheme 46).[67]



Scheme 46. Synthesis of ethyl α-fluorocyanoacetate (**N110**), and α-fluorocyanoacetic acid (**N111**).

α-Fluoronitrile **N110** reacts with various Michael acceptors giving highly functionalized α-fluorinated nitriles (Table 8).[67]

Table 8. Preparation of derivatives of ethyl α-fluorocyanoacetate **N111-116** via the Michael reaction[67]

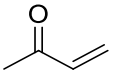
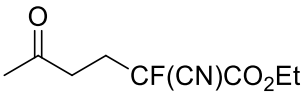
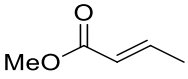
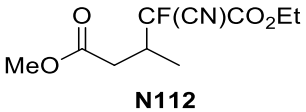
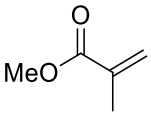
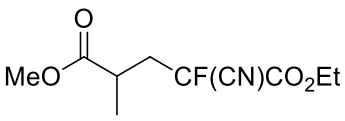
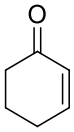
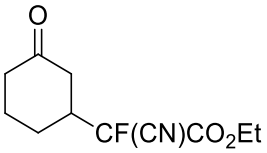
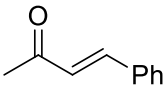
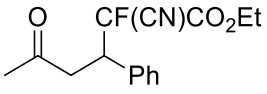
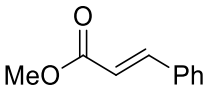
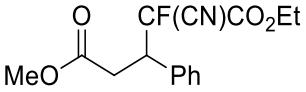
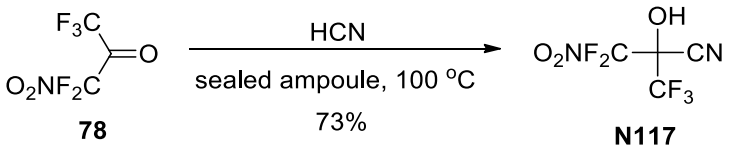
Entry	Michael acceptor	Reaction time	Product	^{19}F NMR yield
1		10 min	 **N111**	79
2		2 h	 **N112**	95
3		2 h	 **N113**	94

Table 8. Continued

Entry	Michael acceptor	Reaction time	Product	19F NMR yield
4		10 min	 **N114**	99
5		10 min	 **N115**	93
6		15 h	 **N116**	92

2.15. Synthesis of α-functionalized R^F-nitriles on the basis of R^F-ketones

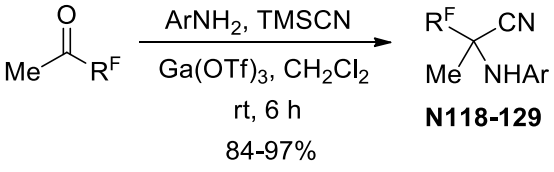
It was reported that the reaction of pentafluoronitroacetone (**78**) with hydrocyanic acid produces α-hydroxy-α-CF_3-nitrile **N117** (an R^F-cyanohydrin), which was isolated in 73% yield (Scheme 47).[68] Similarly, imines of R^F-ketones can react with HCN producing the corresponding α-amino-α-R^F-nitriles (see paragraph 3.3.3, Schemes 109, 113 and 114).



Scheme 47. Synthesis of α-hydroxy-α-CF_3-nitrile **N117**.

Gallium(III) triflate-catalyzed Strecker reaction of 1-mono-, 1,1-di-, and 1,1,1-trifluoroacetone was published: α-amino-functionalized β-fluorinated nitriles **N118-129** were synthesized in 84-97% yield using this method (Table 9).[69]

Table 9. Synthesis of α-amino-R^F-nitriles **N118-129**[69]



R^F = CH_2F, CHF_2, CF_3

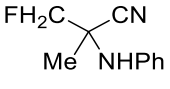
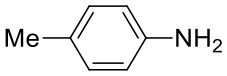
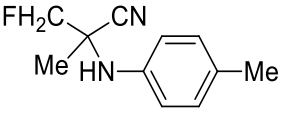
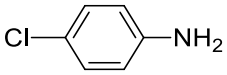
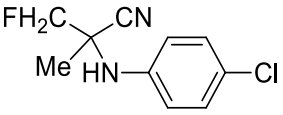
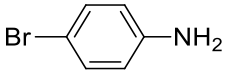
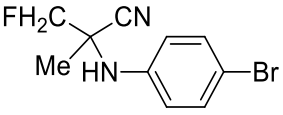
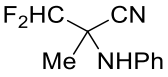
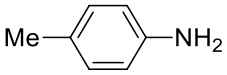
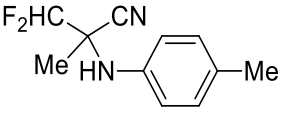
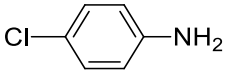
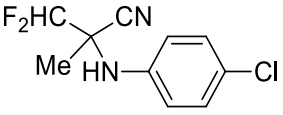
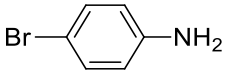
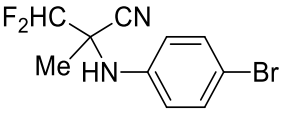
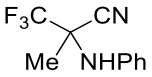
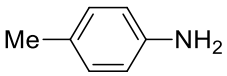
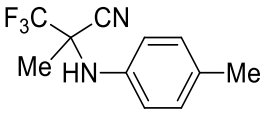
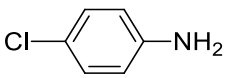
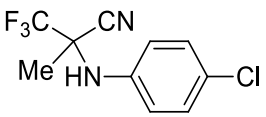
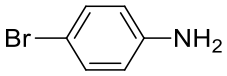
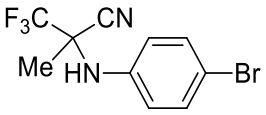
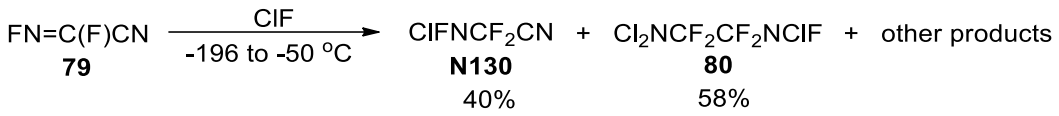
Entry	R^F	Amine	Product	Yield of product, %
1	CH_2F	$PhNH_2$	 **N118**	97

Table 9. Continued

Entry	RF	Amine	Product	Yield of product, %
2	CH_2F		 **N119**	96
3	CH_2F		 **N120**	92
4	CH_2F		 **N121**	90
5	CHF_2	$PhNH_2$	 **N122**	94
6	CHF_2		 **N123**	85
7	CHF_2		 **N124**	91
8	CHF_2		 **N125**	89
9	CF_3	$PhNH_2$	 **N126**	95
10	CF_3		 **N127**	90
11	CF_3		 **N128**	84
12	CF_3		 **N129**	95

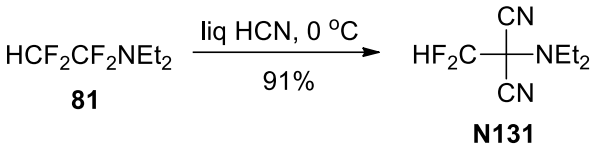
2.16. Other methods

Reaction of *N*-fluoro-1-cyano-1-fluoromethanimine (**79**) with ClF resulted in the formation of difluoroacetonitrile derivative, nitrile $ClFNCF_2CN$ **N130** (40%), together with $Cl_2NCF_2CF_2NClF$ **80** (58%) and other products (Scheme 48).[70]



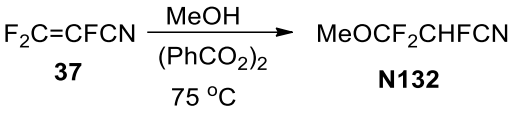
Scheme 48. Synthesis of $ClFNCF_2CN$ **N130**.

2-(Diethylamino)-2-(difluoromethyl)malononitrile (**N131**) was obtained in 91% yield through treatment of *N*,*N*-diethyl-1,1,2,2-tetrafluoroethanamine (**81**) with liquid HCN at 0 °C (Scheme 49).[71]



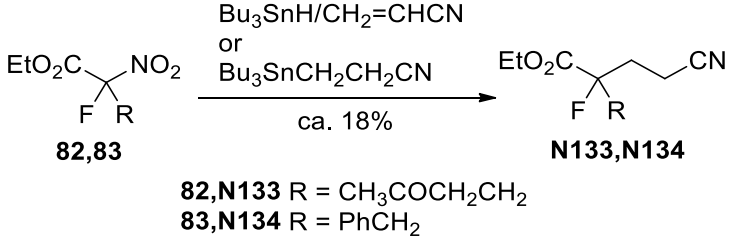
Scheme 49. Synthesis of 2-(diethylamino)-2-(difluoromethyl)malononitrile (**N131**).

Free-radical addition of MeOH to perfluoroacrylonitrile (**37**) in the presence of benzoyl peroxide in a magnetically stirred autoclave at 75 °C afforded 2,3,3-trifluoro-3-methoxypropanenitrile (**N132**) (Scheme 50).[57]



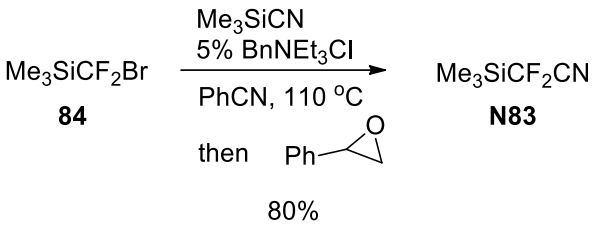
Scheme 50. Synthesis of 2,3,3-trifluoro-3-methoxypropanenitrile (**N132**).

Free-radical alkylation at the fluorine-bearing carbon atom can be used for the synthesis of γ-fluorinated nitriles. Thus, the reaction of α-fluoro-α-nitroesters **82** and **83** with Bu_3SnH/CH_2=CHCN gave γ-fluoronitriles **N133** and **N134**, respectively, in ca. 18% yield.[72] Alternatively, $Bu_3SnCH_2CH_2CN$ can be used as the source of the CH_2CH_2CN group.[72] Similarly, α-bromo-α-fluoroesters can also be utilized in the synthesis of γ-fluoronitriles (Scheme 51).[72]



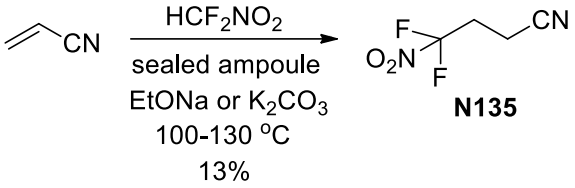
Scheme 51. Synthesis of γ-fluoronitriles **N133** and **N134**.

α-Silylated α-fluoronitrile **N83** (80%) was produced from silane **84** by heating with trimethylsilyl cyanide in the presence of 5 mol.% of benzyltriethylammonium chloride (Scheme 52).[66,73]



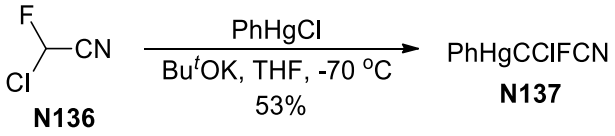
Scheme 52. Synthesis of α-silylated α-fluoronitrile **N83**.

Acrylonitrile was used as the Michael acceptor in the reaction with difluoronitromethane (100-130 °C, sealed ampoule, EtONa or K_2CO_3 as a base), and 4,4-difluoro-4-nitrobutironitrile (**N135**) was obtained as the desired R^F-nitrile in 13% yield (Scheme 53).[74]



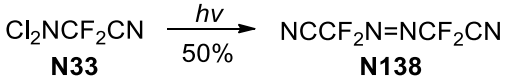
Scheme 53. Synthesis of 4,4-difluoro-4-nitrobutironitrile (**N135**).

Phenylmercurated chloro(fluoro)acetonitrile **N137** was prepared in 53% yield through the reaction of chlorofluoroacetonitrile (**N136**) and Bu^{t}OK with PhHgCl in THF at -70 °C (Scheme 54).[75]



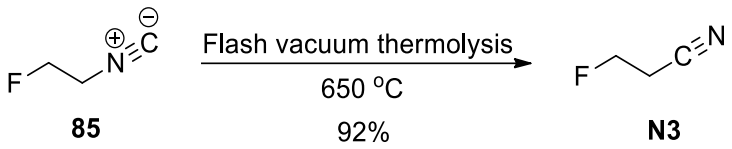
Scheme 54. Synthesis of phenylmercurated chloro(fluoro)acetonitrile **N137**.

Photolysis of nitrile **N33** by Pyrex-filtered sunlight resulted in the formation of tetrafluorinated azonitrile **N138** (Scheme 55). Photolysis of nitrile BrClNCF$_2$CN **N34** produces the same azonitrile in 20% yield.[56]



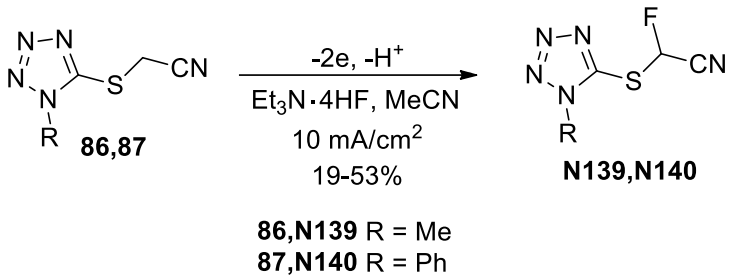
Scheme 55. Photolysis of nitrile **N33**.

3-Fluoropropionitrile (**N3**) was prepared on a half-gram scale in a 92% yield by flash vacuum thermolysis of the 2-fluoroethylisocyanide (**85**) at 650 °C. The product was collected in pure form in a U-trap equipped with stopcocks and immersed in a -90 °C bath (Scheme 56).[76]



Scheme 56. Preparation of 3-fluoropropionitrile (**N3**) from 2-fluoroethylisocyanide (**85**).

Anodic monofluorination of nitriles **86** and **87** in MeCN in the presence of $Et_3N{\cdot}4HF$ resulted in monofluorinated nitriles **N139** and **N140**, respectively, in 19-53% yield (Scheme 57).[77]

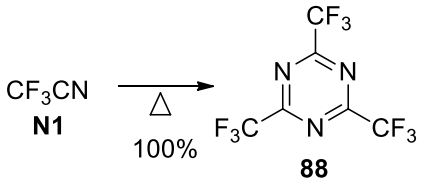


Scheme 57. Anodic monofluorination of nitriles **86** and **87**.

3. Chemical properties of fluoroalkyl cyanides

3.1. Trimerization

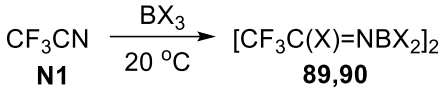
Heating trifluoroacetonitrile (**N1**) in the presence of other compounds often leads to trimerization and the formation of 2,4,6-tris(trifluoromethyl)-1,3,5-triazine (**88**).[78,79] Therefore, heating CF_3CN in the presence of reagents less reactive towards CF_3CN can cause the formation of some amounts of **88**. Thus, CF_3CN doesn't react with tetrafluorohydrazine, N_2F_4, at 100-220 °C, but in the presence of this reagent converts at these temperatures to triazine **88** in 100% yield (Scheme 58).[78] Similarly, in the presence on an imine, nitrile $H(CF_2)_2CN$ gives some amounts of the corresponding HCF_2CF_2-triazine as a by-product (see paragraph 3.3.3, Scheme 102).[79]



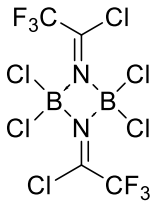
Scheme 58. Trimerization of trifluoroacetonitrile (**N1**).

3.2. Reactions with electrophiles

3.2.1 Reactions with boron(III) and titanium(III) Lewis acids. CF_3CN is a weaker donor than MeCN, and in contrast to the last, it forms no stable coordination compound with $SnCl_4$ or $TiCl_4$, and with the boron trihalides the insertion reaction occurs, giving dimeric ethylideneaminoboranes **89** and **90** (Scheme 59).[80]



89 X = Cl
90 X = Br

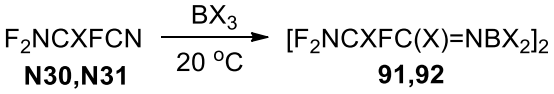


89

Scheme 59. Formation of dimeric ethylideneaminoboranes **89** and **90**.

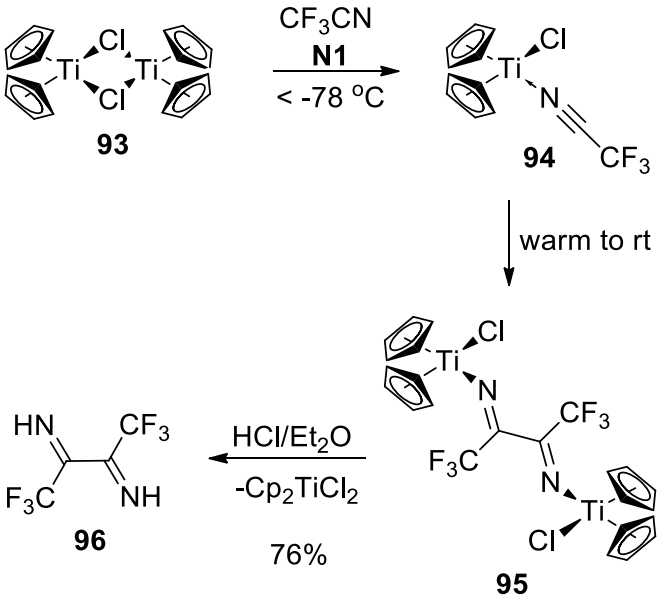
It was also reported that fluoroacetonitrile (**N2**)[81] and pentafluorpropionitrile (**N6**)[82] react with boron Lewis acids forming dimer products of type **89**.

The reaction of $F_2NCClFCN$ **N30** and $F_2NCBrFCN$ **N31** with BCl_3 and BBr_3 also leads to the formation of the corresponding dimeric products **91** and **92** (Scheme 60).[54]



N30,91 X = Cl
N31,92 X = Br

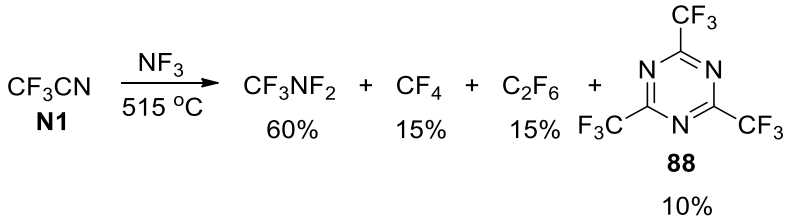
Scheme 60. Formation of dimeric products **91** and **92** from $F_2NCClFCN$ **N30** and $F_2NCBrFCN$ **N31**.



Scheme 61. Synthesis of 1,1,1,4,4,4-hexafluoro-2,3-butanediimine (**96**).

It was shown that the reductive coupling of trifluoroacetonitrile (**N1**) with bis(cyclopentadienyl)titanium(III) chloride (**93**) resulted in the formation of corresponding μ-diimino titanium dimer **95** (through intermediate product **94**).[83] Treatment of dimer **93** with HCl/Et_2O liberated the free diimine, 1,1,1,4,4,4-hexafluoro-2,3-butanediimine (**96**) in 76% yield (Scheme 61).[83]

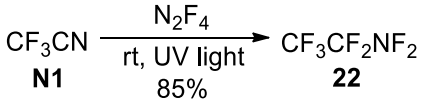
3.2.2 Reactions with NF_3 and N_2F_4. Reaction of trifluoroacetonitrile (**N1**) with NF_3 at 515 °C gave a mixture of CF_3NF_2 (60%), CF_4 (15%), C_2F_6 (15%), and triazine **88** (10%). The reaction doesn't proceed at 480 °C or lower temperatures (Scheme 62).[78]



Scheme 62. Reaction of trifluoroacetonitrile (**N1**) with NF_3 at 515 °C.

The suggested plausible mechanism of the formation of the above mixture of products involves the dissociation of the starting compounds at 515 °C to free radicals $F_3C\cdot$, $NC\cdot$, $F\cdot$, $F_2N\cdot$, and the recombinations of the latter.[78]

Trifluoroacetonitrile (**N1**) doesn't undergo the trimerization at room temperature and can react with various reagents. Thus, the reaction of CF_3CN with N_2F_4 at room temperature under UV light produces for 48 hours $C_2F_5NF_2$ **22** in 85% yield (Scheme 63).[78]

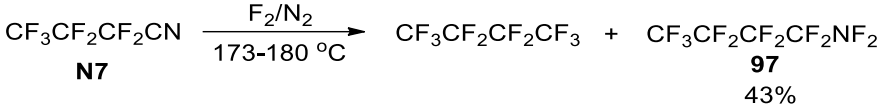


Scheme 63. Synthesis of *N*,*N*-difluoro(perfluoroethyl)amine **22** from CF_3CN **N1** and N_2F_4.

3.2.3 Reactions with halogens. The first direct fluorination of R^F-nitriles was published in 1959.[84] Fluorination of CF_3CN and C_2F_5CN with F_2 diluted with helium resulted in the formation of a mixture of products. The fluorination of CF_3CN at 275 °C yielded a mixture of CF_4, C_2F_6, $CF_3CF_2NF_2$, and, probably, CF_2=NF. The fluorination of CF_3CN under milder conditions (30-47 °C) gave C_2F_6, F_5C_2N=NC_2F_5, and unreacted CF_3CN. The fluorination of C_2F_5CN at 275 °C yielded a mixture of CF_4, C_2F_6, C_3F_8, and $CF_3CF_2CF_2NF_2$. The fluorination of C_2F_5CN under milder conditions (54-65 °C) gave F_7C_3N=NC_3F_7 and unreacted C_2F_5CN.[84]

Direct fluorination of trifluoroacetonitrile with F_2/N_2 at 140 °C gave a mixture of CF_4, C_2F_6, $C_2F_5NF_2$, CF_3CF=NF, CF_3N=NC_2F_5, and C_2F_5N=NC_2F_5. The CF_3CF=NF was obtained pure by analytical chromatography.[85]
Direct fluorination of $CClF_2CN$ with F_2/N_2 at 140 °C yielded a crude product, which was rectified, and thus pure samples of $CClF_2CF_2NF_2$, $CClF_2CF_2N$=NCF_3, and $CClF_2CF$=NF were obtained.[85] The fluorination of $CClF_2CN$ at 175 °C yielded a product, which contained CF_4, NF_3, $CClF_3$, C_2F_5Cl, and trace amounts of CF_3N=NCF_3, and $CClF_2CF_2NF_2$.[85]

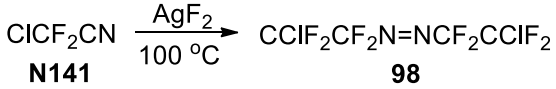
Direct fluorination of perfluorobutyronitrile (**N7**) with F_2/N_2 at 173-180 °C gave a mixture of perfluorobutane and *N*,*N*-difluoro(perfluorobutyl)amine (**97**) (43%) (Scheme 64).[40]



Scheme 64. Direct fluorination of $CF_3CF_2CF_2CN$ **N7**.

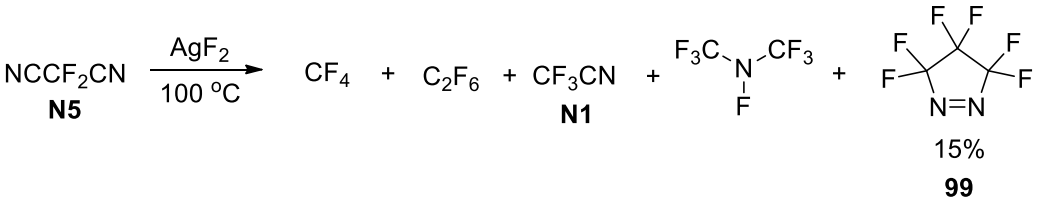
Direct fluorination of difluoromalononitrile, tetrafluoroscuccinonitrile, and hexafluoroglutaronitrile with F_2/N_2 gives complex mixtures of fluorinated products. By the fluorination of tetrafluoroscuccinonitrile, perfluoropyrrolidine was found as one of the products.[40]

Indirect fluorination of such R^F-nitriles as chlorodifluoroacetonitrile, difluoromalononitrile, tetrafluorosuccinonitrile, and hexafluoroglutaronitrile with argentic fluoride was investigated.[86] Thus, the reaction of chlorodifluoroacetonitrile (**N141**) with excess AgF_2 gave 2,2-dichlorooctafluoroazoethane (**98**) in approximately 45% conversion (Scheme 65).[86]



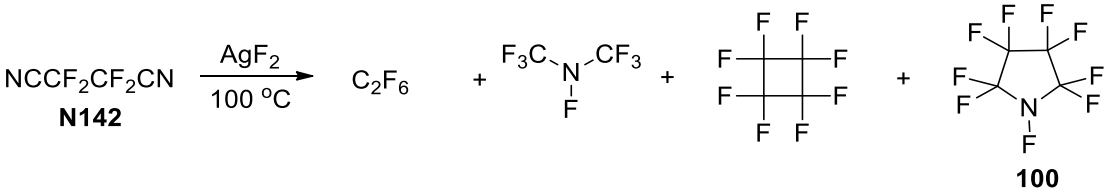
Scheme 65. Fluorination of $ClCF_2CN$ **N141** with AgF_2.

The fluorination of difluoromalononitrile (**N5**) with AgF_2 at 100 °C proceeded not selectively producing a mixture of products such as CF_4, C_2F_6, CF_3CN, $(CF_3)_2NF$, and hexafluoro-1-pyrazoline (**99**) (15%) (Scheme 66).[86]



Scheme 66. Fluorination of difluoromalononitrile (**N5**) with AgF_2.

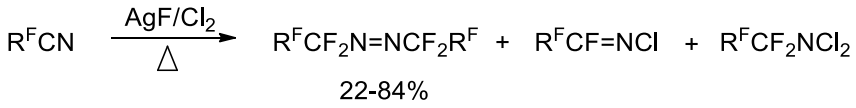
The fluorination of tetrafluorosuccinonitrile (**N142**) with AgF_2 at 100 °C gave a mixture of products such as C_2F_6, $(CF_3)_2NF$, perfluorocyclobutane, and perfluoropyrrolidine (**100**) (Scheme 67).[86]



Scheme 67. Fluorination of tetrafluorosuccinonitrile (**N142**) with AgF_2.

The fluorination of hexafluoroglutaronitrile with AgF_2 at 100 °C gave a mixture of CF_4, C_2F_6, C_3F_8, and $(CF_3)_2NF$ as major components, and some $(CF_3)_2NH$.[86]

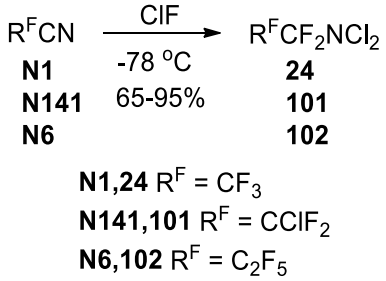
Treatment of R^F-nitriles with AgF and Cl_2 gave the corresponding polyfluoroazoalkanes (22-84%), however, other products frequently formed such as *N*-chlorofluoroalkylidenimines and *N*,*N*-dichlorofluoroalkylamines (Scheme 68).[87]



Scheme 68. Chlorination of R^F-nitriles with Cl_2 in the presence AgF.

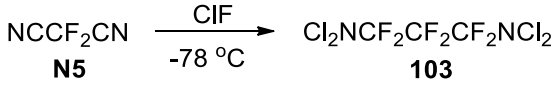
Photolytically induced reaction of CF_3CN with Cl_2 produced $CF_3CCl=NCl$, $CF_3CCl=N-N=CClCF_3$, and CF_3CCl_3 as well as minor quantities of $CF_3C(Cl)=N-CCl_2CF_3$, $CF_3CCl_2C(CF_3)=N-N=C(Cl)CF_3$, $CF_3CCl_2-N=N-CCl_2CF_3$, $CF_3CCl_2C(CF_3)=N-CCl_2CF_3$, and $CF_3CCl_2C(CF_3)=N-N=C(CF_3)CCl_2CF_3$.[88]

Reaction of R^FCN with ClF at -78 °C resulted in the formation of fluorinated aliphatic dichloramines $R^FCF_2NCl_2$ in 65-95% yield (Scheme 69).[89]



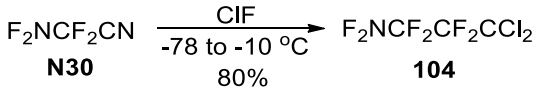
Scheme 69. Reaction of R^FCN with ClF.

Similarly, fluorinated tetrachlorodiamine $Cl_2NCF_2CF_2CF_2NCl_2$ **103** was synthesized from difluoromalononitrile (**N5)** and ClF (Scheme 70).[89]



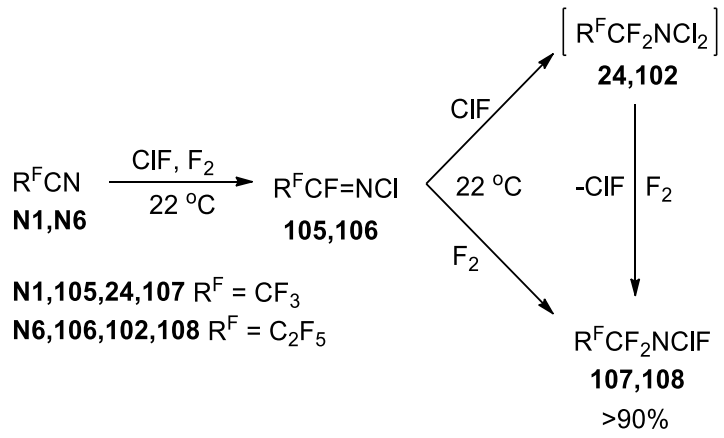
Scheme 70. Reaction of difluoromalononitrile (**N5**) with ClF.

The reaction of F_2NCF_2CN **N30** with ClF proceeded easily in a stainless steel Hoke cylinder to give *N*,*N*-dichloro-*N*',*N*',1,1,2,2-hexafluoro-1,2-ethanediamine (**104**) in 80% yield (Scheme 71).[53]



Scheme 71. Reaction of F_2NCF_2CN **N30** with ClF.

Treatment of R^F-nitriles with ClF/F_2 produced *N*-chloro-*N*-fluorofluoroalkylamines R^FCF_2NClF **107** and **108** in yields above 90%. The mixture of R^FCN, ClF and F_2 was kept at 22 °C for 40 to 63 h. Under these conditions, ClF does not react with F_2 forming ClF_3, and F_2 does not react with R^FCN (Scheme 72).[90,91]



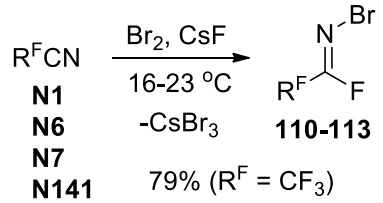
Scheme 72. Synthesis of R^FCF_2NClF **107** and **108**.

Chlorination and bromination of trifluoroacetonitrile (**N1**) in the presence of HgF_2 gave $C_2F_5NCl_2$ **24** (94%) and $C_2F_5NBr_2$ **109** (90%), respectively (Scheme 73).[92,93]

Scheme 73. Chlorination and bromination of CF_3CN **N1** in the presence of HgF_2.

Bromination of CF_3CN at 22 °C in the presence of CsF can produce in different proportions, dependently on the amount of Br_2, CF_3CF=NBr and F_5C_2N=NC_2F_5.[94]

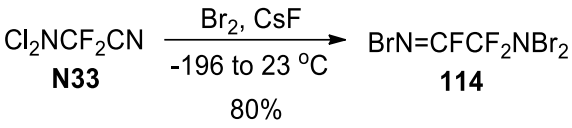
R^F-nitriles **N1,N6,N7** and **N141** have been found to react readily with bromine and CsF at 16-23 °C to afford high yields of corresponding *N*-bromoimidoylfluorides **110-113**.[95] Products **110-113** are the result of the oxidation of the $R^FCF=N^-$ anions with Br_2 (Scheme 74).[96]



N1,110 $R^F = CF_3$
N6,111 $R^F = C_2F_5$
N7,112 $R^F = n\text{-}C_3F_7$
N141,113 $R^F = CClF_2$

Scheme 74. Bromination of R^F-nitriles **N1,N6,N7** and **N141** with Br_2/CsF.

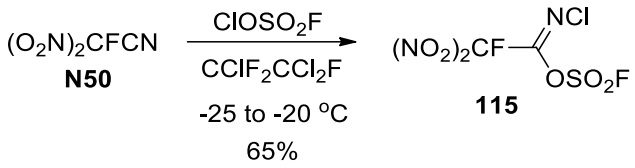
Cesium fluoride-promoted bromination of α,α-difluoronitrile Cl_2NCF_2CN **N33** with excess Br_2 (1.5:10 mol. ratio) at -196 to 23 °C yielded *N*-brominated imidoyl fluoride **114**, $BrN=CFCF_2NBr_2$, in 80% yield (Scheme 75).[56]



Scheme 75. Preparation of *N*-brominated imidoyl fluoride **114**.

A lower excess of Br_2 (1:2 mol. ratio) at -196 to 23 °C led to the following mixture of products: $(BrN=CF)_2$, $(ClN=CF)_2$, $ClN=CFCF_2NCl_2$, ClN=CFCF=NBr, $BrN=CFCF_2NCl_2$, $BrN=CFCF_2NBrCl$, $ClN=CFCF_2NBrCl$, and $ClN=CFCF_2NBr_2$.[56]

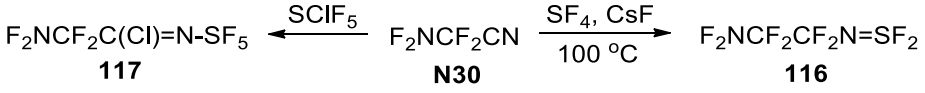
3.2.4 Reactions with chlorine fluorosulfate ($ClOSO_2F$), SF_4 and $SClF_5$. Reaction of fluorodinitroacetonitrile (**N50**) with chlorine fluorosulfate in 1,1,2-trichlorotrifluoroethane (the solvent) at -25 to -20 °C resulted in *N*-chloroiminoflorodinitroacetyl fluorosulfate (**115**) (65%) (Scheme 76).[97]



Scheme 76. Synthesis of *N*-chloroiminoflorodinitroacetyl fluorosulfate (**115**).

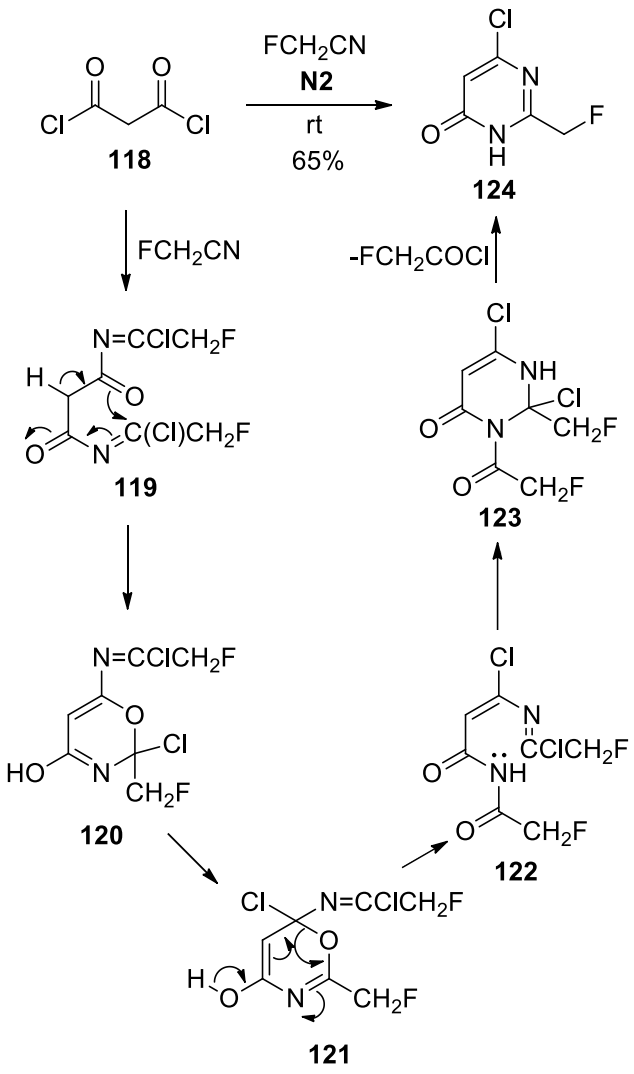
Similarly, other R^F-*N*-chloroiminofluorosulfates were synthesized from CF_3CN, CF_3OCF_2CN, $CF_3(CF_2)_2CN$, $CF_3(CF_2)_3CN$, and O_2NCF_2CN.[98]

Reactions of F_2NCF_2CN **N30** with SF_4/CsF at 100 °C and with $SClF_5$ give imino-compounds **116** and **117**, respectively (Scheme 77).[55]



Scheme 77. Reactions of F_2NCF_2CN **N30** with SF_4/CsF and SF_5Cl.

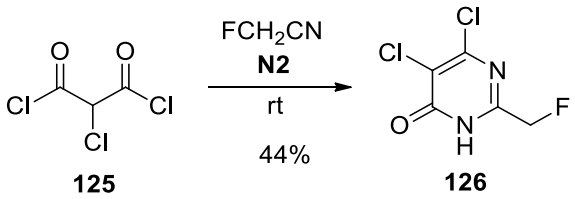
3.2.5 Reactions with *C*-electrophiles. The reaction of fluoroacetonitrile (**N2**) with malonyl chloride gave 4-chloro-2-fluoromethyl-6-pyrimidone (**124**) in 65% yield. The suggested plausible mechanism involves the formation of diimidoyl chloride **119** and the subsequent cyclic transformations with the formation of intermediates **120-123** (Scheme 78).[99]



Scheme 78. Reaction of fluoroacetonitrile (**N2**) with malonyl chloride (**118**).

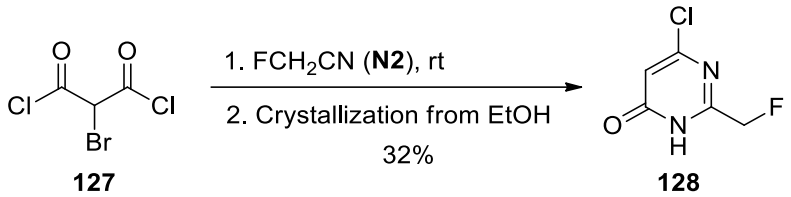
No solid product was isolated when a mixture of cyanoacetyl chloride and **N2** was kept at room temperature for several days.[99]

The reaction of fluoroacetonitrile (**N2**) with chloromalonyl chloride (**125)** gave 4,5-dichloro-2-fluoromethyl-6-pyrimidone (**126**) in 44% yield (Scheme 79).[99]



Scheme 79. Reaction of fluoroacetonitrile (**N2**) with chloromalonyl chloride (**125**).

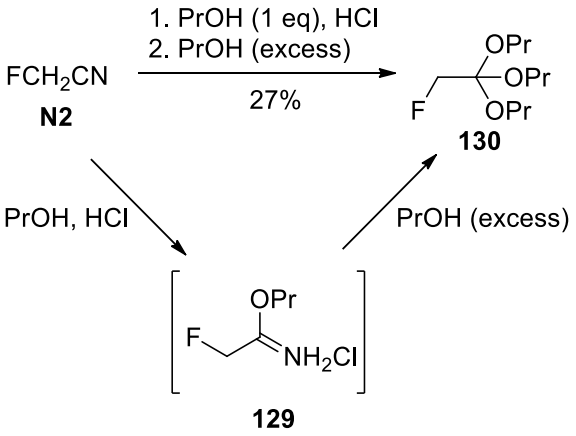
The reaction of **N2** with bromoromalonyl chloride (**127**) gave a solid, which was crystallized from EtOH. The crystallized product was 4-chloro-2-fluoromethyl-6-pyrimidone (**128**) (32%) (Scheme 80).[99] Most likely, EtOH in this case plays the role of a reducing agent (debromination).



Scheme 80. Reaction of fluoroacetonitrile (**N2**) with bromoromalonyl chloride (**127**).

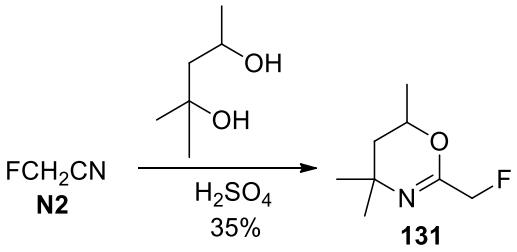
3.3. Reactions with nucleophiles

3.3.1 Reactions with *O*-nucleophiles. The Pinner reaction of fluoroacetonitrile (**N2**) with propanol in the presence of HCl resulted in the corresponding ortho ester, 1-(2-fluoro-1,1-dipropoxyethoxy)propane (**130**) (through the formation of the intermediate iminoester hydrochloride **129**), which was isolated in 27% yield (Scheme 81).[100]



Scheme 81. Reaction of fluoroacetonitrile (**N2**) with propanol.

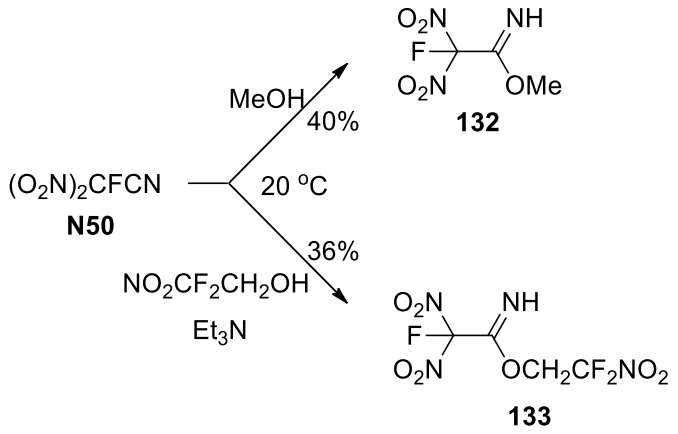
Cyclic iminoester **131** was synthesized in 35% yield from **N2** and 2-methyl-1,3-pentanediol in H_2SO_4 at -5 to 0 °C (Scheme 82).[101] Oxazine **131** can be α-metalated rapidly at -78 °C by *n*-butyllithium, *tert*-butyllithium, or *n*-butyllithium/HMPA, and, moreover, **131** and its α-alkylated derivatives can be reduced with $NaBH_4$, and thus can be used for the preparation of α-fluorinated aldehydes.[101]



Scheme 82. Synthesis of cyclic imino ester **131** from fluoroacetonitrile (**N2**).

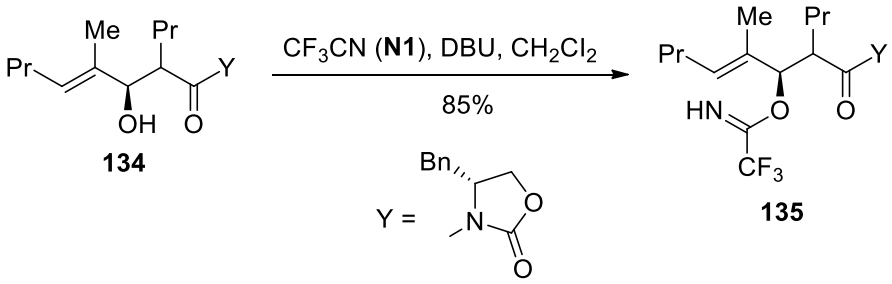
The reaction of fluorodinitroacetonitrile (**N50**) with MeOH proceeds at 20 °C without any catalyst, whereas the corresponding reaction with less reactive 2,2-difluoro-2-nitroethanol was carried out in the

presence of Et_3N as a catalyst. In both cases, the corresponding imino esters **132** and **133** were isolated in 40% and 36% yield, respectively (Scheme 83).[102]



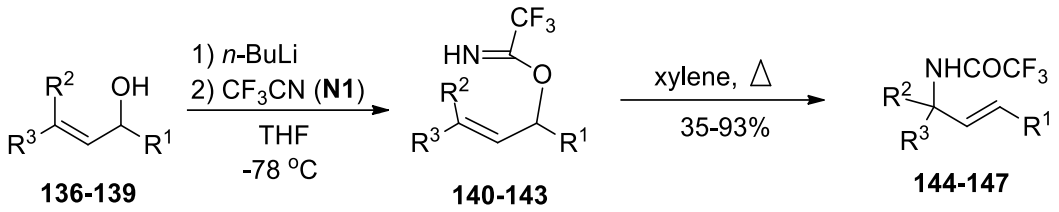
Scheme 83. Reaction of fluorodinitroacetonitrile (**N50**) with MeOH and 2,2-difluoro-2-nitroethanol.

The reaction of highly functionalized alcohol **134** with CF_3CN in the presence of DBU was explored. Trifluoroacetimidate **135** was isolated in 85% yield (Scheme 84).[103]



Scheme 84. Synthesis of trifluoroacetimidate **135**.

Trifluoroacetimidates **140-143** were prepared from the corresponding alcohols **136-139** by treatment with *n*-butyllithium followed by addition of an excess of trifluoroacetonitrile (**N1**) at -78 °C in THF.[104] Best yields were obtained using less than one mole equivalent of *n*-BuLi. The [3.3] rearrangements of **140-143** were then carried out by heating in xylene under reflux and gave the allylic trifluoroacetamides **144-147** in 35-90% yield (Scheme 85).[104]

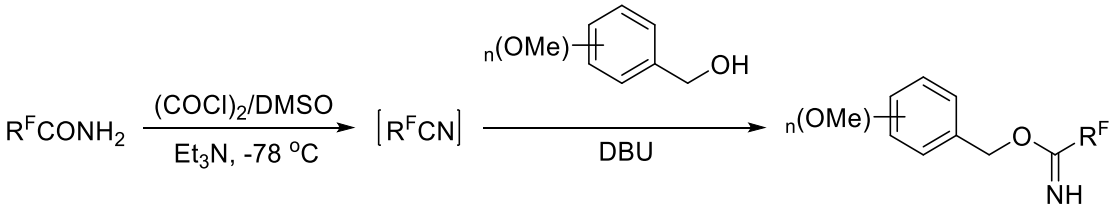


136,140,144 $R^1 = R^2 = H$, $R^3 = Ph$
137,141,145 $R^1 = H$, $R^2 = Me$, $R^3 = (CH_2)_2CHC(CH_3)_2$
138,142,146 $R^1 = R^2 = H$, $R^3 = CHCHMe$
139,143,147 $R^1 = Me$, $R^2 = H$, $R^3 = C_3H_5O_2$

Scheme 85. Synthesis of trifluoroacetimidates **140-143** and trifluoroacetamides **144-147**.

Various R^F-imidates **148-162** were synthesized through the reaction of *in situ* formed R^F-nitriles with benzyl alcohols in the presence of DBU. The obtained R^F-imidates were purified by silica gel column chromatography and were stable for a month at room temperature (Table 10).[105]

Table 10. Synthesis of R^F-imidates **148-162** from R^F-nitriles and benzyl alcohols[105]

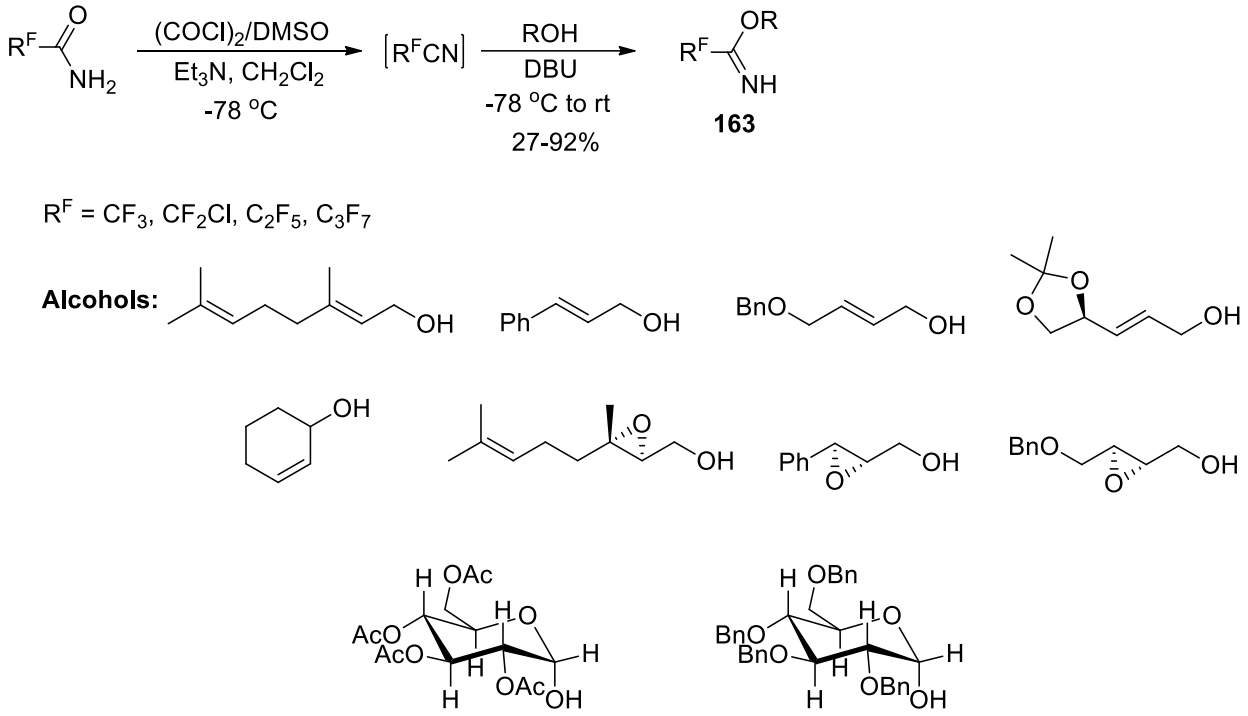


n = 0, 1, 2

Entry	R^F	Benzyl alcohol	Yield[a,b]	Imidate
1	ClF_2C	$PhCH_2OH$	81 (40)	**148**
2	ClF_2C	4-$MeOC_6H_4CH_2OH$	83	**149**
3	ClF_2C	3,4-$(MeO)_2C_6H_3CH_2OH$	81 (36)	**150**
4	F_3C	$PhCH_2OH$	64 (28)	**151**
5	F_3C	4-$MeOC_6H_4CH_2OH$	85 (48)	**152**
6	F_3C	3,4-$(MeO)_2C_6H_3CH_2OH$	81 (56)	**153**
7	$F(CF_2)_2$	$PhCH_2OH$	78 (29)	**154**
8	$F(CF_2)_2$	4-$MeOC_6H_4CH_2OH$	80	**155**
9	$F(CF_2)_2$	3,4-$(MeO)_2C_6H_3CH_2OH$	82 (58)	**156**
10	$F(CF_2)_3$	$PhCH_2OH$	77 (58)	**157**
11	$F(CF_2)_3$	4-$MeOC_6H_4CH_2OH$	80	**158**
12	$F(CF_2)_3$	3,4-$(MeO)_2C_6H_3CH_2OH$	70	**159**
13	$F(CF_2)_2$	$PhCH_2OH$	74 (14)	**160**
14	$F(CF_2)_4$	$PhCH_2OH$	76 (35)	**161**
15	$F(CF_2)_6$	$PhCH_2OH$	90 (41)	**162**

[a] Isolation yield after Kugelrohr distillation; [b] Parentheses show the yields in the absence of DBU.

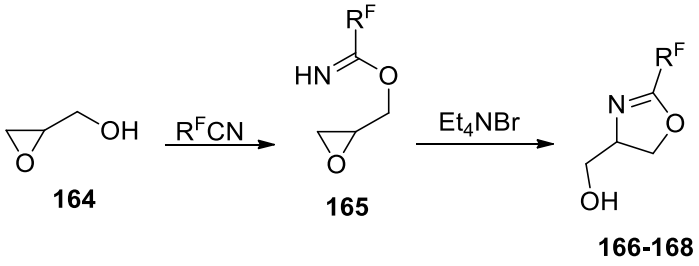
Similarly, treatment of R^F-nitriles with $(COCl)_2$/DMSO in the presence of Et_3N at -78 °C, and the subsequent treatment of the reaction mixtures with an alcohol in the presence of DBU resulted in the formation of various perfluoroimidates **163** in 27-92% yield (Scheme 86).[106]



Scheme 86. Synthesis of various perfluoroimidates **163**.

Reaction of R^F-nitriles with 1,2-epoxy-3-hydroxypropane (**164**) gave 2-R^F-4-(hydroxymethyl)oxazolines **166-168** (via intermediate R^F-imidates **165**) in 46-93% yield (Table 11). $BF_3{\cdot}Et_2O$ can also be used as a catalyst to synthesize R^F-isoxazolines.[107]

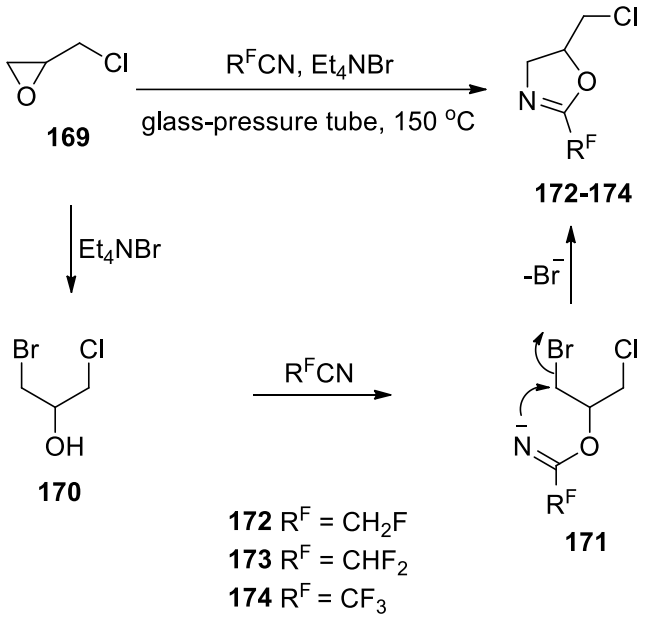
Table 11. 2-R^F-4-(hydroxymethyl)oxazolines **166-168**[107]



Entry	R^F	Reaction temperature, °C	Product	Yield of product, %
1	CH_2F	70	**166**	93
2	CHF_2	150	**167**	56
3	CF_3	150	**168**	46

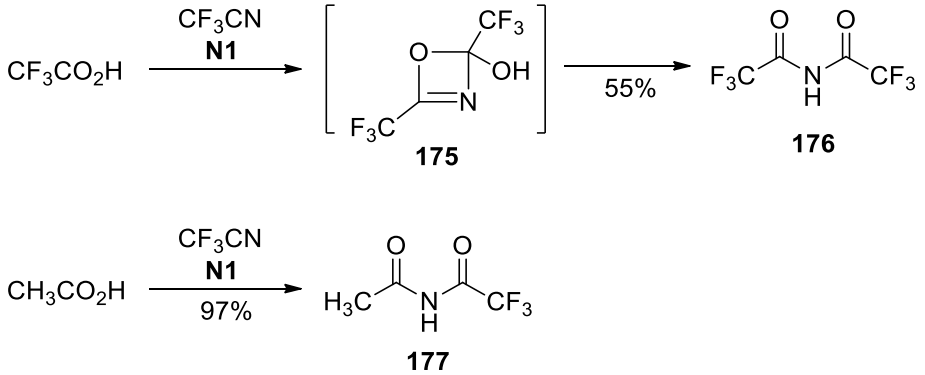
The above R^F-isoxazolines **166-168** can be used in the synthesis of fluorine-containing analogues of 2-methyl-5-dimethylaminomethyl-2-oxazoline methiodide, which is the 2-oxazoline analogue of Fourbeau's dioxolane that equals acetylcholine in potency and belongs to the highly active cholinomimetics.[108]

Heating 1-chloro-2,3-epoxypropane (**169**) with R^F-nitriles at 150 °C in a glass-pressure tube in the presence of tetraethylammonium bromide as the catalyst led to the formation of the corresponding R^F-oxazolines **172-174** in moderate yields.[109] The suggested plausible mechanism involves the nucleophilic addition of intermediate 1-bromo-3-chloropropan-2-ol (**170**) to the activated cyano group of R^FCN and subsequent cyclization of anion **171** to give **172-174** (Scheme 87).[109]



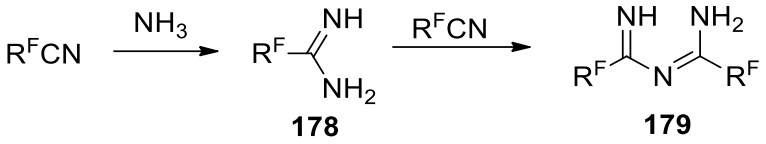
Scheme 87. Reaction of 1-chloro-2,3-epoxypropane (**169**) with R^F-nitriles.

The reaction of trifluoroacetonitrile (**N1**) with carboxylic acids was reported in 1963.[110] Analytically pure imides: trifluoroacetyltrifluoroacetimide, $(CF_3CO)_2NH$ (**176**) and acetyltrifluoroacetimide, $CH_3CONHCOCF_3$ (**177**), were synthesized from trifluoroacetonitrile (**N1**) and the corresponding carboxylic acids. The authors believe that the reaction of CF_3CO_2H with CF_3CN proceeds through four-membered cyclic intermediate **175** (Scheme 88).[110] Imide **177** is a relatively unstable compound: it slowly decomposes to a mixture containing CF_3CO_2H and MeCN (Scheme 88).[111]



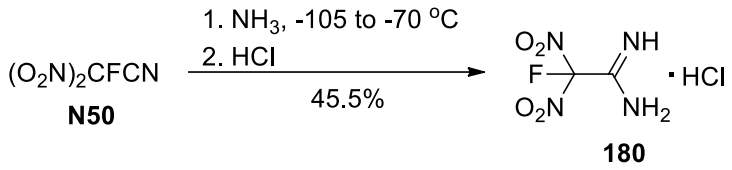
Scheme 88. Reaction of CF_3CN with CF_3CO_2H and AcOH.

3.3.2 Reactions with *N*-nucleophiles. The reaction of R^F-nitriles with ammonia produces R^F-amidines **178**, which then can react with R^FCN in the reaction mixture to give products **179** (Scheme 89).[112]



Scheme 89. Reactions of R^F-nitriles with ammonia.

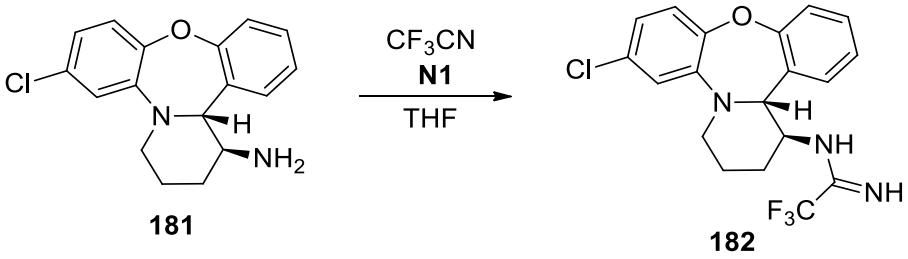
The reaction of fluorodinitroacetonitrile (**N50**) with NH_3, and subsequent treatment of the reaction mixture with HCl gave the corresponding amidine hydrochloride **180** in 45.5% yield (Scheme 90).[102]



Scheme 90. Synthesis of amidine hydrochloride **180**.

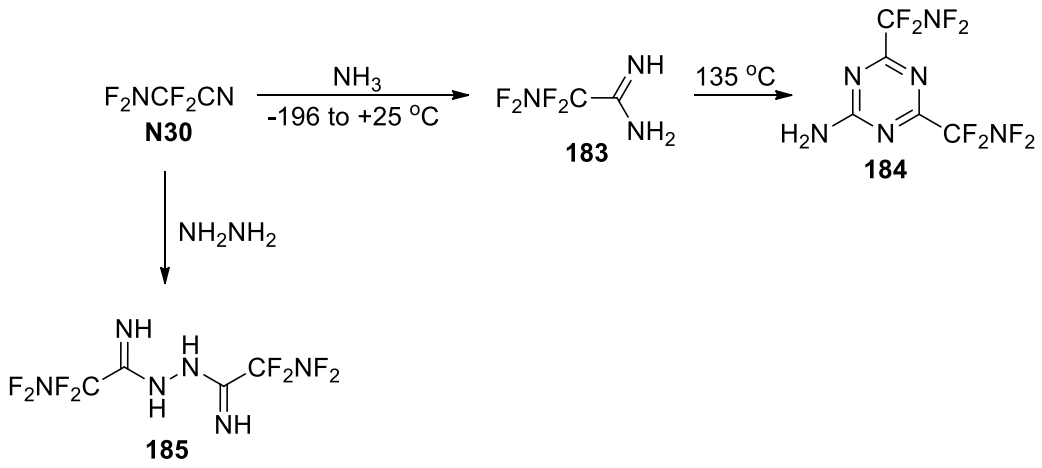
Similarly, difluoronitroacetamidine, $O_2NCF_2C(NH_2)=NH$ (63%) was synthesized from O_2NCF_2CN and ammonia.[113]

Amidine **182** was prepared from amine **181**, by treatment with trifluoroacetonitrile (Scheme 91).[114]



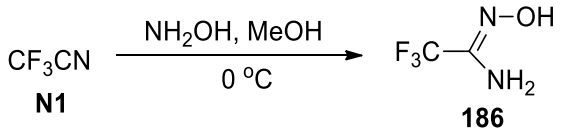
Scheme 91. Preparation of amidine **182**.

Reaction of F_2NCF_2CN **N30** with ammonia at -196 to 25 °C yielded amidine **183**, which was further transformed into triazine **184**, whereas the reaction of **N30** with hydrazine gave imidohydrazide **185** (Scheme 92).[115]



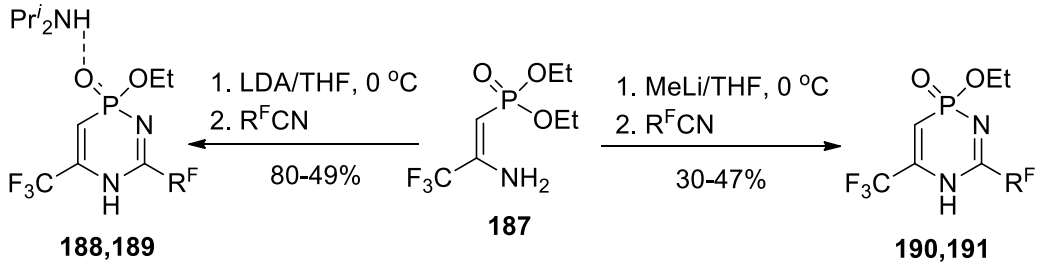
Scheme 92. Reactions of F_2NCF_2CN **N30** with ammonia and hydrazine.

Reaction of trifluoroacetonitrile (**N1**) with hydroxylamine generates trifluoroacetamide oxime (**186**) (Scheme 93), which then can be used for the synthesis of trifluoromethyl-1,2,4-oxadiazoles.[116]



Scheme 93. Synthesis of trifluoroacetamide oxime (**186**).

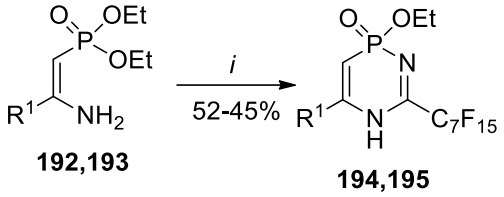
Reaction of CF_3-enaminophosphonate **187** with fluoroalkylated nitriles gave R^F-substituted diisopropylamine-2,5-dihydro-1,5,2-diazaphosphinines adducts **188** and **189** in 80-49% yield.[117] R^F-substituted 2,5-dihydro-1,5,2-diazaphosphinines **190** and **191** (30-47%) can be prepared in their pure forms after treatment of **187** with MeLi at 0 °C, and then with an R^F-nitrile (Scheme 94).[117]



188 $R^F = C_2F_5$
189 $R^F = C_7F_{15}$
190 $R^F = CF_3$
191 $R^F = C_7F_{15}$

Scheme 94. Reaction of CF_3-enaminophosphonate **187** with R^F-nitriles.

Aromatic (**192**) and heteroaroamatic (**193**) β-enaminophosphonates reacted with perfluorooctanenitrile to give 2-ethoxy-2-oxo-4-phenyl- (**194**) and 2-ethoxy-4-(2-furyl)-2-oxo-6-(perfluoroheptyl)-2,5-dihydro-1,5,2-diazaphosphinine (**195)** in 52-45% yield (Scheme 95).[117]

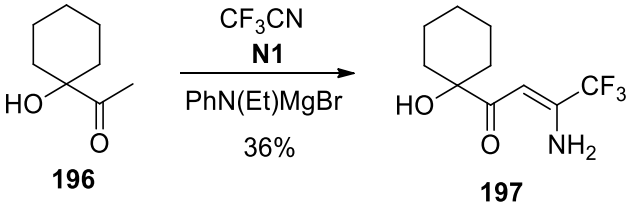


i: 1. BuLi/THF, 0 °C; 2. $C_7F_{15}CN$, 0 °C to rt; 3. H_2O

192,194 R^1 = Ph
193,195 R^1 = 2-Furyl

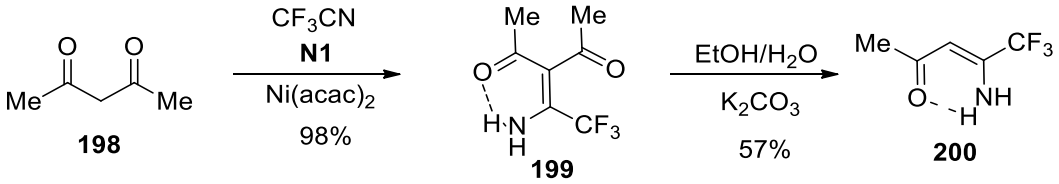
Scheme 95. Reaction of β-enaminophosphonates **192** and **193** with perfluorooctanenitrile.

3.3.3 Reactions with *C*-nucleophiles. It was shown that the condensation of 1-acetylcyclohexanol (**196**) with trifluoroacetonitrile (**N1**) in the presence of ethylphenylaminomagnesium bromide results in the formation of α-hydroxyoxoenamine **197** (36 %) (Scheme 96).[118]



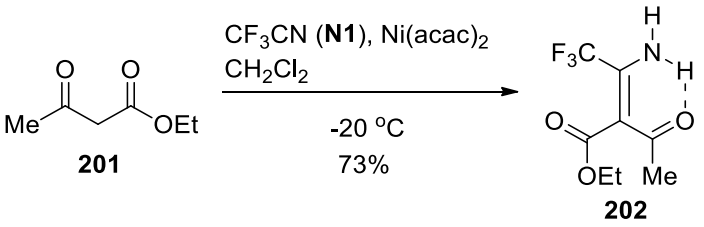
Scheme 96. Synthesis of α-hydroxyoxoenamine **197**.

Acetylacetone (**198*I***) adds smoothly to the C≡N bond of trifluoroacetonitrile (**N1**) in the presence of catalytic amounts of nickel acetylacetonate, $Ni(acac)_2$, to give 1,1,1-trifluoro-2-amino-3-acetyl-2-penten-4-one (**199**) (98%), a functional enaminone. Upon action of K_2CO_3 in aqueous EtOH, **199** is deacetylated to give enaminone **200**, which was isolated by sublimation in vacuum (Scheme 97).[119]



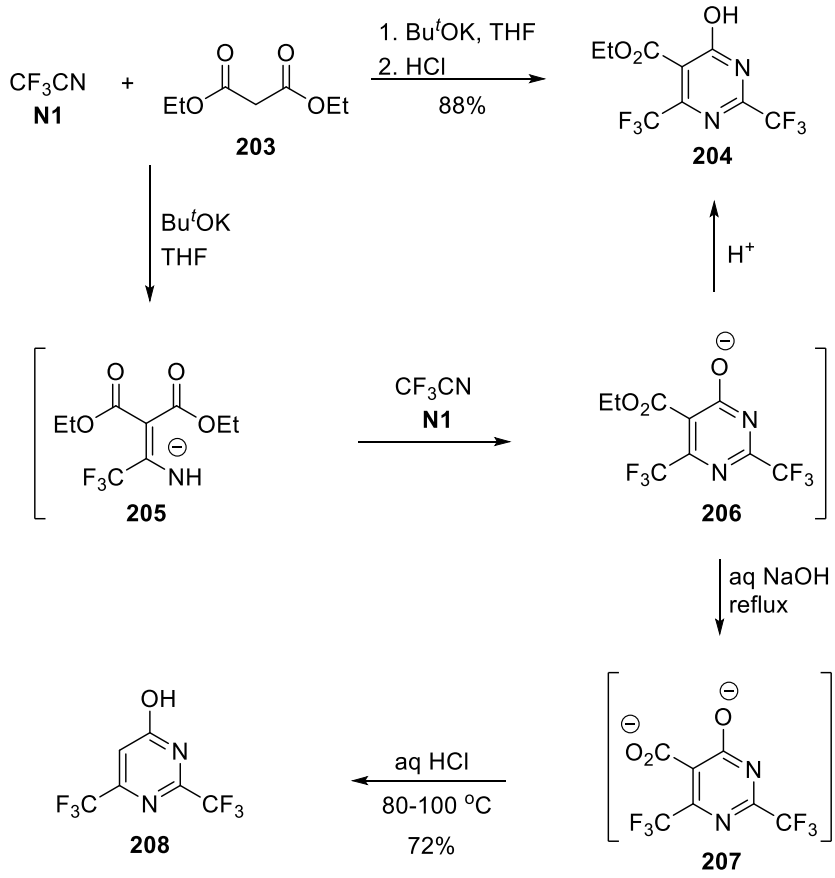
Scheme 97. Reaction of acetylacetone with CF_3CN in the presence of $Ni(acac)_2$.

Ethyl acetoacetate (**201**) readily reacts with CF_3CN in the presence of 1 mol.% of $Ni(acac)_2$ to give ethyl 2-acetyl-3-amino-4,4,4-trifluoro-2-butenoate (**202**) in 73% yield. The reaction occurs more slowly than in the case of acetylacetone (Scheme 98).[120]



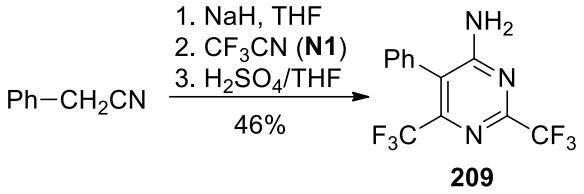
Scheme 98. Reaction of ethyl acetoacetate with CF_3CN.

It was reported that trifluoroacetonitrile (**N1**) reacts with diethyl malonate (**203**) in the presence of KOBu^t in THF to give 2,6-bis(trifluoromethyl)-4-hydroxypyrimidine-5-carboxylate (**204**) in 88% yield.[121] *In situ* saponification of ion **206** with aqueous NaOH and subsequent treatment of the reaction mixture with HCl resulted in the formation of 2,6-bis(trifluoromethyl)-4-hydroxypyrimidine (**208**) in 72% yield (Scheme 99).[121]



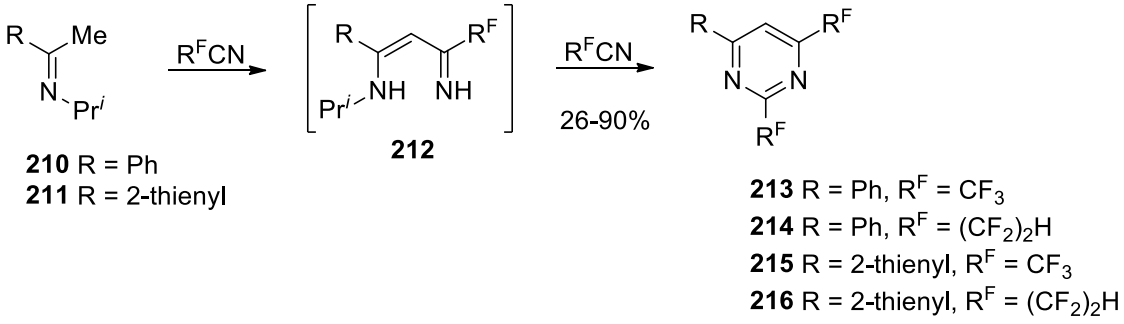
Scheme 99. Synthesis of CF_3-pyrimidines **204** and **208**.

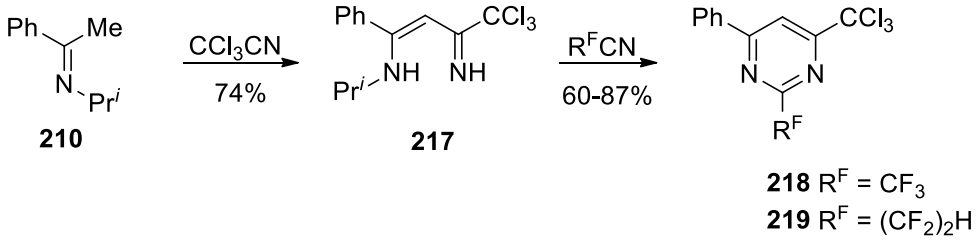
Cyclotrimerization of trifluoroacetonitrile (**N1**) and phenylacetonitrile in the presence of NaH in THF afforded 5-phenyl-2,6-bis(trifluoromethyl)pyrimidin-4-amine (**209**) in 46% yield (Scheme 100).[122]



Scheme 100. Cyclotrimerization of CF_3CN and phenylacetonitrile in the presence of NaH.

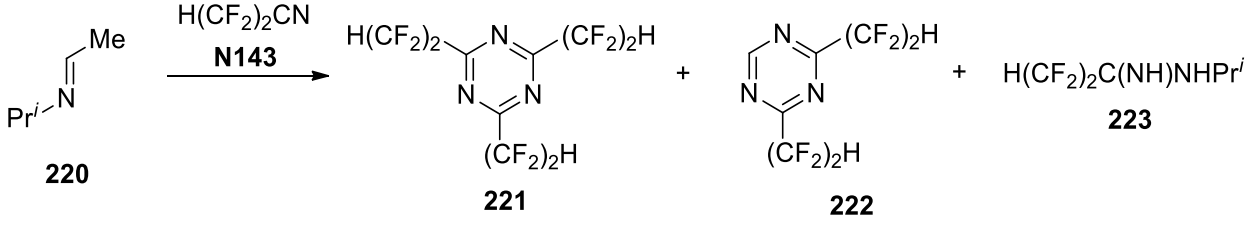
Condensation of R^F-nitriles with imines was reported,[79] and it was shown that trifluoroacetonitrile and 2,2,3,3-tetrafluoropropanenitrile react with aromatic methyl ketimines **210** and **211** producing the corresponding R^F-pyrimidines **213-216** (26-90%). Intermediate R^F-enaminoimines **212** were not isolated, while their CCl_3-analogue **217** was synthesized from imine **210** and trichloroacetonitrile in 74% yield. The reaction of CCl_3-enaminoimine with R^FCN gave CCl_3-bearing R^F-pyrimidines **218** and **219** in 60-87% yield (Scheme 101).[79]





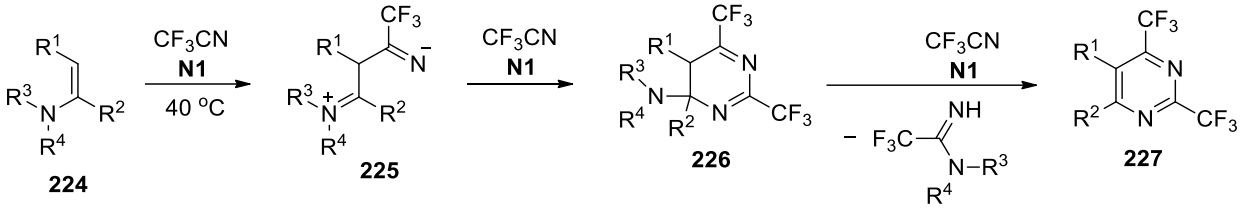
Scheme 101. Synthesis of R^F-pyrimidines from aromatic methyl ketimines and R^F-nitriles.

Reaction of aldimine **220** with $H(CF_2)_2CN$ **N143** gave a mixture of at least three products, but only triazine **221** (the trimerization product) was isolated in an analytically pure form (Scheme 102).[79]



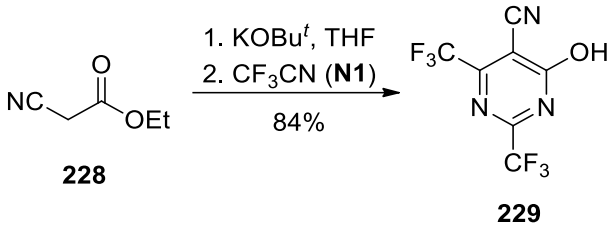
Scheme 102. Reaction of aldimine **220** with $H(CF_2)_2CN$.

Enamines **224**, having an H-atom at the β-position, reacted with trifluoroacetonitrile (**N1**) at 40-80 °C, producing 2,4-bis(trifluoromethyl)pyrimidines **227**. A plausible mechanism of this transformation involves the formation of intermediated **225** and **226** (Scheme 103).[123,124]



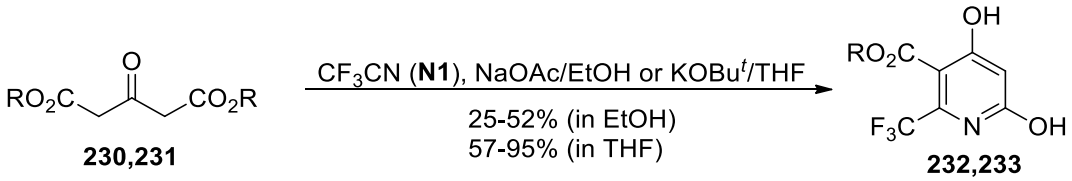
Scheme 103. Reaction of CF_3CN with enamines **224**.

It was reported that CF_3-pyrimidinol **229** (84%) was generated from ethyl cyanoacetate (**228**) utilizing both CF_3CN from commercial cylinders and that formed *in situ* (Scheme 104).[42]



Scheme 104. Synthesis of CF_3-pyrimidinol **229**.

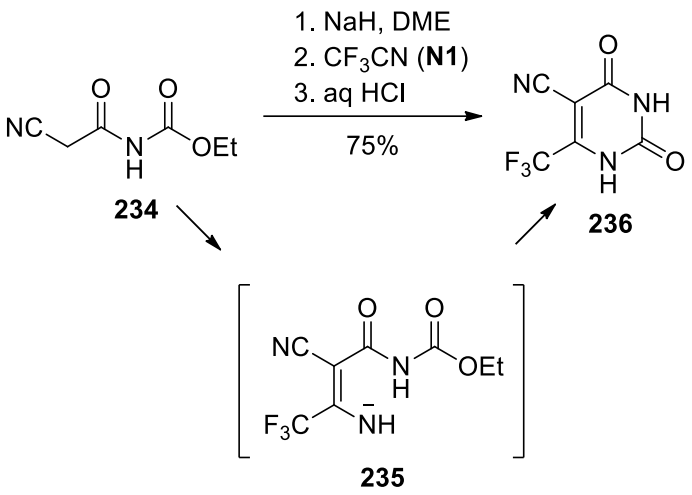
Passing gaseous CF_3CN into a solution of 3-oxopentanedioates **230** and **231** in EtOH containing excess aqueous AcONa provided CF_3-pyridinediols **232** and **233** in poor to moderate yields (25-52%) after an acidic workup.[125] It was found that the best yields of **232** and **233** were obtained by passing CF_3CN into a THF solution of **230** or **231** in the presence of 1 equiv of $KOBu^t$. The yields of **232** and **233** were good to excellent (57-95%) by this procedure (Scheme 105).[125]



230,232 R = Me
231,233 R = Et

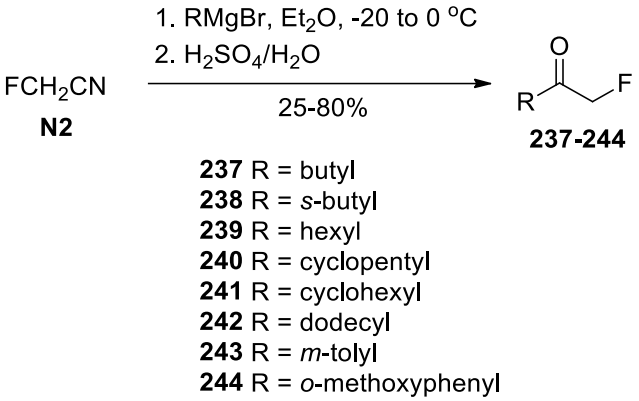
Scheme 105. Synthesis of CF_3-pyridinediols **232** and **233**.

Treatment of **234** with NaH followed by reaction of the resulting anion with trifluoroacetonitrile (**N1**) gave 5-cyano-6-(trifluoromethyl)uracil (**236**) in 75% yield (Scheme 106).[126]



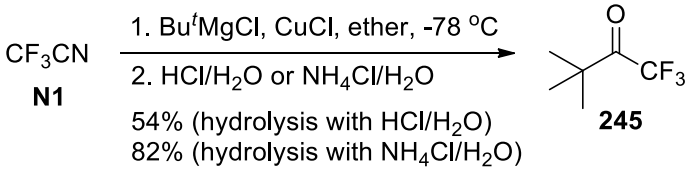
Scheme 106. 5-cyano-6-(trifluoromethyl)uracil (**236**).

It was reported, that fluoroacetonitrile (**N2**) reacts normally with Grignard reagents, giving alkyl or aryl fluoromethyl ketones in 25-80% yield (Scheme 107).[127]



Scheme 107. Synthesis of α-fluoroketones **237-244** from FCH_2CN.

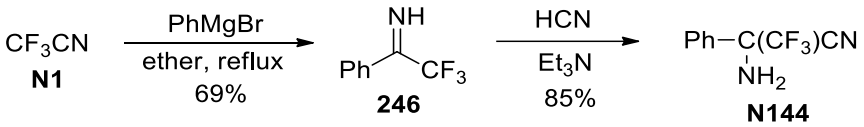
tert-Butyl trifluoromethyl ketone **245** (54-82%) was synthesized through the reaction between trifluoroacetonitrile (**N1**) and *tert*-butylmagnesium chloride in the presence of CuCl (Scheme 108).[128]



Scheme 108. Synthesis of *tert*-butyl trifluoromethyl ketone **245**.

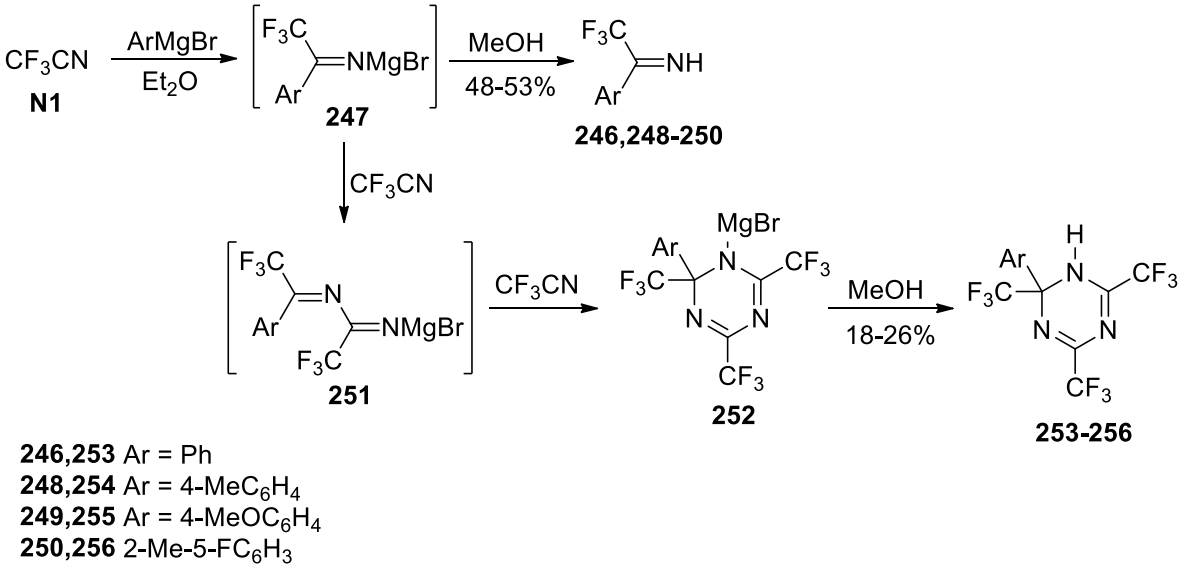
The reaction of trifluoroacetonitrile (**N1**) with PhMgBr resulted in the formation of phenyl trifluoromethyl ketimine **246** in 69%.[102] Imine **246** was used for the preparation of α-amino-α-(trifluoromethyl)phenylacetonitrile (**N144**), which is a good precursor for the synthesis of some

trifluoromethylated amino acids (Scheme 109). R^F-nitrile **N144** is a potential reagent for ^{19}F NMR determination of enantiomeric purity of acids.[102]



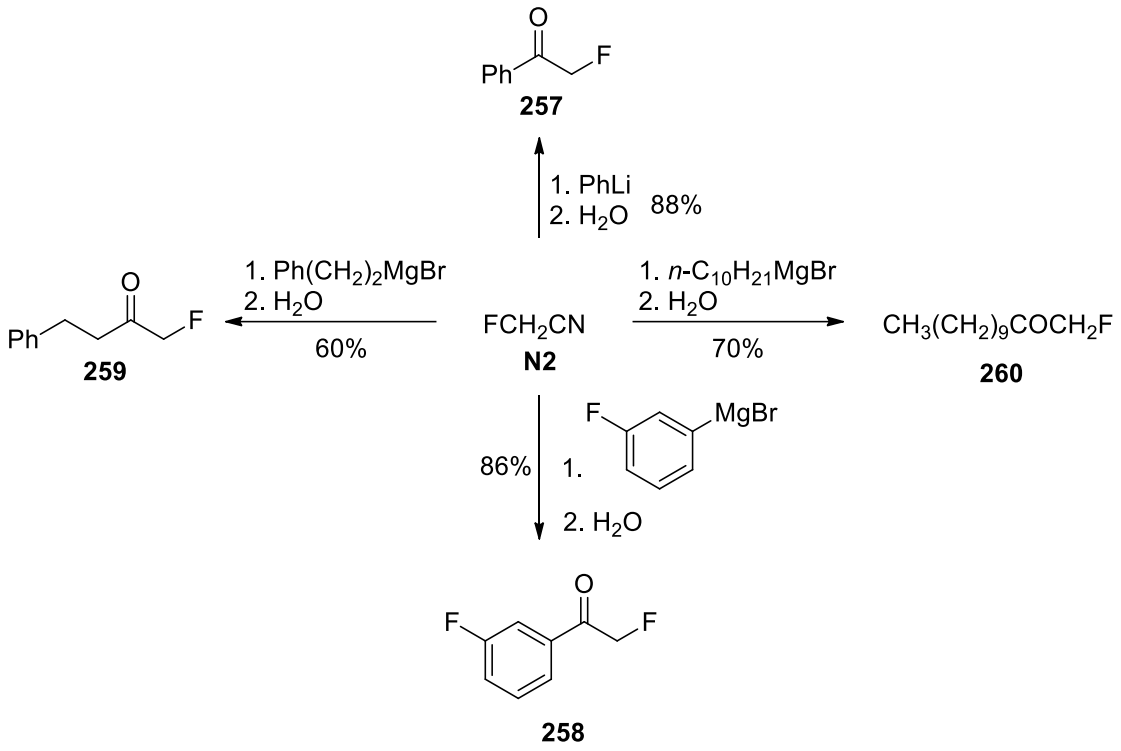
Scheme 109. Reaction of CF_3CN with PhMgBr and subsequent synthesis of R^F-nitrile **N144**.

It was found that apart from imines **246,248-250** (48-53%), 2-aryl-2,4,6-tris(trifluoromethyl)-1,2-dihydro-1,3,5-triazines **253-256** are formed (18–26%) in the reactions of CF_3CN with arylmagnesium bromides, due to the reaction of intermediate imine salt **247** with CF_3CN (Scheme 110).[129] Excess CF_3CN increases the yield of dihydrotriazine **254** up to 66%.[129]



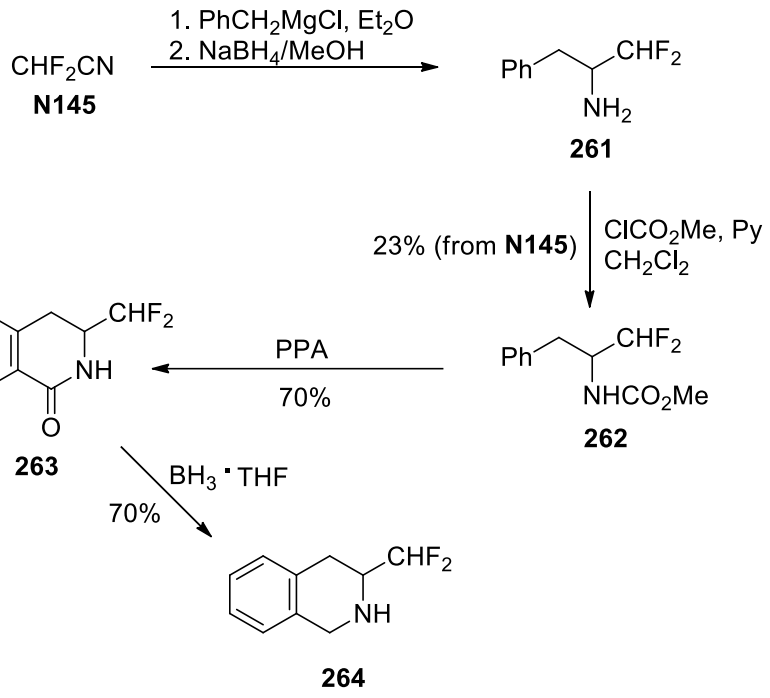
Scheme 110. Synthesis of CF_3-imines **246,248-250** and dihydrotriazines **253-256**.

Phenyllithium and 3-fluorophenylmagnesium bromide provided α-fluoroacetophenones **257** and **258** (88-86%) in the reaction with FCH_2CN **N2**. Aliphatic Grignard reagents gave the fluorinated ketones **259** and **260** in good yields (60-70%) (Scheme 111).[130]



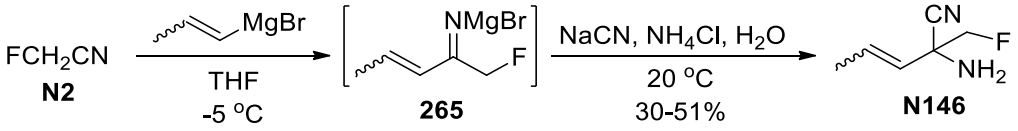
Scheme 111. Reactions of FCH_2CN with PhLi and Grignard reagents.

1,1-Difluoro-3-phenylpropan-2-amine (**261**) was synthesized from difluoroacetonitrile (**N145**) and benzylmagnesium chloride.[30] Amine **261** was used for the synthesis of 3-(difluoromethyl)-1,2,3,4-tetrahydroisoquinoline (**264**), an inhibitor of phenylethanolamine *N*-methyltransferase (PNMT). Thus, compound **261** was treated with methyl chloroformate in CH_2Cl_2 and pyridine to afford carbamate **262**. Cyclization of **262** with polyphosphoric acid yielded lactam **263** (70%), the key intermediate in the synthesis of potent PNMT. Reduction of **263** with BH_3·THF gave 3-(difluoromethyl)-1,2,3,4-tetrahydroisoquinoline (**264**) (70%) (Scheme 112).[30]



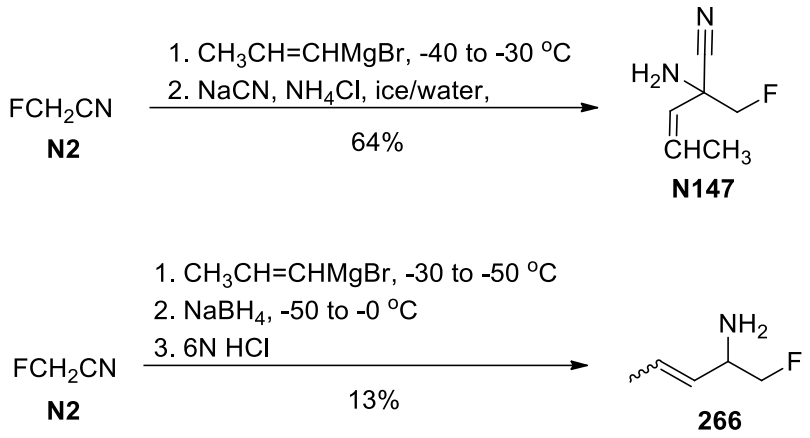
Scheme 112. 1,1-Difluoro-3-phenylpropan-2-amine (**261**) and 3-(difluoromethyl)-1,2,3,4-tetrahydroisoquinoline (**264**).

Synthesis of 2-amino-2-fluoromethyl-3-pentenenitrile (**N146**) (30-51%), a key intermediate in the synthesis of 2,5-diamino-2-fluoromethyl-3(*E*)-pentenoic acid, an enzyme-activated inhibitor of ornithine decarboxylase activity, was reported.[131] The approach is based on the reaction of fluoroacetonitrile (**N2**) with 1-propenylmagnesium bromide and the subsequent treatment of intermediate **265** with NaCN and NH_4Cl in H_2O (Scheme 113).[131]



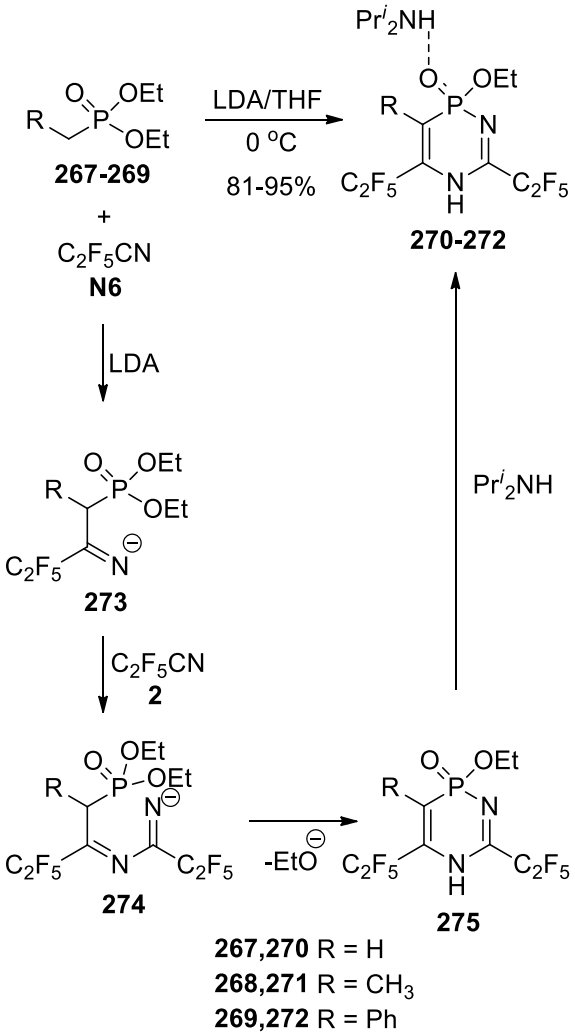
Scheme 113. Synthesis of α-fluoromethylated α-aminonitrile **N146**.

2-Amino-2-(fluoromethyl)-3-pentenenitrile (**N147**) was synthesized in 64% from fluoroacetonitrile (**N2**), propenylmagnesium bromide, and NaCN.[132] Treatment of the reaction mixture formed after the addition of the Grignard reagent with $NaBH_4$ gave 1-fluoropent-3-en-2-amine (**266**) as a *cis/trans* mixture (13%) (Scheme 114).[132]



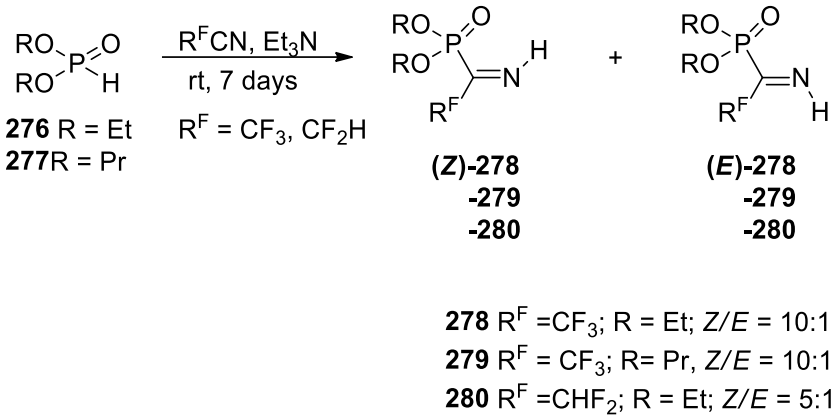
Scheme 114. Synthesis of monofluorinated α-aminonitrile **N147** and fluoroamine **266**.

Reaction of alkylphosphonates **267-269** with pentafluoropropionitrile (**N6**) at 0 °C leads to the formation of C_2F_5-substituted diisopropylamine-2,5-dihydro-1,5,2-diazaphosphinines adducts **270-272**, which were isolated in 81-95% yield.[117] The plausible mechanism involves the formation of intermediates **273-275** (Scheme 115).[117]



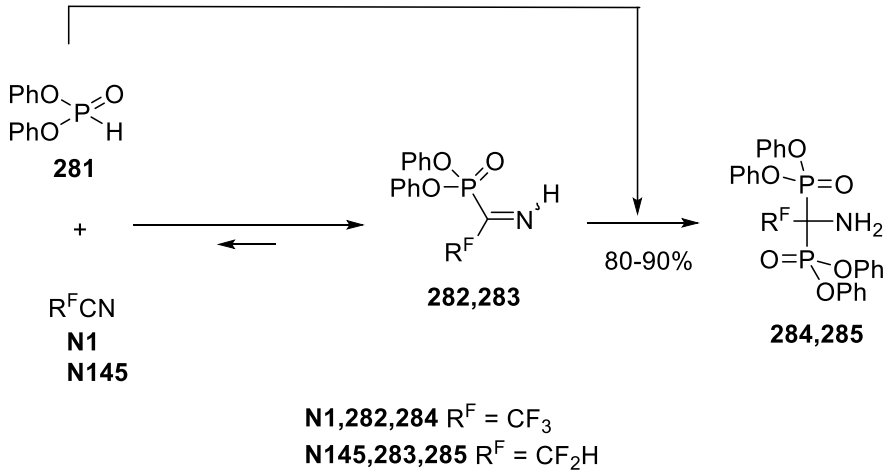
Scheme 115. Synthesis of C_2F_5-substituted diisopropylamine-2,5-dihydro-1,5,2-diazaphosphinines adducts **270-272**.

Dialkyl phosphites **276** and **277** reacted with difluoroacetonitrile and trifluoroacetonitrile in the presence of catalytic amounts of a nitrogen base at room temperature to form iminophosphonates **278-280** in high yields.[133] In solution, imidoyl phosphonates **278-280** exist as equilibrium mixtures of the *Z/E*-isomers, the more sterically hindered *Z*-configuration being thermodynamically preferable. The *Z/E* ratio essentially depends on the R^F substituent at the C=N bond, but it is practically independent of the nature of the phosphonyl group (Scheme 116).[133]



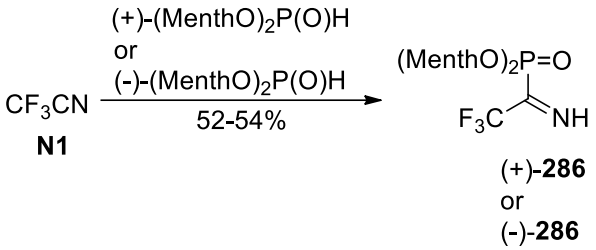
Scheme 116. Synthesis of imidoyl phosphonates **278-280**.

Less nucleophilic diphenyl phosphite (**281**) reacts with fluorinated nitriles in the same manner to afford imidoyl phosphonates **282** and **283**, as a dynamic mixture of *Z/E*-isomers.[133] Iminophosphonates **282** and **283** undergo partial dissociation to the initial compounds on storage at room temperature.[133] Diphenyl phosphite, formed upon dissociation, quickly adds to the activated C=N bond of the starting iminophosphonates to form stable geminal bisphosphonates **284** and **285**, which are the desired products of this reaction (Scheme 117).[133] A series of trihaloacetonitriles, bearing a different number of fluorine and chlorine atoms in the molecule, were also investigated in the above reaction.[134]



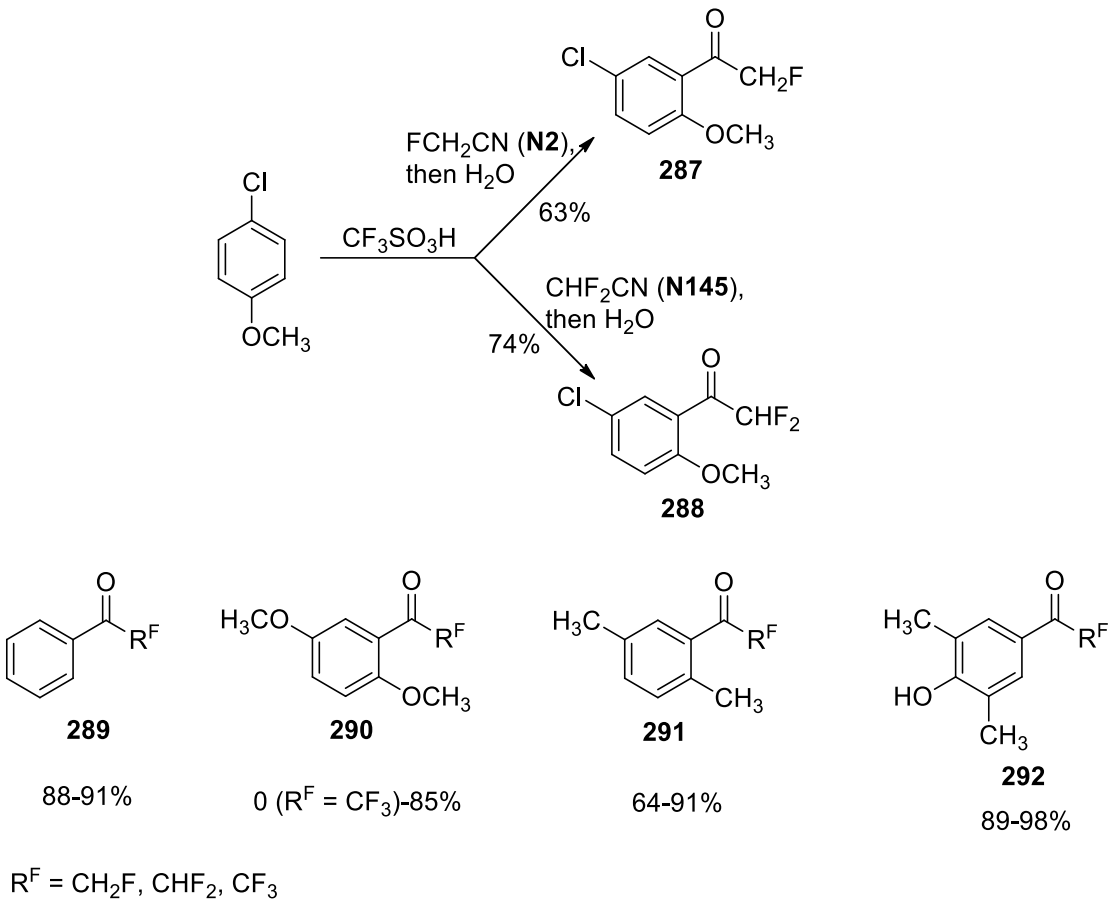
Scheme 117. Formation of imidoyl phosphonates **282** and **283**, and geminal bisphosphonates **284** and **285**.

Optically pure CF_3-bearing dimenthyl iminophosphonates (+)-**286** and (-)-**286** were prepared by the reaction of readily accessible (+)- and (-)-dimenthyl phosphites with CF_3CN (Scheme 118).[135]



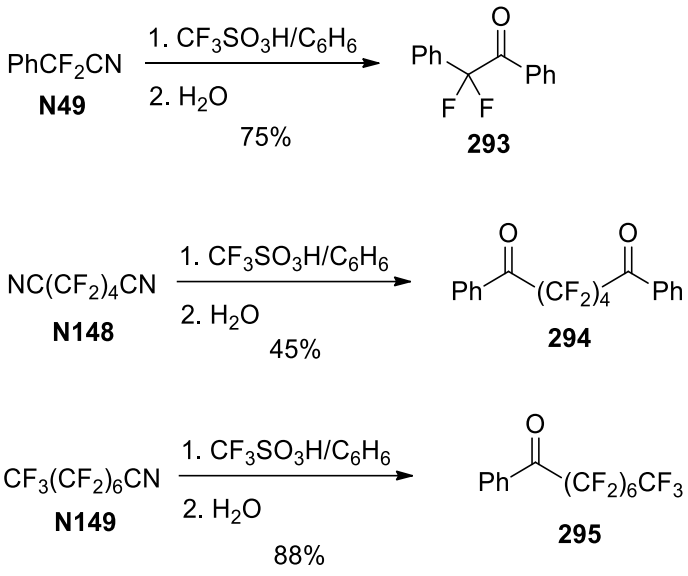
Scheme 118. Synthesis of optically pure CF_3-bearing dimenthyl iminophosphonates (+)-**286** and (-)-**286**.

R^F-nitriles undergo the Houben–Hoesch reaction with arenes in CF_3SO_3H to give α-fluorinated ketones in good yields.[130] The fluorine substituents appear to enhance the reactivities of the nitriles (and the nitrilium ion intermediates) compared to similar aliphatic nitriles.[130] Thus, FCH_2CN and F_2CHCN reacted with *p*-chloroanisole in the presence of trifluoromethanesulfonic acid and the respective ketones **287** and **288** were formed in good yields (63-74%). Other ketones bearing CH_2F, CHF_2 and CF_3 groups **289-292** were also synthesized in uo to 98% yield by using of the corresponding aromatic substrates, CH_2FCN, CHF_2CN and CF_3CN (Scheme 119).[130]



Scheme 119. Houben–Hoesch reaction of R^FCN with arenes in CF_3SO_3H.

Besides fluorinated acetonitriles, several other types of R^F-nitriles gave ketone products in moderate to good yields. α-Difluorinated nitrile **N49** leads to ketone **293** (75%). R^F-Dinitrile **N148** provides the R^F-1,6-diketone **294** (45%), while ketone **295** (88%) is formed from perfluorooctanenitrile (**N149**) (Scheme 120).[130]

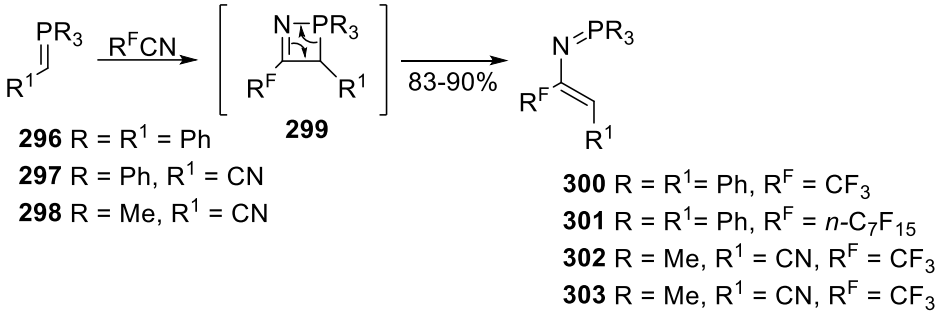


Scheme 120. Houben–Hoesch reaction of R^F-nitriles with benzene in CF_3SO_3H.

3.4. Cycloadditions

Due to the presence in molecules of R^F-nitriles the highly polarized triple bond that belongs to the highly electron-deficient C≡N group, these compounds are reactive enophiles, dienophiles and dipolarophiles: they can undergo cycloadditions with isolated double bonds (including ylides) and conjugated systems.

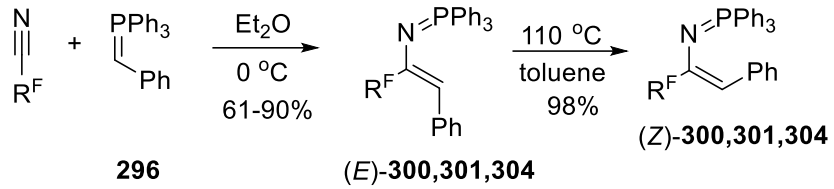
Fluoroalkyl substituted *N*-vinylic phosphazenes **300-303** were prepared by [2 + 2]-cycloaddition of phosphorus ylides **296-298** and R^F-nitriles (Scheme 121).[136] R^F-phosphazenes **300-303** can be used in the aza-Wittig reaction with aldehydes for the preparation of fluoroalkylated 2-azadienes.[136]



Scheme 121. Synthesis of R^F-phosphazenes **300-303**.

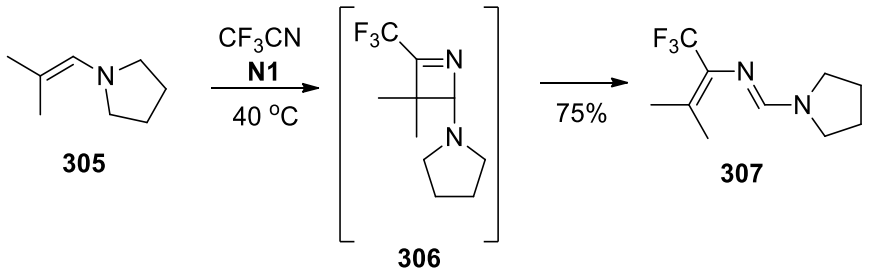
In accordance with an improved procedure, gaseous CF_3CN and CF_3CF_2CN were bubbled through a cooled (0 °C) solution of a phosphorus ylide **296** to afford the corresponding R^F-phosphazenes **300,301,304** (the *E*-isomers) in 61-90% yield.[137] Heating (*E*)-**300,301,304** at 110 °C in toluene leads to their isomerization, producing the *Z*-isomers, (*Z*)-**300,301,304**, which were isolated in 98% yield (Table 12).[137]

Table 12. Synthesis of R^F-phosphazenes **300,301,304**[137]



Entry	R^F	Product	Yield, %
1	CF_3	(*E*)-**300**	90
2	CF_3	(*Z*)-**300**	98
5	*n*-C_7F_{15}	(*E*)-**301**	83
6	*n*-C_7F_{15}	(*Z*)-**301**	98
3	C_2F_5	(*E*)-**304**	61
4	C_2F_5	(*Z*)-**304**	98

β,β-Disubstituted enamine **305** reacted with CF_3CN at 40 °C to give 2-aza-1,3-pentadiene derivative **307** (75%). The authors noted that most likely, the reaction proceeds via the formation of 1-azetine intermediate **306** (Scheme 122).[123]

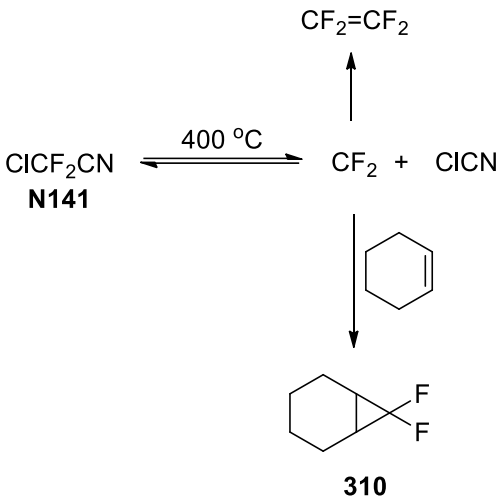


Scheme 122. Reaction of β,β-disubstituted enamine **305** with CF_3CN.

The Diels-Alder cycloaddition of R^F-nitriles and 1,2-butadiene proceeds at 400 °C to give R^F-pyridines **309** in 97-99% yield (R^F = CF_3, C_2F_5, $CF_3CF_2CF_2$) and 12% yield (R^F = $CClF_2$) (Scheme 123).[138]

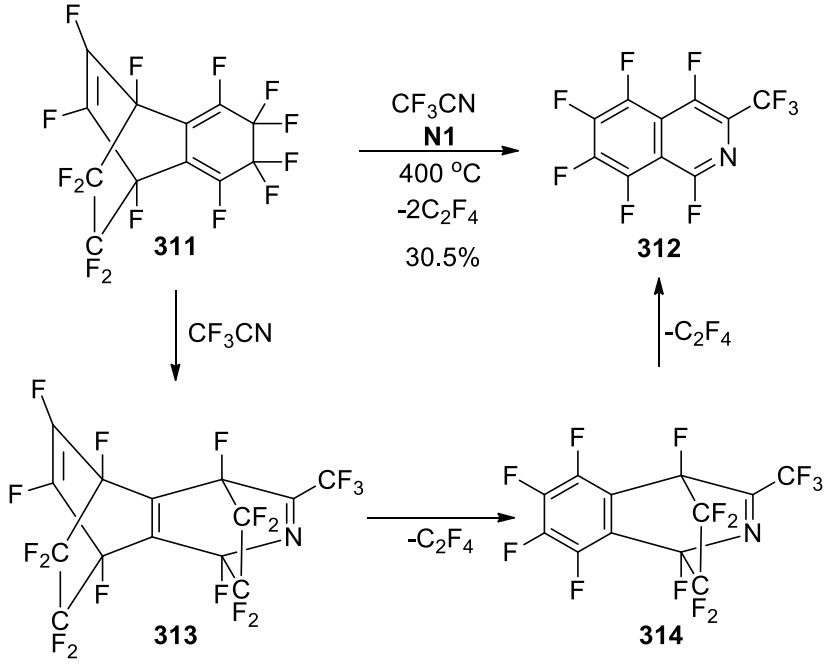
Scheme 123. Diels-Alder cycloaddition of R^F-nitriles and 1,2-butadiene.

The low yield in the case of $ClCF_2CN$ **N141** might be explained by the fact that this nitrile decomposes at high temperatures into difluorocarbene and ClCN, that has been proven through the formation of tetrafluoroethylene and isolation of the CF_2 addition product **310** (Scheme 124).[139]



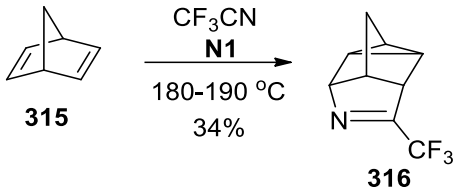
Scheme 124. Dissociation of $ClCF_2CN$ **N141** at 400 °C and formation of tetrafluoroethylene, and CF_2 addition product **310**.

The Diels-Alder reaction of perfluorotriene **311** with CF_3CN at 400 °C gave 1,4,5,6,7,8-hexafluoro-3-(trifluoromethyl)isoquinoline (**312**) in 30.5 % yield.[140] Some amounts of intermediate compounds **313** and **314** were also isolated (Scheme 125).[140]



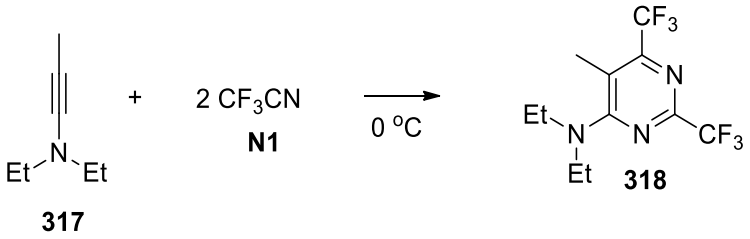
Scheme 125. Synthesis of 1,4,5,6,7,8-hexafluoro-3-(trifluoromethyl)isoquinoline (**312**).

Norbornadiene (**315**) reacts with trifluoroacetonitrile only at high temperatures (180–190 °C), and a long reaction time (40 h) was required to obtain CF_3-azatetracyclononene (**316**) as the [2+2+2]-cycloadduct, in 34% yield (Scheme 126).[141]



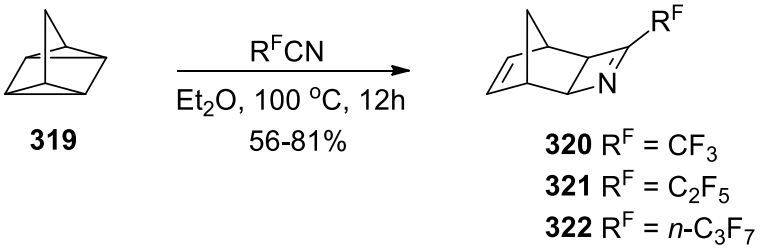
Scheme 126. Cycloaddition of CF_3CN and norbornadiene.

The reaction of ynamine **317** and CF_3CN at 0 °C resulted in the formation of pyrimidine **318** ([2+2+2]-cycloaddition) (Scheme 127).[123]



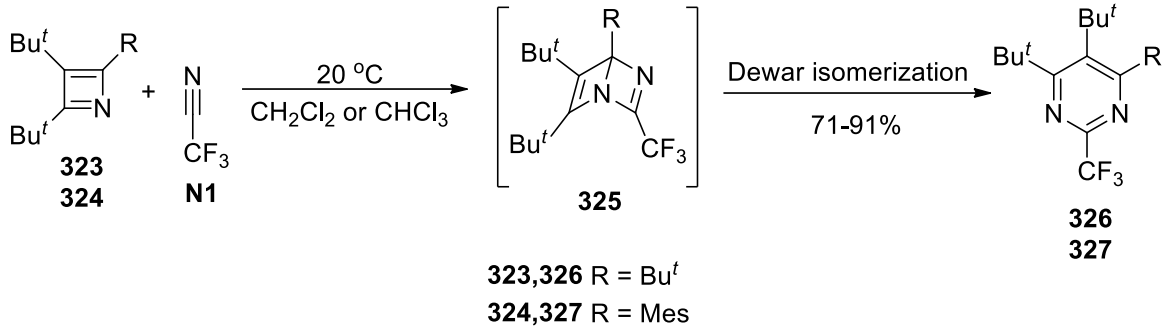
Scheme 127. [2+2+2]-Cycloaddition of ynamine **317** and CF_3CN.

The cycloaddition reaction of quadricyclane (**319**) and R^F-nitriles was studied.[142] Nitriles, in general, are not active towards **319**.[143] However, it was found that R^F-nitriles have surprisingly high reactivity towards **319**. In contrast to MeCN, which is totally inert towards quadricyclane (100 °C, 16 h), CF_3CN, C_2F_5CN, and *n*-C_3F_7CN rapidly react with **319** at elevated temperature producing *exo*-3-aza-4-perfluoroalkyltricyclo[4.2.1.$0^{2,5}$]non-3,7-dienes **320-322** (Scheme 128).[142]



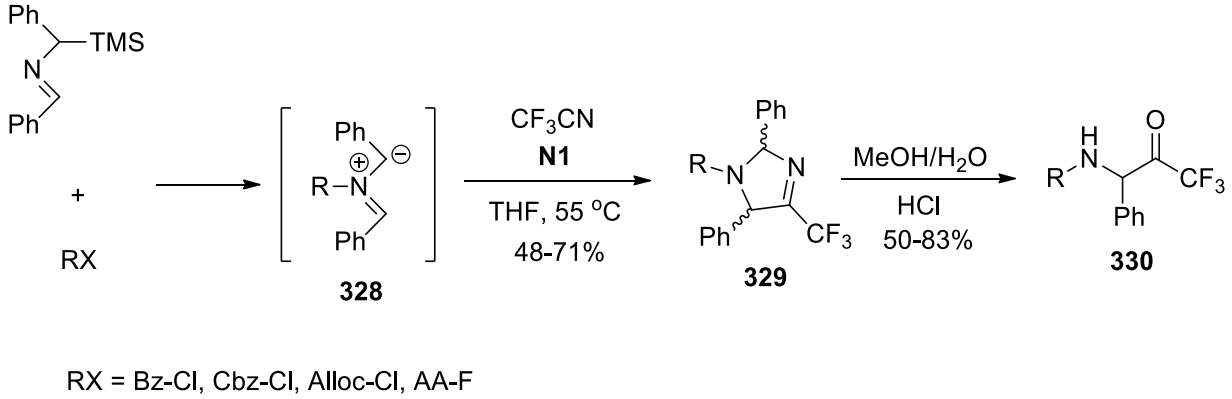
Scheme 128. Cycloaddition of quadricyclane (**319**) and R^F-nitriles.

The [4 + 2]-cycloaddition of azetes **323** and **324**, and CF_3CN at 20 °C in either CH_2Cl_2 or $CHCl_3$, and the subsequent Dewar isomerization of bicyclic intermediates **325** resulted in isolation of CF_3-pyrimidines **326** and **327** in 71-91% yield (Scheme 129).[144]



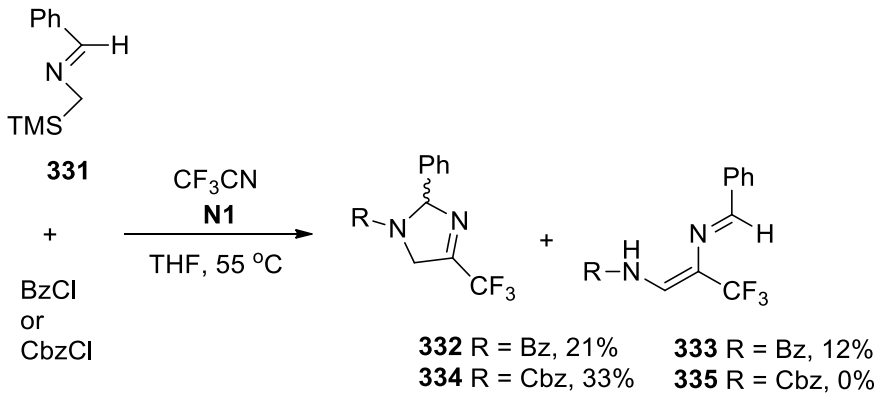
Scheme 129. [4 + 2] cycloaddition of azetes **323** and **324**, and CF_3CN at 20 °C, and subsequent Dewar isomerization to CF_3-pyrimidines **326** and **327**.

Trifluoroacetonitrile was used in a three-component reaction for the synthesis of 4-trifluoromethyl-Δ^3-imidazolines **329**.[145] The reaction of an acyl halide with an α-trimethylsilylimine generates an azomethine ylide **328**, which then undergoes a 1,3-dipolar cycloaddition reaction with CF_3CN to afford 4-trifluoromethyl-Δ^3-imidazolines **329**.[145] Such acylating agents benzoyl chloride, benzyl chloroformate, allyl chloroformate, and amino acid fluorides (AA-F) were used.[145] The acid chlorides and chloroformates initiated the dipolar cycloadditions effectively at 55 °C, whereas the acid fluorides required temperatures around 75 °C.[145] The Alloc and Cbz protecting groups are very effective in the cycloaddition and showed high stability to a wide range of conditions, including acid and strong base. Imidazolines **329** are readily hydrolyzed in MeOH or $MeCN/H_2O$ in the presence of dilute HCl to afford *N*-protected phenyl glycine-derived CF_3-ketones **330** (Scheme 130).[145]



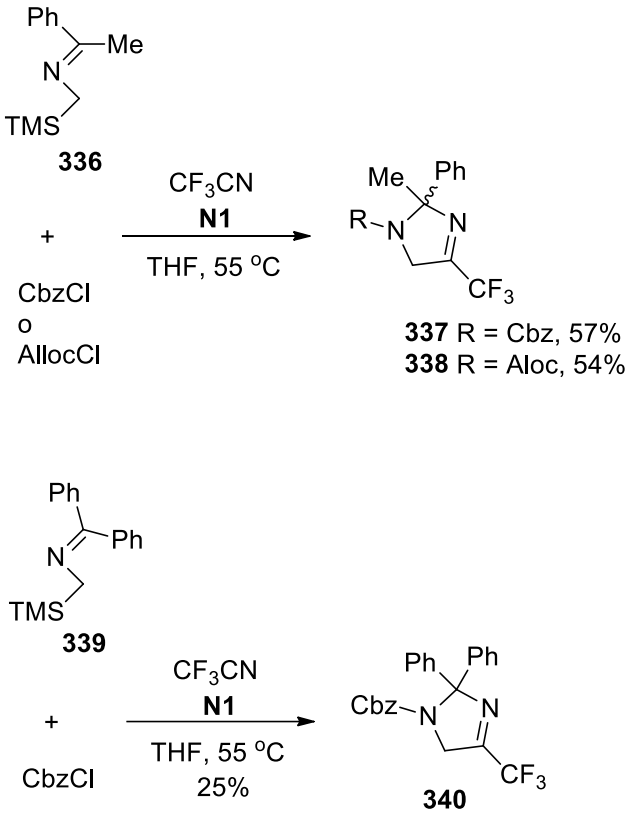
Scheme 130. 1,3-Dipolar cycloaddition of intermediate azomethine ylide **328** and CF_3CN.

The reaction of imine **331** with BzCl and CF_3CN afforded a mixture of imidazoline **332** and acyclic enediamine-imine derivative **333**. Imine **331** proved to be a fairly poor substrate for the cycloaddition reactions, as shown by the low yield of **332** (21%) and the tendency for **332** to undergo ring-opening to **333**.[145] The reaction of CbzCl with **331** did not produce the corresponding ring-opened compound **335**, but the yield of desired imidazoline **334** was still low (33%) (Scheme 131).[145]



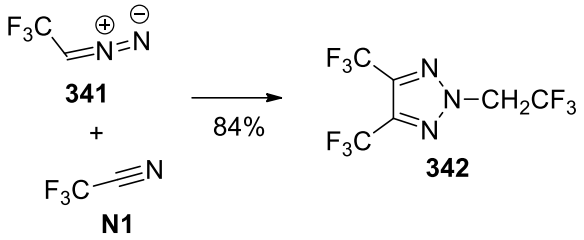
Scheme 131. Reaction of imine **331** with CF_3CN in the presence of either BzCl or CbzCl.

In contrast to **331**, imine **336** afforded 2-methyl-2-phenyl substituted imidazolines **337** and **338** in improved yield (57-54%), and with excellent regioselectivity.[145] The cycloaddition reaction also tolerated the significant bulk from two germinal phenyl substituents of imine **339** and afforded a modest yield of imidazoline **340** (Scheme 132).[145]



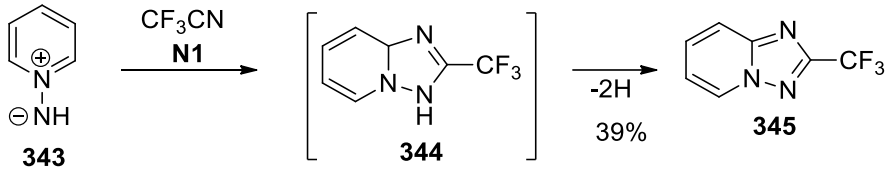
Scheme 132. Synthesis of CF_3-imidazolines **337**,**338**, and **340**.

2,2,2-Trifluorodiazoethane (**341**) and CF_3CN reacted completely in two days to give nitrogen, recovered CF_3CN, and 2-(2,2,2-trifluoroethyl)-4,5-bistrifluoromethyl-1,2,3-triazole (**342**) (84%) (Scheme 133).[146]



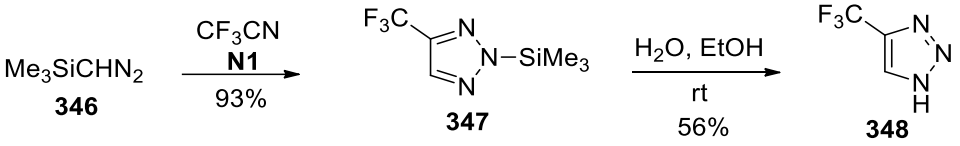
Scheme 133. Synthesis of triazole **342**.

N-Iminopyridinium ylide (**343**) reacts with trifluoroacetonitrile (1,3-dipolar cycloaddition) giving 2-(trifluoromethyl)-*s*-triazolo[1,5-*a*]pyridine (**345)** (Scheme 134).[147] Compound **345** was isolated in 39% yield in 75-mol.% purity.[147]



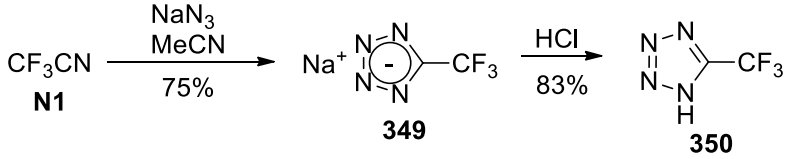
Scheme 134. Synthesis of 2-(trifluoromethyl)-*s*-triazolo[1,5-*a*]pyridine (**345**).

It was shown in 1973 that diazomethyltrimethylsilane (**346**) reacts with CF_3CN to give *N*-trimethylsilyl-4-trifluoromethyl-1,2,3-triazole, probably the 2-trimethylsilyl isomer **347**.[148] Cycloadduct **347** was readily hydrolyzed by aqueous EtOH or by atmospheric moisture to give 4-trifluoromethyl-1,2,3-triazole (**348**) (Scheme 135).[148]



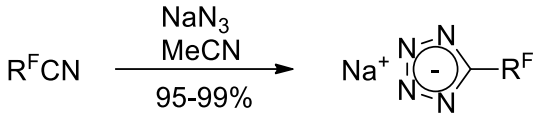
Scheme 135. Synthesis of 4-CF_3-1,2,3-triazoles **347** and **348**

The reactions of R^FCN with azides can be considered as 1,3-dipolar [3 + 2]-cycloadditions. Thus, sodio-5-trifluoromethyltetrazole (**349**) was synthesized in 75% yield through the reaction of CF_3CN with NaN_3 in MeCN (the temperature of the reaction mixture rose spontaneously to 60 °C).[149] Treatment of salt **349** with aqueous HCl resulted in analytically pure 5-trifluoromethyltetrazole (**350**) (Scheme 136).[149]



Scheme 136. Synthesis of sodio-5-trifluoromethyltetrazole (**349**) and 5-trifluoromethyltetrazole (**350**).

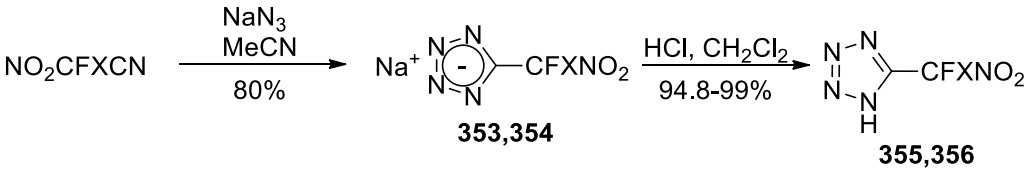
Furthermore, besides the reaction of CF_3CN with NaN_3, the reactions of the CF_3CF_2CN and $CF_3CF_2CF_2CN$ with NaN_3 in MeCN forming sodio-5-R^F-tetrazoles **351** and **352**, were undertaken (Scheme 137).[43]



349 $R^F = CF_3$
351 $R^F = CF_2CF_3$
352 $R^F = CF_2CF_2CF_3$

Scheme 137. Synthesis of sodio-5-R^F-tetrazoles **349, 351**, and **352**.

A similar approach for the synthesis of sodio-5-(trifluoromethyl)tetrazole **349** (40%) through bubbling CF_3CN into a solution of NaN_3 in MeCN at 25 °C was described.[44]
The reaction of $(O_2N)_2CFCN$ and O_2NCF_2CN with NaN_3 proceeds at ~20 °C, giving the corresponding R^F-sodio-tetrazoles **353** and **354** (80%), and is accompanied by practically no exothermic effect.[150] Treatment of **353** and **354** with dry HCl in CH_2Cl_2 gave R^F-tetrazoles **355** and **356** (94.8-99%) (Scheme 138).[150]



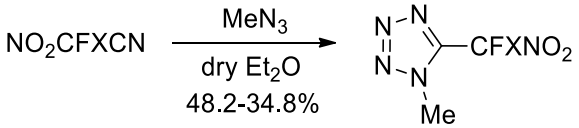
353,354

355,356

353,355 X = NO_2
354,356 X = F

Scheme 138. Synthesis of R^F-tetrazoles **355** and **356**.

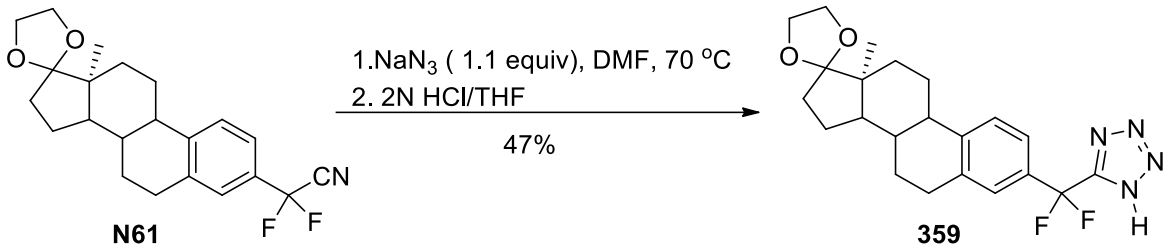
1,5-Disubstituted tetrazoles can also be synthesized from R^F-nitriles. Thus, reaction of fluorodinitroacetonitrile and difluoronitroacetonitrile with methyl azide in dry ether resulted in the corresponding R^F-tetrazoles **357** and **358**, which were isolated in 48.2-34.8% yield (Scheme 139).[150]



357 X = NO_2
358 X = F

Scheme 139. Synthesis of R^F-tetrazoles **357** and **358**.

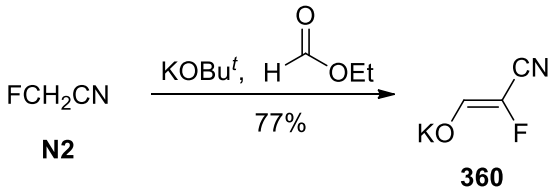
Tetrazole **359**, a fluorine-containing estrone derivative, was prepared in 47% yield through the reaction of difluoronitrile **N61** with NaN_3 (Scheme 140).[63]



Scheme 140. Synthesis of R^F-triazole **359**.

3.5. R^F-nitriles as active methylene compounds

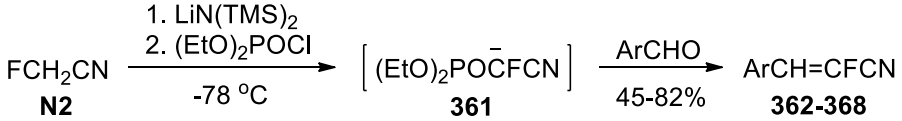
Fluoroacetonitrile and its α-monosubstituted derivatives are active methylene compounds, which can be used in various synthetic strategies for the preparation of fluorine-containing substances. Thus, the reaction of fluoroacetonitrile with ethyl formate in the presence of KOBu^t gave potassium (*Z*)-2-cyano-2-fluoroethenolate (**360**) (77%) (Scheme 141),[35] an attractive and readily available building-block for the synthesis of fluorinated heterocycles such as fluorinated pyrimidines and pyrazoles.[151] The approach was expanded by using of various bases such as KOBu^t, NaOBu^t, NaOAmyl^t, NaHMDS, and methyl/ethyl formates, that allowed preparation of sodium and potassium (*Z*)-2-cyano-2-fluoroethenolates in 35-79% yield. No target product was isolated when such bases as NaOMe, NaH, KOEt were used.[35]



Scheme 141. Synthesis of potassium (*Z*)-2-cyano-2-fluoroethenolate (**360**).

The reaction of FCH_2CN with diethylchlorophosphate at -78 °C, in the presence of $LiN(TMS)_2$, and the subsequent treatment of the reaction mixture (intermediate anion **361**) with aromatic aldehydes, gave 1-cyano-1-fluoroalkenes **362-368** in 45-82% yield.[152] Aliphatic aldehydes don't allow preparation of 1-cyano-1-fluoroalkenes, producing complex mixtures (Table 13).[152]

Table 13. Synthesis of α-fluoro-α,β-unsaturated nitriles **362-368**[152]



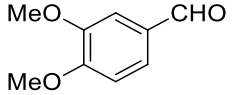
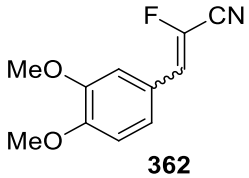
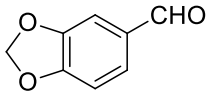
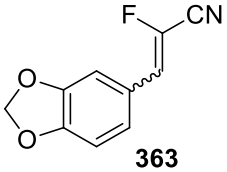
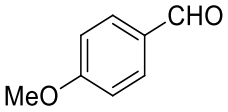
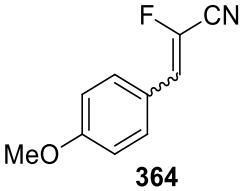
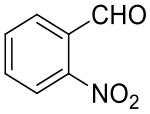
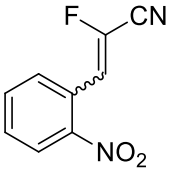
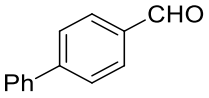
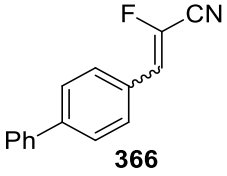
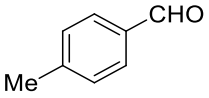
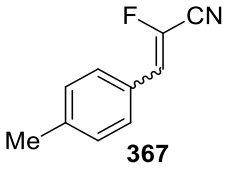
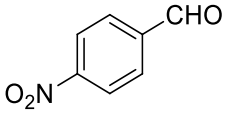
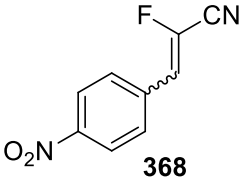
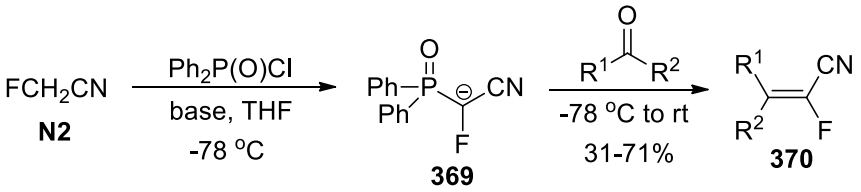
Entry	Aldehyde	Product	Yield, %
1		 **362**	46

Table 13. Continued

Entry	Aldehyde	Product	Yield, %
2		 **363**	45
3		 **364**	52
4		 **365**	62
5		 **366**	82
6		 **367**	51
7		 **368**	45

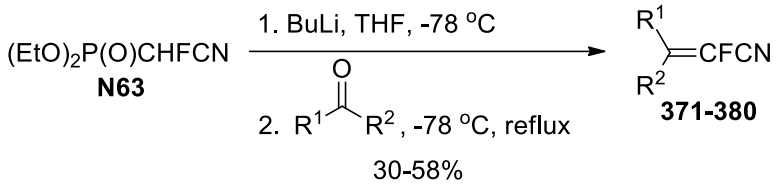
The use of fluoroacetonitrile in the Horner–Wittig reaction allows preparation of α-fluoro acrylonitriles. The reaction of FCH_2CN with $Ph_2P(O)Cl$ leads to the formation of nucleophilic anions **369**, which then react with aldehydes and ketones to give α-fluoro-α,β-unsaturated nitriles **370**, which were isolated in 31-73% yield (Scheme 142).[153]

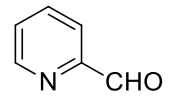
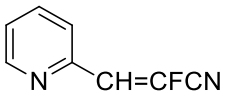
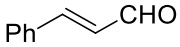
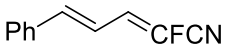
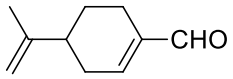
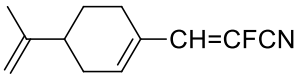
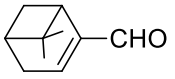
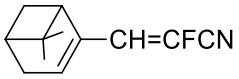
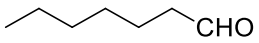
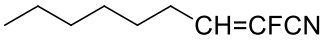
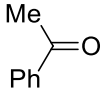
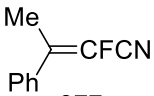
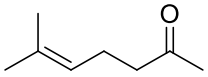
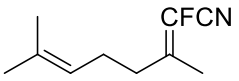
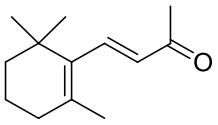
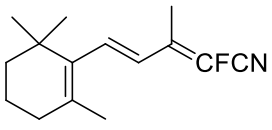


Scheme 142. Synthesis of α-fluoro-α,β-unsaturated nitriles **370**.

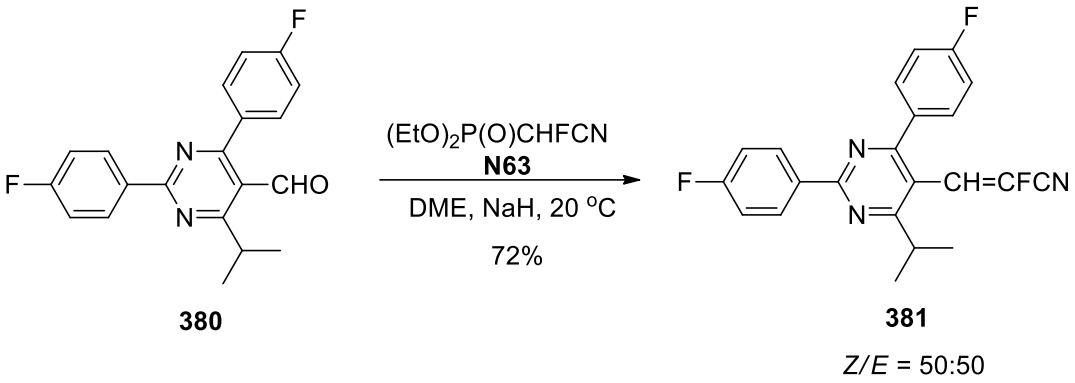
The Wittig-Horner reaction of diethyl cyanofluoromethanephosphonate (**N63**), an α-fluorinated nitrile, with aldehydes and ketones yielded various α-fluoro-α,β-unsaturated nitriles **371-380** as *Z*:*E* mixtures in 30-58% yield (Table 14).[64]

Table 14. Synthesis of α-fluoro-α,β-unsaturated nitriles **371-380**[64]



Entry	Carbonyl compound	Product	Yield of product, %	*Z*:*E*
1	PhCHO	PhCH=CFCN (**371**)	54	1:2
2		 **372**	53	2:3
3		 **373**	38	2:3
4		 **374**	42	1:2
5		 **375**	54	1:2
6		 **376**	30	7:3
7		 **377**	58	1:1
8		 **378**	40	1:1
9		 **379**	46	1:2
10	$PhCH_2CHO$	$PhCH_2CH$=CFCN (**380**)	50	3:2

Treatment of aldehyde **380** with 2-(*O*,*O*-diethylphosphono)-2-fluoroacetonitrile (**N63**) in the presence of NaH in DME gave α,β-unsaturated α-fluoronitrile **381** as a 1:1 mixture of the *E* and *Z* isomers, that was part of work on the preparation of a new fluoro-substituted HMG-COA reductase inhibitor (Scheme 143).[153]

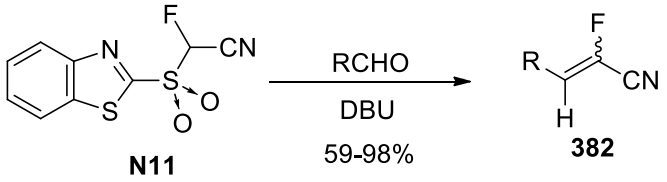


380 **381**

Z/*E* = 50:50

Scheme 143. Synthesis of α,β-unsaturated α-fluoronitrile **381**.

α-Fluoronitrile **N11** was used as a building-block to synthesize various α α,β-unsaturated α-fluoronitriles **382** in high yields and with good *Z*-stereoselectivity.[46] The reaction of **N11** with aliphatic, aromatic and heteroaromatic aldehydes in the presence of DBU as a base gave **382** in 59-98% yield (Scheme 144).[46]

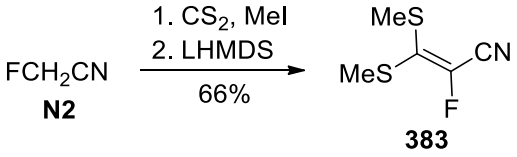


N11 **382**

R = Alkyl, Aryl, Heteroaryl

Scheme 144. Synthesis of α,β-unsaturated α-fluoronitriles **382**.

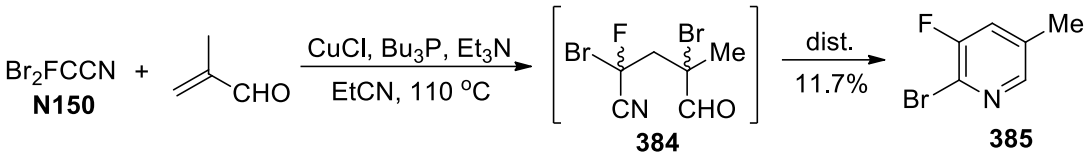
Treatment of fluoroacetonitrile (**N2**) with CS_2 and MeI, and then LHMDS, yielded α-fluoroacrylonitrile derivative **383** in 66% yield (Scheme 145).[155]



383

Scheme 145. Reaction of FCH_2CN with CS_2 in the presence of MeI and LHMDS.

The reaction of dibromofluoroacetonitrile (**N150**) with methacrolein was conducted in manner similar to that described for Cl_2FCCN (see paragraph 2.12, Scheme 45): the reaction in propionitrile at 110 °C, in the presence of CuCl as catalyst and Bu_3P/Et_3N as cocatalysts, resulted in the formation of functionalized α-fluoronitrile **384** as a mixture of diastereomers.[37] Attempts to purify crude **384** by distillation, instead, lead to the isolation of 2-bromo-3-fluoro-5-methylpyridine (**385**) in 11.7% yield (Scheme 146).[37]



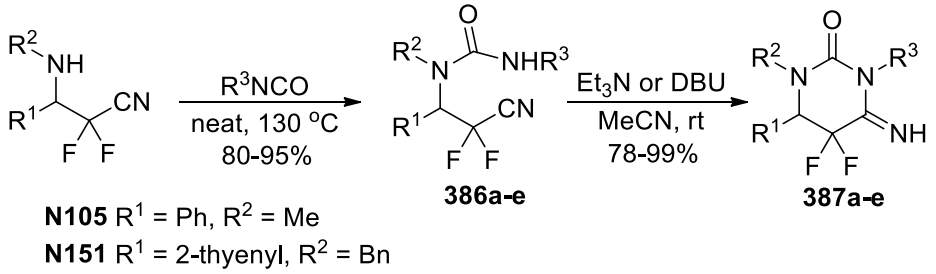
Scheme 146. Reaction of dibromofluoroacetonitrile (**N150**) with methacrolein in the presence of $CuCl/Bu_3P/Et_3N$.

No pyridine products were found during the distillation of the adducts formed from Cl_2FCCN **N80** and methacrolein: all pyrolytic attempts at ring closure resulted in the formation of tars and multiple reactions products.[37]

3.6. Heterocyclizations of of 3-amino-2,2-difluoropropanenitriles with isocyanates and cyanoacetic acid

Reaction of 3-amino-2,2-difluoropropanenitriles **N105** and **N151** with isocyanates at 130 °C, and the subsequent treatment of intermediates **386** with either Et_3N or DBU in MeCN at rt yielded iminopyrimidones **387** in 78-99% yield. Intermediate substances **386** were also isolated (80-95%) and characterized (Table 15).[156]

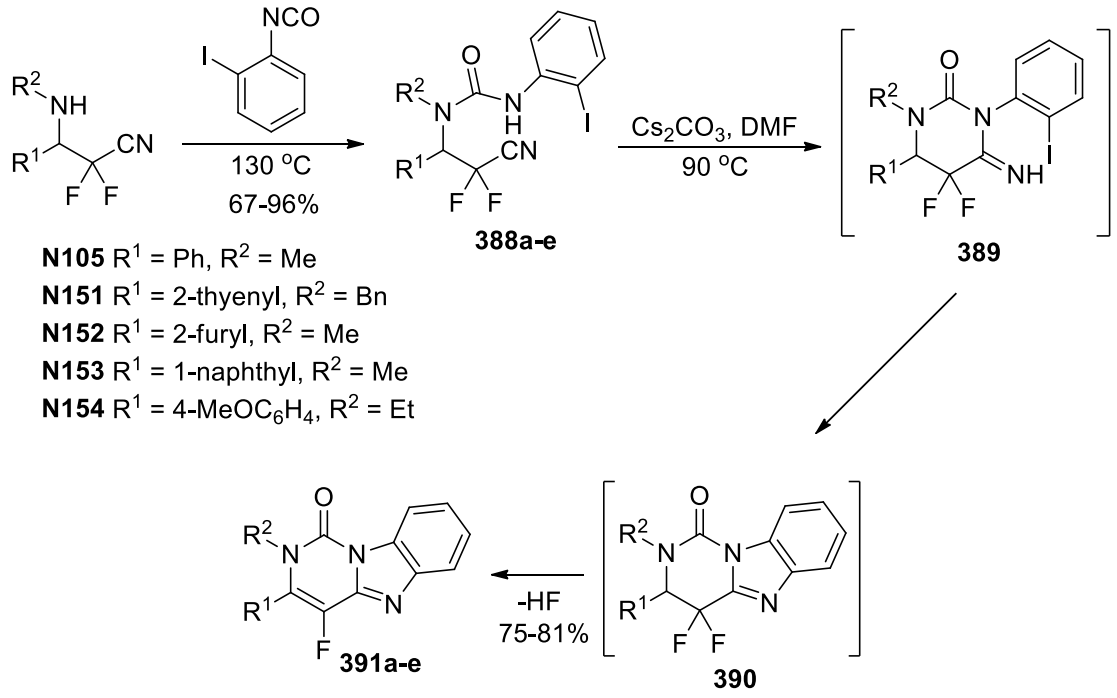
Table 15. Synthesis of iminopyrimidones **387**[156]



Entry	R^1	R^2	R^3	**386**	Yield of **386**, %	**387**	Base	Yield of **387**, %
1	Ph	Me	Ph	**386a**	95	**387a**	Et_3N	95
2	Ph	Me	4-ClC_6H_4	**386b**	95	**387b**	Et_3N	97
3	2-thyenyl	Bn	Ph	**386c**	83	**387c**	Et_3N	98
4	2-thienyl	Bn	4-ClC_6H_4	**386d**	80	**387d**	Et_3N	99
5	Ph	Me	Pr	**386e**	93	**387e**	DBU	78

Pyrimido[1,6-*a*]benzimidazolones **391** were synthesized in 75-81% yields from 3-amino-2,2-difluoropropanenitriles **N105**, **N151-154** and *o*-iodophenylisocyanate, and intermediate substances **388** were also isolated (67-96%) and characterized (Table 16).[156]

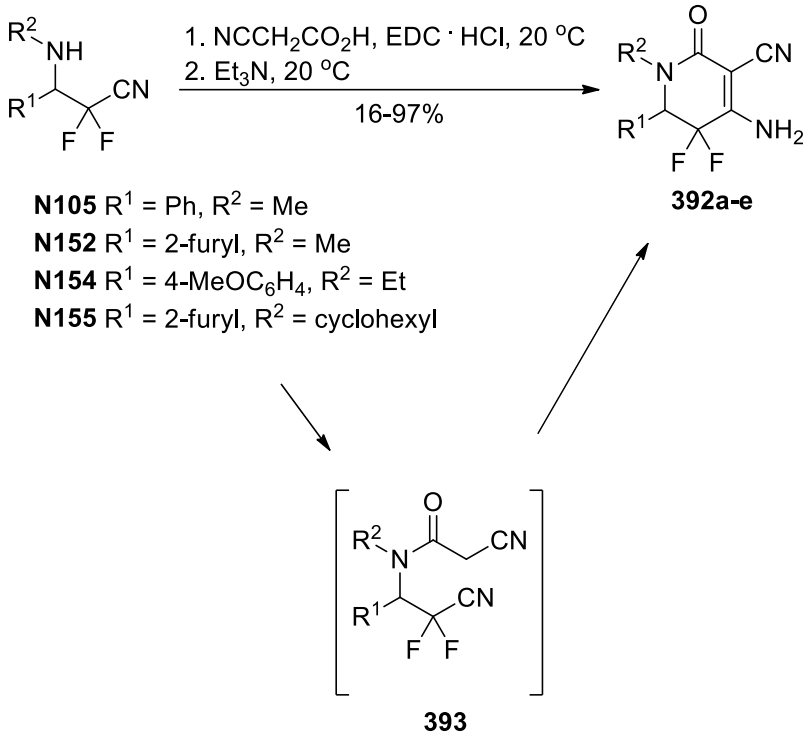
Table 16. Synthesis of pyrimido[1,6-*a*]benzimidazolones **391**[156]



Entry	R^1	R^2	**388**	Yield of **388**, %	**391**	Yield of **391**, %
1	Ph	Me	**388a**	94	**391a**	81
2	2-thienyl	Bn	**388b**	67	**391b**	80
3	2-furyl	Me	**388c**	96	**391c**	77
4	1-naphthyl	Me	**388d**	95	**391d**	79
5	4-$MeOC_6H_4$	Et	**388e**	92	**391e**	75

Fluorinated 4-amino-5,6-dihydropyridin-2(1*H*)-ones **392** (16-97%) were synthesized from α,α-difluoronitriles **N105**, **N152**, **N154** and **N155** and cyanoacetic acid in the presence of EDC·HCl.[157] The plausible mechanism involves the formation intermediates **393** formed in the acylation step, which then undergo the ring closure (the Thorpe—Ziegler reaction) to give **392** (Table 17).[157]

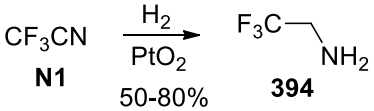
Table 17. Synthesis of fluorinated 4-amino-5,6-dihydropyridin-2(1*H*)-ones **392**[157]



Entry	R^1	R^2	Product **392**	Yield of **392**, %
1	Ph	Me	**392a**	95
2	2-furyl	Me	**392b**	97
3	4-$MeOC_6H_4$	Et	**392c**	93
4	2-thienyl	Bn	**392d**	43
5	2-furyl	cyclohexyl	**392e**	16

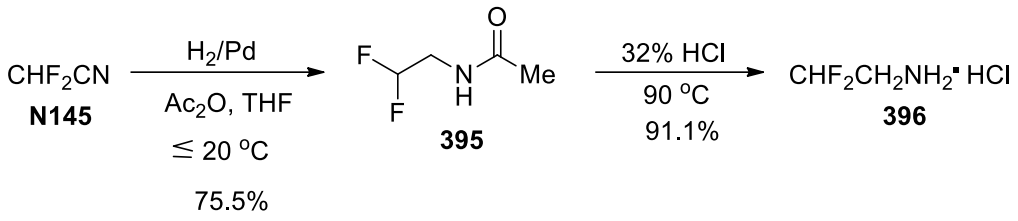
3.7. Reduction

It was shown, that CF_3CN can be reduced to 2,2,2-trifluoroethylamine (**394**) (50-80%) by hydrogenation in the presence of PtO_2 (Scheme 147).[29]



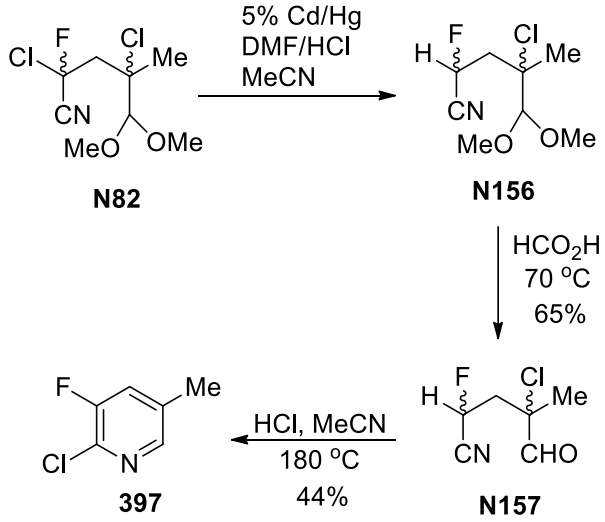
Scheme 147. Synthesis of 2,2,2-trifluoroethylamine.

2,2-Difluoroethylamine hydrochloride (**396**) (91.1%) was prepared in 69% overall yield via the reduction of CHF_2CN with H_2/Pd in Ac_2O/THF at ~20 °C, and the subsequent hydrolysis of intermediate amide **395** with 32% HCl at 90 °C (Scheme 148).[158] Other acylating agents and reductants can also be used for the preparation of **396**.[158]



Scheme 148. Preparation of 2,2-difluoroethylamine hydrochloride (**396**).

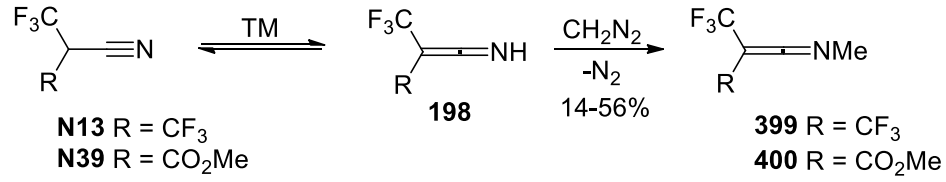
The α-chlorine atom can selectively be removed from a molecule of α-chloro-α-fluoronitriles by reduction. Thus, the reduction of α-fluoronitrile (**N82**) with 5% Cd/Hg α-dechlorinated α-fluoronitrile **N156**, which was hydrolyzed with formic acid to afford functionalized α-fluoronitriles **N157** in 65% yield.[37] Cyclization of **N157** under the action of HCl in MeCN at 180 °C gave 2-chloro-3-fluoro-5-methylpyridine (**397**) in 44% yield (Scheme 149).[37]



Scheme 149. Synthesis of functionalized α-fluoronitriles **N156** and **N157**, and fluoropyridine **397**.

3.8. Other reactions

β-Fluorinated nitriles **N13** and **N39** undergo the nitrile-ketenimine tautomerism, and they were methylated with diazomethane to give trifluoromethylated *N*-methylketenimines **399** and **400** in 14 and 56% yields, respectively (Scheme 150).[58]



Scheme 150. Nitrile-ketenimine tautomerism and synthesis of *N*-methylketenimines **399** and **400**.

Treatment of bis(triphenylphosphine)platinum *trans*-stilbene with excess of CF_3CN gives the complex bis(triphenylphosphine)platinum-CF_3CN **401**.[159] The proposed structure is based on the 56.4 MHz ^{19}F NMR

spectrum and an intense IR absorption of 1734 cm^{-I} in the region normally assigned to the C=N stretching frequency.[159] Another product, isolated from the reaction of CF_3CN and $Pt(PPh_3)_4$, for which chemical analysis shows the molecular formula $(PPh_3)_2Pt(CF_3CX)_2N$ **402**, was subjected to a single-crystal X-ray diffraction structure determination (Figure 1).[159]

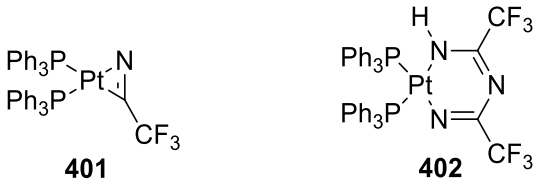


Figure 1. Formation of platinum complexes **401** and **402**.

Kinetics and mechanism of free-radical addition of CF_3CN to ethylene at 350-450 °C were explored, and such products as 4,4,4-trifluorobutyronitrile, 6,6,6-trifluorohexanenitrile, perfluoroethane, 1,1,1,4,4,4-hexafluorobutane, and 1,1,1,6,6,6-hexafluorohexane were detected.[160,161]

4. Conclusions

Thus, fluoroalkyl cyanides, attractive electrophilic, enophilic, and dienophilic building-blocks, can be synthesized via a large variety of synthetic methods, that makes them both synthetically valuable and readily available reagents. R^F-Nitriles are versatile reagents: They can react with electrophiles at the C≡N group to produce various unusual reactive structures, they can play role of active methylene compounds, and they can be used as highly reactive building-blocks in cyclizations for the syntheses of fluorine-containing heterocyclic compounds. Fluoroalkyl cyanides are important reactants in medicinal chemistry for the design, development, and synthesis of pharmaceutical drugs.

5. Abbreviations

Alloc	allyloxycarbonyl
aq	aqueous
Cbz	benzyloxycarbonyl
DAST	diethylaminosulfur trifluoride
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DEG	diethylene glycol
DME	1,2-dimethoxyethane
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
EDC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
HMDS	hexamethyldisilazane
HMPA	hexamethylphosphoramide
LDA	lithium diisopropylamide

LiHMDS	lithium bis(trimethylsilyl)amide
liq	liquid
Menth	menthyl
NFSI	*N*-fluorobenzenesulfonimide
PPA	polyphosphoric acid
R^F	fluoroalkyl
rt	room temperature
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TM	tautomerism
TMS	trimethylsilyl
TMSCN	trimethylsilyl cyanide

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Author's Biography

Boris Usachev graduated from Ural State University with bachelor's (1997) and master's (1999) degrees in chemistry. He received his PhD degree in 2002, and in the same year, he was appointed as an Assistant Professor at Ural State University, Department of Chemistry, and since 2005 continued with work at the University as an Associate Professor. In 2011, he received his Doctorate degree (DSc) in chemistry from Ural Federal University, and in the same year, he was promoted to Professor. Then, Dr. Usachev served at National University of Chimborazo, Fiji National University, and University of Suriname.