

Chemistry of fluoroalkyl cyanides

Boris I. Usachev

Department of Chemistry, Faculty of Mathematical & Physical Sciences, University of Suriname, Leysweg 86,
Tammenga, Suriname
Email: biusachev@gmail.com

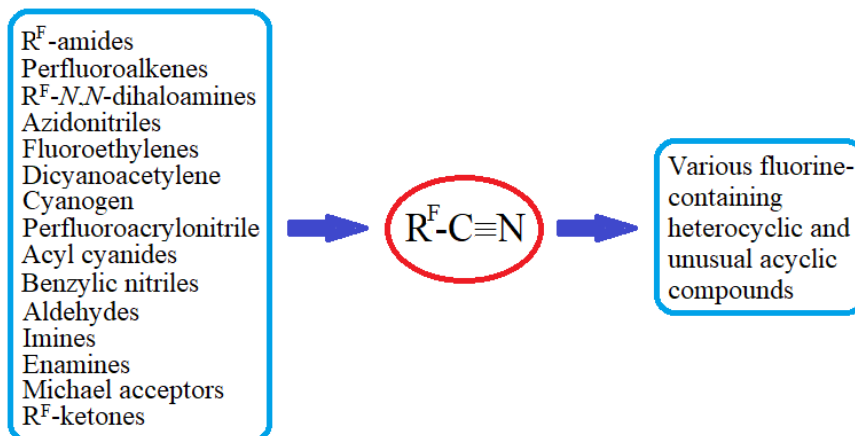
Received 08-19-2020

Accepted 10-22-2020

Published on line 11-03-2020

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 ($NCCHF_2CN$, $NCCF_2CN$, $NCCF_2CF_2CN$, etc.) are considered. The synthesis of functionalized R^F -nitriles such as F_2NCF_2CN , $F_2NCCIFCN$, 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

Table of Contents

1. Introduction
2. Synthesis of Fluoroalkyl Cyanides
 - 2.1. Dehydration of R^F -amides
 - 2.2. Hydroamination of perfluoroalkenes
 - 2.3. Nucleophilic substitution of alkyl halides
 - 2.4. Synthesis from *N,N*-dihaloamines
 - 2.5. Synthesis from azidonitriles
 - 2.6. Reactions of alkenes and alkynes with N_2F_4
 - 2.7. Halogenation of nitriles
 - 2.8. Reaction of fluoroalkenes with HMDS
 - 2.9. Reaction of acyl cyanides with DAST
 - 2.10. Fluorination of active methylene nitriles
 - 2.11. Reactions of active methylene CF_3 -nitriles with electrophiles
 - 2.12. Addition of dichlorofluoroacetonitrile to alkenes
 - 2.13. Fluoroalkylation of aldehydes, imines, and enamines
 - 2.14. Syntheses of ethyl α -fluorocyanoacetate and its derivatives
 - 2.15. Synthesis of α -functionalized R^F -nitriles on the basis of R^F -ketones
 - 2.16. Other methods
3. Chemical Properties of Fluoroalkyl Cyanides
 - 3.1. Trimerization
 - 3.2. Reactions with Electrophiles
 - 3.2.1. Reactions with boron(III) and titanium(III) Lewis acids
 - 3.2.2. Reactions with NF_3 and N_2F_4
 - 3.2.3. Reactions with halogens
 - 3.2.4. Reactions with chlorine fluorosulfate ($ClOSO_2F$), SF_4 and $SClF_5$
 - 3.2.5. Reactions with C-electrophiles
 - 3.3. Reactions with nucleophiles
 - 3.3.1. Reactions with O-nucleophiles
 - 3.3.2. Reactions with N-nucleophiles
 - 3.3.3. Reactions with C-nucleophiles
 - 3.4. Cycloadditions
 - 3.5. R^F -nitriles as active methylene compounds
 - 3.6. Heterocyclizations of 3-amino-2,2-difluoropropanenitriles with isocyanates and cyanoacetic acid
 - 3.7. Reduction
 - 3.8. Other reactions
4. Conclusions
5. Abbreviations
6. References

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 $C\equiv N$ group. This fact dramatically increases the electrophilic as well as dienophilic properties of the $C\equiv N$ group.

R^F -cyanides ($R^F CN$) 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 $\mu = 1.262 \pm 0.010$ 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 $-C-C\equiv N$ 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 $\nu_8 = 2$. 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 ($100-200\text{ GHz}$) were recorded at -78°C ($P \sim 0.01\text{ torr}$).²⁰ These spectra are complex, similar to the spectra of $CF_3C\equiv CH$ in the $\nu_{10} = 2$ state,²¹ having a superposition of three series for each J'' corresponding to $l = 0$ and $l = \pm 2$ ($kl > 0$ 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 \AA .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 \AA 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° , kcal/mol) are: 21.9 for $\text{CF}_3\text{C}(\text{F})=\text{N}^-$, 23.1 for $\text{C}_2\text{F}_5\text{C}(\text{F})=\text{N}^-$, and 23.6 for $\text{CF}_3\text{CF}_2\text{CF}_2\text{C}(\text{F})=\text{N}^-$.²⁶

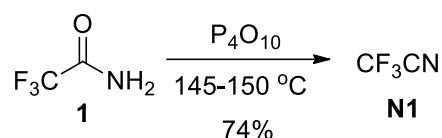
α -Functionalized R^{F} -nitriles are attractive intermediates in organic synthesis. α -Nitro groups significantly increase the reactivity of α -fluorinated nitriles. Thus, $\text{O}_2\text{NCF}_2\text{CN}$ adds the CH_3 radical to the $\text{C}\equiv\text{N}$ group four times as fast as CF_3CN , and $(\text{O}_2\text{N})_2\text{CFCN}$ is more reactive than $\text{O}_2\text{NCF}_2\text{CN}$.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

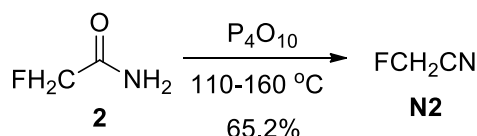
2.1. Dehydration of R^{F} -amides

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} .

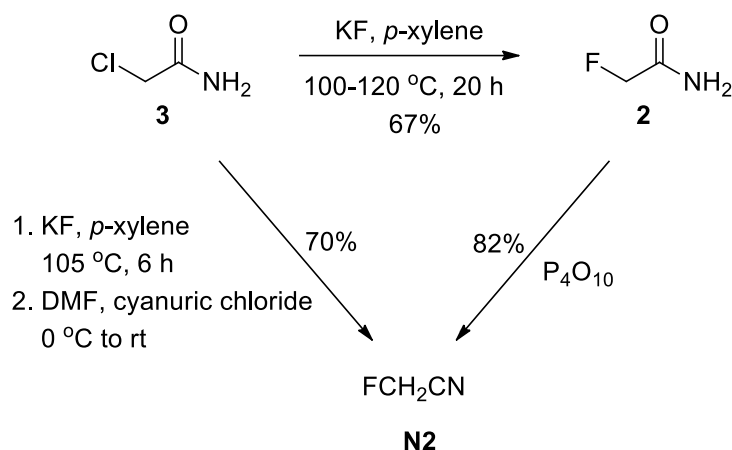
The first synthesis of fluoroacetonitrile (**N2**) was published by Swarts in 1922 who claimed that it was necessary to distil the amide with phosphoric anhydride under reduced pressure and to collect the distillate at -50 °C.³¹ In 1949, Buckle *et al.* used a similar approach to the synthesis of fluoroacetonitrile (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 be synthesized from chloroacetamide (**3**) either via two separate procedures (a Finkelstein halogen exchange reaction with the formation of intermediate

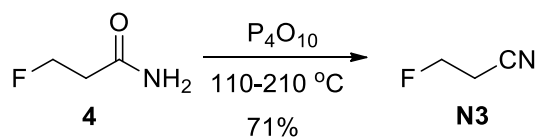
fluoroacetamide (**2**) (67%) and a dehydration reaction that gives **N2** in 82% yield) or via one-pot approach (70%) (Scheme 3).³⁵



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

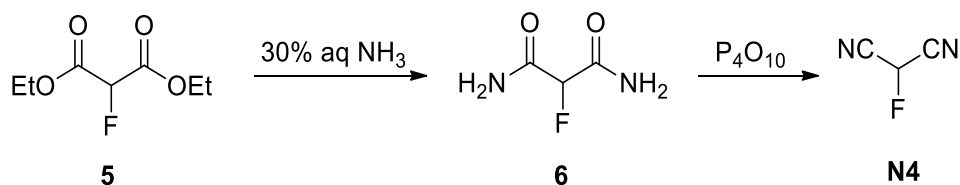
Chlorofluoroacetonitrile, ClFCHCN ,³⁶ dichlorofluoroacetonitrile, Cl_2FCCN , and dibromofluoroacetonitrile, Br_2FCCN ³⁷ were also prepared through the dehydration of the corresponding amides with P_4O_{10} .

3-Fluoropropionitrile (**N3**) (71%) was synthesized by heating amide **4** with P_4O_{10} at $110-210\text{ }^{\circ}\text{C}$ (Scheme 4).³⁴



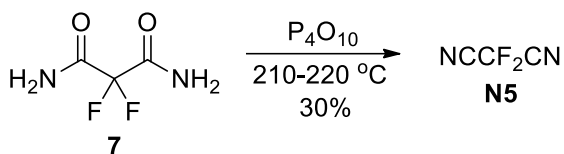
Scheme 4. Preparation of 3-fluoropropionitrile (**N3**) from 3-fluoropropioamide (**4**) and P_4O_{10} .

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} .

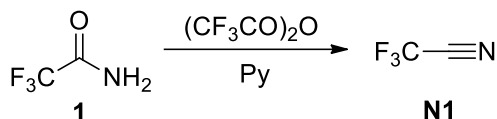
Dehydration of difluoromalonamide (**7**) with P_4O_{10} at 210-220 °C gave difluoromalononitrile (**N5**) in 30% yield (Scheme 6).⁴⁰



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

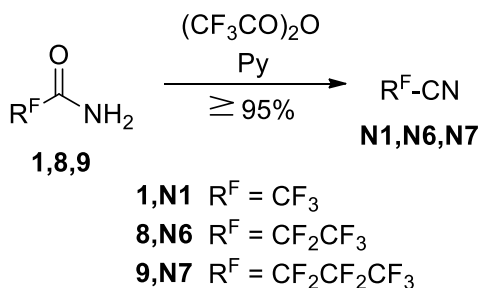
Similarly, tetrafluorosuccinonitrile, $\text{NCCF}_2\text{CF}_2\text{CN}$ (9%),⁴⁰ hexafluoroglutaronitrile, $\text{NCCF}_2\text{CF}_2\text{CF}_2\text{CN}$,⁴⁰ and octafluoroadiponitrile, $\text{NCCF}_2\text{CF}_2\text{CF}_2\text{CF}_2\text{CN}$ (64%) were prepared from the corresponding fluorinated diamides 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, $(\text{CF}_3\text{CO})_2\text{O}$ 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



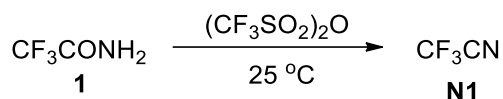
Scheme 7. Preparation of trifluoroacetonitrile (**N1**) from trifluoroacetamide (**1**) and $(\text{CF}_3\text{CO})_2\text{O}$.

The high-yield syntheses of CF_3CN **N1**, $\text{C}_2\text{F}_5\text{CN}$ **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

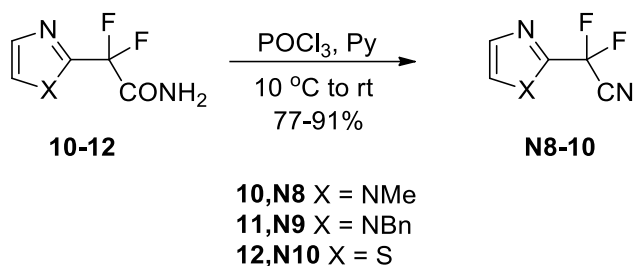


Scheme 8. Dehydration of R^{F} -amides with $(\text{CF}_3\text{CO})_2\text{O}/\text{Py}$.

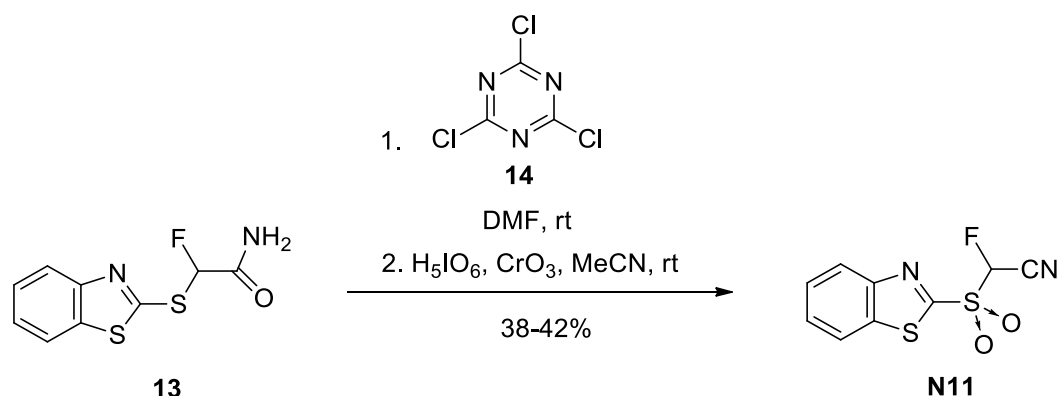
Many other dehydrating agents can be used to transform R^{F} -amides into R^{F} -nitriles. Thus, trifluoromethanesulfonic anhydride was used to transform trifluoroacetamide (**1**) into trifluoroacetonitrile (**N1**) at 25 °C (Scheme 9).⁴⁴

**Scheme 9.** Dehydration of trifluoroacetamide (**1**) with (CF₃SO₂)₂O.

Difluoroamides **10-12** were transformed into the corresponding nitriles **N8-10** in 77–91% yield upon treatment with POCl₃ in pyridine at 10 °C to rt (Scheme 10).⁴⁵

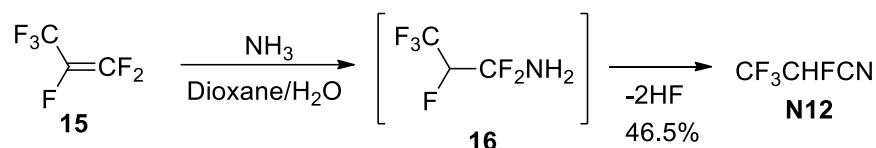
**Scheme 10.** Synthesis of α-functionalized α,α-difluoronitriles **N8-10**

Reaction of α-fluoroamide **13** with cyanuric chloride (**14**) afforded monofluorinated nitrile **N11**: the crude reaction mixture was subjected to oxidation with H₅IO₆/CrO₃ without prior purification, to give the desired **N11** in isolated yields ranging from 38 to 42% (Scheme 11).⁴⁶

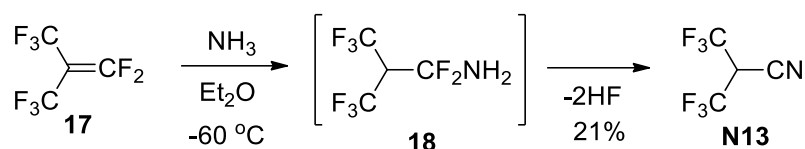
**Scheme 11.** Dehydration of amide **13** with cyanuric chloride (**14**).

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**).

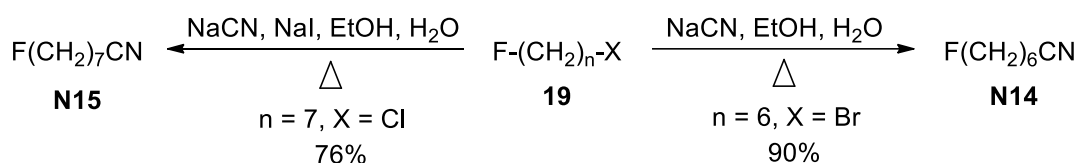
Similarly, 3,3,3-trifluoro-2-(trifluoromethyl)propanenitrile (**N13**) was synthesized from perfluoroisobutylene (**17**) and NH_3 via the HF elimination from intermediate amine **18** (Scheme 13).⁴⁷



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

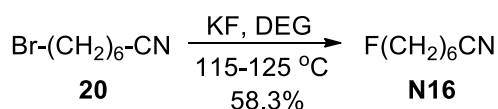
2.3. Nucleophilic substitution of alkyl halides

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.

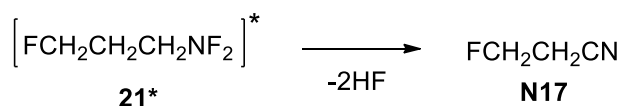
The reaction of 7-bromoheptanenitrile (**20**) with anhydrous KF in DEG gave 7-fluoroheptanenitrile (**N16**) in 58.3% yield (Scheme 15).³⁴



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

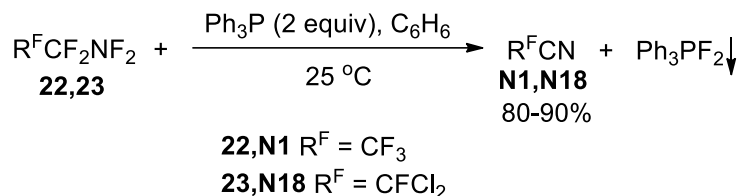
2.4. Synthesis from *N,N*-dihaloamines

Irradiation (253.7 nm) of cyclopropane with tetrafluorohydrazine, N_2F_4 , resulted in a complex mixture including $\text{F(CH}_2)_3\text{NF}_2$ (**21**) and $\text{F(CH}_2)_2\text{CN}$ (**N17**), and the last is the result of dehydrofluorination of 1-difluoramino-3-fluoropropane (**21**) in its excited state $[\text{F(CH}_2)_3\text{NF}_2]^*$ **21*** (Scheme 16).⁴⁸



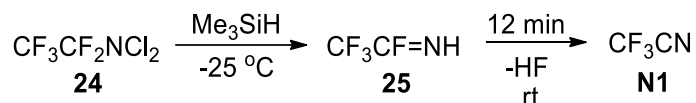
Scheme 16. Formation of 3-fluoropropanenitrile from $\text{F(CH}_2)_3\text{NF}_2$ **21** in its excited state $[\text{F(CH}_2)_3\text{NF}_2]^*$ **20***.

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



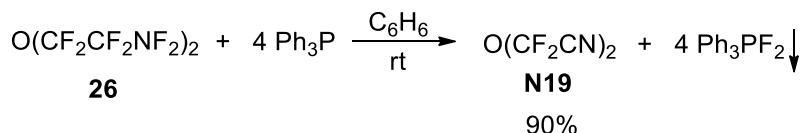
Scheme 17. Synthesis of R^F-nitriles **N1,N18** from R^F-*N,N*-difluoroamines **22,23**.

The reaction of *N,N*-dichloro(pentafluoroethyl)amine (**24**) with Me₃SiH 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-bisdifluoramine (**26**) with Ph₃P in benzene at room temperature afforded R^F-dinitrile of formula O(CF₂CN)₂ **N19** in 90% yield (Scheme 19).⁴⁹



Scheme 19. Synthesis of O(CF₂CN)₂.

2.5. Synthesis from azidonitriles

It was shown that azidonitriles **27** react with NO⁺BF₄[−] 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⁺BF₄[−] in CDCl₃ 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⁺BF₄[−] 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

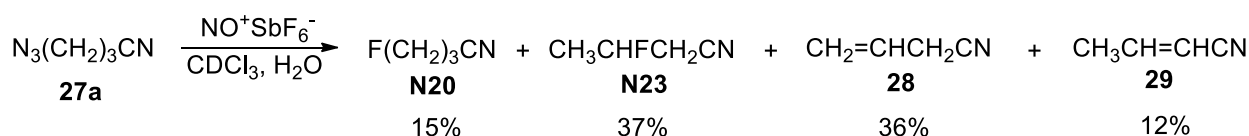
Some amounts of H₂O (1-2 equiv) added to the nitrosonium salt prior to the azidonitrile produced an observable increase in the rate of gas evolution but did not measurably affect the reaction products.⁵¹ Treatment of 4-azidobutanenitrile (**27a**) with nitrosonium hexafluoroantimonate, NO⁺SbF₆[−], in deuteriochloroform containing 1.0 equiv of H₂O 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 $25\text{ }^\circ\text{C}$ ⁵¹

$$\text{N}_3(\text{CH}_2)_n\text{CN} \xrightarrow[-\text{N}_2, -\text{N}_2\text{O}]{\text{NO}^+\text{BF}_4^-} \text{F}(\text{CH}_2)_n\text{CN} + \text{CH}_3\text{CHF}(\text{CH}_2)_{n-2}\text{CN} + \text{CH}_3\text{CH}_2\text{CHF}(\text{CH}_2)_{n-3}\text{CN} + \text{BF}_3$$

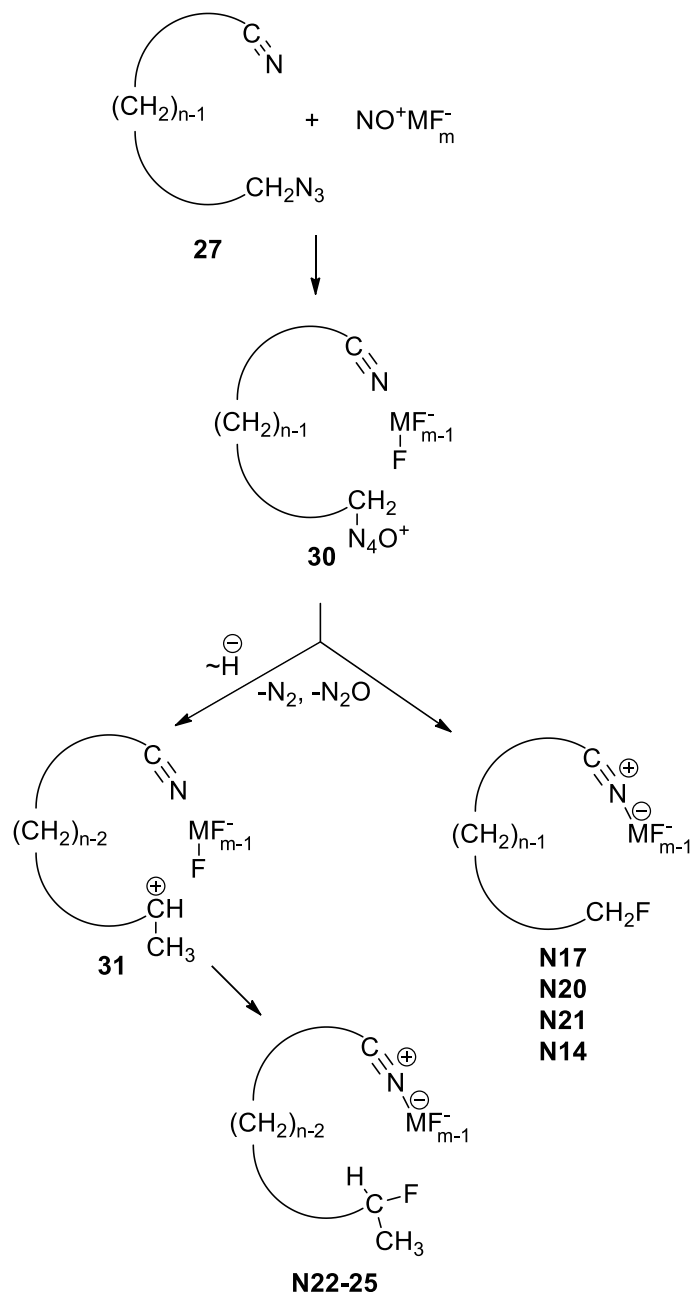
27	N17 N20 N21 N14	N22 N23 N24 N25	N26 N27 N28 N29
-----------	--	--	--

Entry	n	R ^F -nitriles	Yield, %		
			$\text{F}(\text{CH}_2)_n\text{CN}$	$\text{CH}_3\text{CHF}(\text{CH}_2)_{n-2}\text{CN}$	$\text{CH}_3\text{CH}_2\text{CHF}(\text{CH}_2)_{n-3}\text{CN}$
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 $\text{NO}^+\text{SbF}_6^-$

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 noted⁵¹ 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 ($\text{SbF}_5 > \text{PF}_5 > \text{BF}_3$), 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

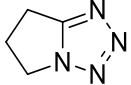


Scheme 21. Mechanism of formation of monofluoronitriles **N17**, **N20**, **N21**, **N14** and **N22-25**.

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 $\text{NO}^+\text{SbF}_6^-$, gave mixtures fluoroalkyl cyanides and nonfluorinated substances.⁵²

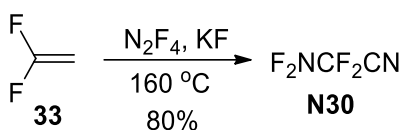
Thus, reactions of these nitrosonium salts with 4-azidobutanenitrile (**27a**) at 25 °C produced mixtures of $\text{F}(\text{CH}_2)_3\text{CN}$ **N21**, $\text{CH}_3\text{CHFCH}_2\text{CN}$ **N24**, $\text{CH}_2=\text{CHCH}_2\text{CN}$ **28**, $\text{CH}_3\text{CH}=\text{CHCN}$ **29**, and trimethylenetetrazole (**32**) (Table 2).⁵²

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

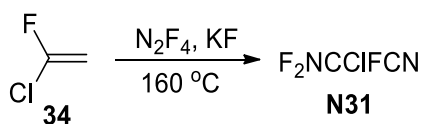
Reactant	Yield, %				
	F(CH ₂) ₃ CN N21	CH ₃ CHFCH ₂ CN N24	CH ₂ =CHCH ₂ CN 28	CH ₃ CH=CHCN 29	 32
NO ⁺ BF ₄ ⁻	26	37	5	4	28
NO ⁺ PF ₆ ⁻	15	61	< 1	< 1	24
NO ⁺ SbF ₆ ⁻	4	10	10	8	68
NO ⁺ BF ₄ ⁻ + H ₂ O	38	61	1	< 1	< 1
NO ⁺ PF ₆ ⁻ + H ₂ O	18	72	7	3	< 1
NO ⁺ SbF ₆ ⁻ + H ₂ O	15	37	36	12	< 1
BF ₃ + NO ⁺ BF ₄ ⁻	22	16	< 1	< 1	62
SbF ₅ + NO ⁺ SbF ₆ ⁻	< 1	< 1	< 1	< 1	100

2.6. Reactions of alkenes and alkynes with N₂F₄

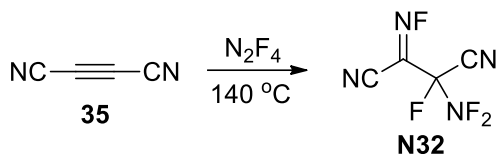
α-Functionalized R^F-nitriles are a large group of synthetically attractive building-blocks. (Difluoroamino)difluoroacetonitrile, compound **N30**, was synthesized in 80% yield through the reaction of 1,1-difluoroethylene (**33**) and tetrafluorohydrazine in the presence of KF (Scheme 22).⁵³

**Scheme 22.** Synthesis of (difluoroamino)difluoroacetonitrile (**N30**) from 1,1-difluoroethylene (**33**) and N₂F₄.

Similarly, F₂NCCIFCN **N31** was synthesized from 1-chloro-1-fluoroethylene (**34**) and N₂F₄ (Scheme 23).⁵⁴

**Scheme 23.** Synthesis of F₂NCCIFCN **N31**.

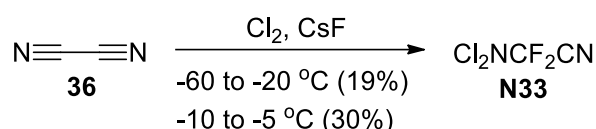
Treatment of dicyanoacetylene (**35**) with N₂F₄ at 140 °C gave functionalized α-fluorodinitrile **N32** (Scheme 24).⁵⁵



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

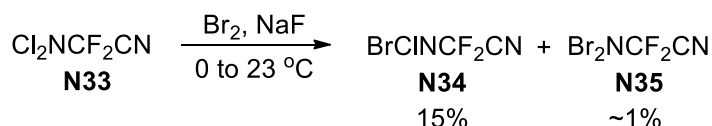
2.7. Halogenation of nitriles

Cesium fluoride promoted chlorination of cyanogen (**36**) with Cl_2 (1.2 equiv) at -60 to -20 $^{\circ}\text{C}$ gave $\text{Cl}_2\text{NCF}_2\text{CN}$ **N33** in 19% yield.⁵⁶ Harsher conditions (-10 to -5 $^{\circ}\text{C}$) 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, $\text{N}\equiv\text{C}-\text{C}(\text{F})=\text{N}^-$).⁵⁶



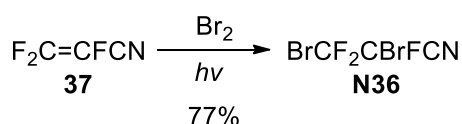
Scheme 25. Cesium fluoride promoted chlorination of cyanogen (**36**) with Cl_2 .

Reaction of $\text{Cl}_2\text{NCF}_2\text{CN}$ **N33** with Br_2 at 0 to 23 $^{\circ}\text{C}$ in the presence of NaF afforded difluoronitriles $\text{BrClNCF}_2\text{CN}$ **N34** (15%) and $\text{Br}_2\text{NCF}_2\text{CN}$ **N35** (~1%) (Scheme 26).⁵⁶



Scheme 26. Bromination of $\text{Cl}_2\text{NCF}_2\text{CN}$ **N33** in the presence of NaF.

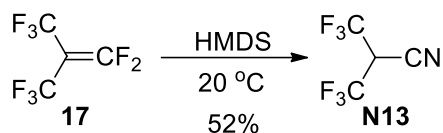
Bromination of perfluoroacrylonitrile (**37**) with Br_2 yielded 2,3-dibromo-2,3,3-trifluoropropanenitrile (**N36**) in 77% yield. Irradiation from an infrared lamp was required to start the reaction (Scheme 27).⁵⁷



Scheme 27. Bromination of perfluoroacrylonitrile with Br_2 .

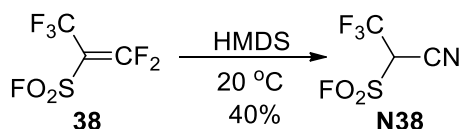
2.8. Reaction of fluoroalkenes with HMDS

2H-hexafluoroisobutyronitrile (**N13**) was obtained in 52% yield by the reaction of HMDS with a large excess of perfluoroisobutylene (**17**) at 20 $^{\circ}\text{C}$ (Scheme 28).⁵⁸



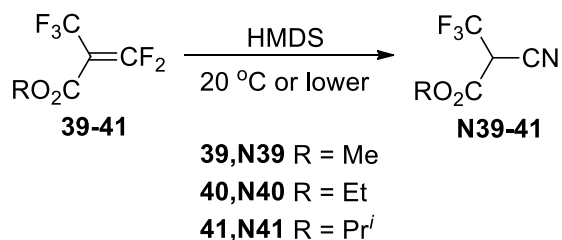
Scheme 28. Synthesis of 2*H*-hexafluoroisobutyronitrile (**N13**).

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**.

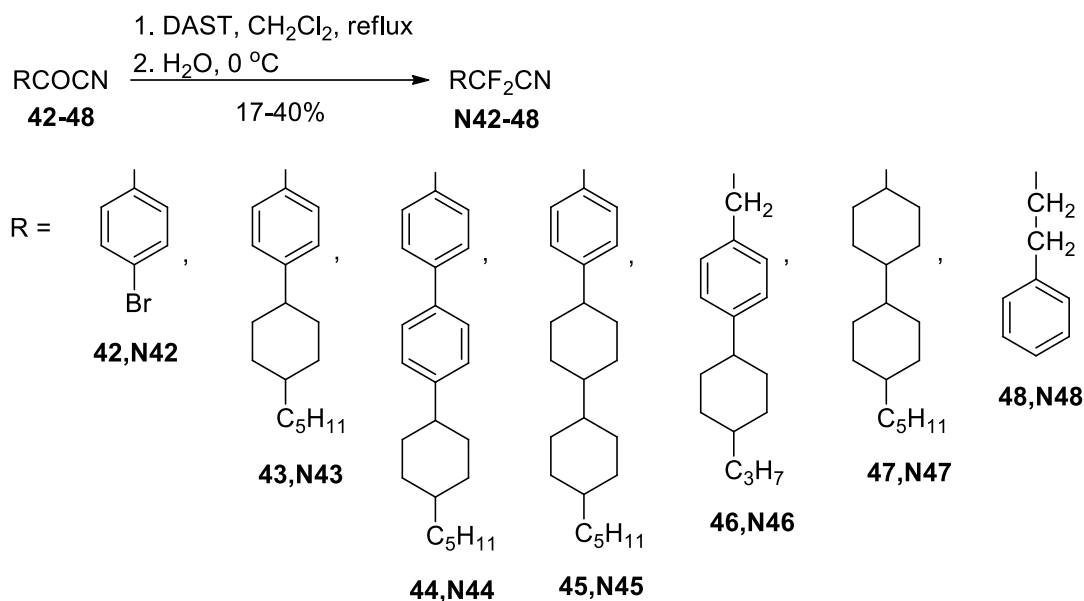
The same approach was used for the preparation of esters of 2-cyano-3,3,3-trifluoropropionic acid **N39-41**, which were synthesized in high yields from esters of perfluoromethacrylic acid **39-41** by reaction with HMDS (Scheme 30).⁵⁸



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

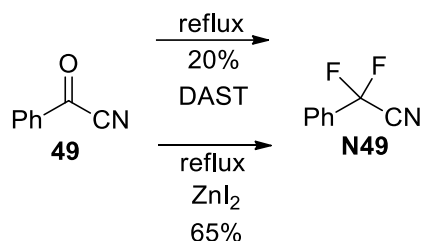
2.9. Reaction of acyl cyanides with DAST

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.

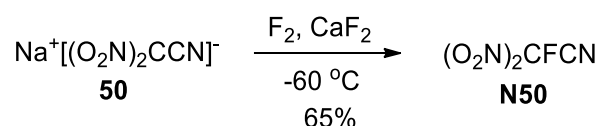
The reaction of benzoyl cyanide (**49**) with DAST gave 2-phenyl-2,2-difluoroacetonitrile (**N49**) in 20% yield. The same reaction conducted in the presence of ZnI_2 as a catalyst resulted in **N49** in 65% yield (Scheme 32).⁶⁰



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

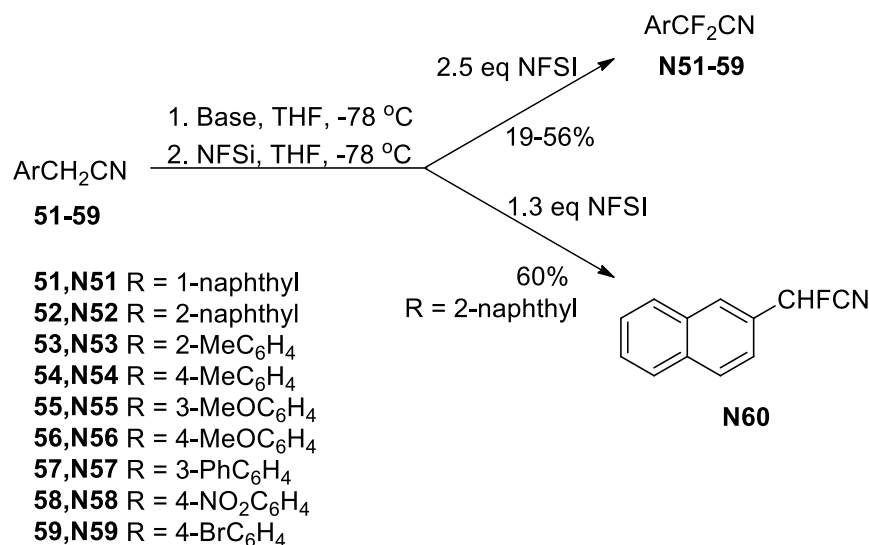
2.10. Fluorination of active methylene nitriles

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



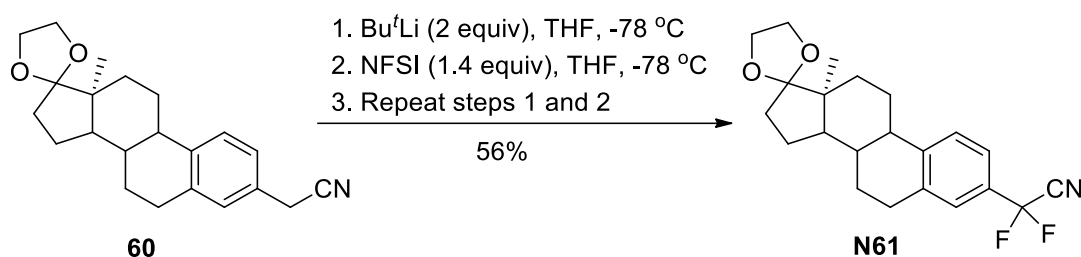
Scheme 33. Synthesis of fluorodinitroacetonitrile (**N50**).

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



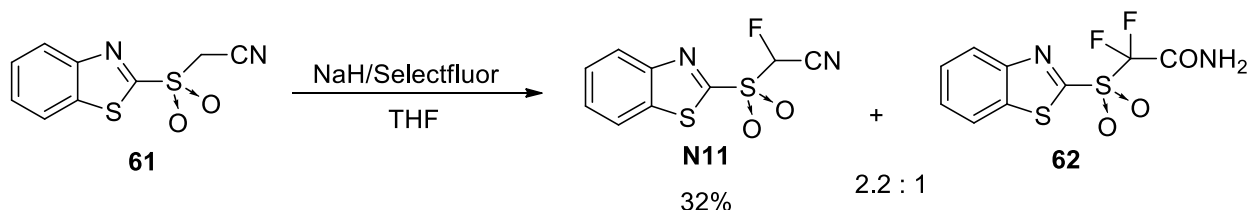
Scheme 34. Synthesis of α -fluorinated nitriles **N51-60**.

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



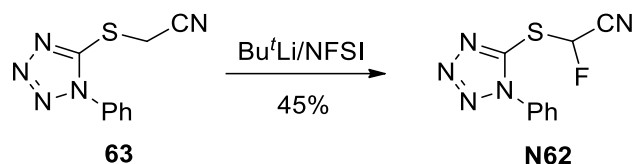
Scheme 35. Synthesis of α,α -difluoronitrile **N61**.

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 -difluoronitrile, after the reaction mixture was quenched with aqueous NH₄Cl.⁴⁶

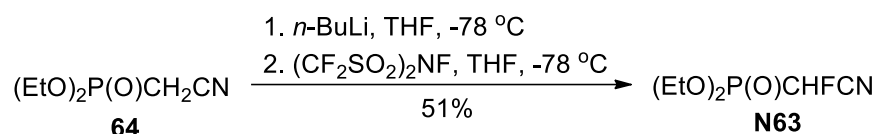


Scheme 36. Synthesis of α -monofluorinated nitrile **N11** from nitrile **61**.

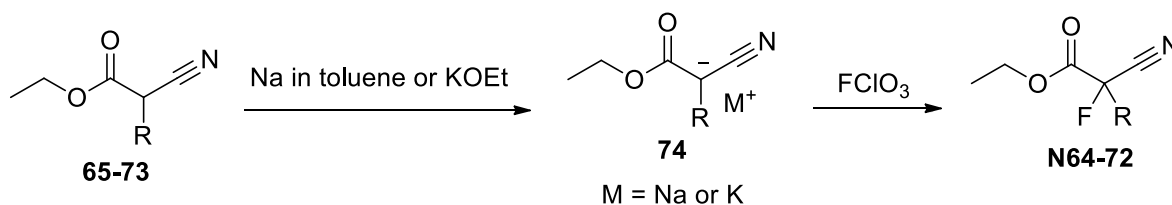
Monofluorinated nitrile **N62** was synthesized in 45% yield from nitrile **63** and Bu^tLi/NFSI (Scheme 37).⁴⁶

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

Fluorination of diethyl cyanomethanephosphonate (**64**) with $(\text{CF}_3\text{SO}_2)_2\text{NF}$ 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**.

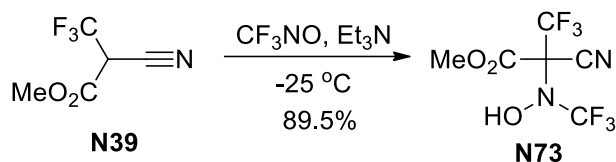
Fluorination of ethyl α -cyanoalkanoates **65-73** with perchloryl fluoride, FCIO_3 , gives ethyl α -cyano- α -fluoroalkanoates **N64-72** via intermediate salts **72**. The synthesized **N64-72** and their yields are shown in Table 3.⁶⁵

Table 3. Fluorination of alkylated ethyl α -fluorocyanoacetate derivatives **65-73** with FCIO_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 ₂ CH ₂	73	N72	71

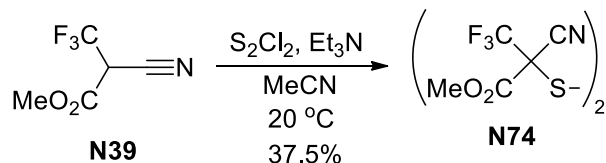
2.11. Reactions of active methylene CF_3 -nitriles with electrophiles

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



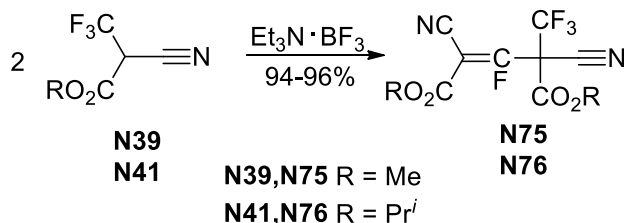
Scheme 39. Synthesis of α -trifluoromethylated hydroxylaminonitrile **N73**.

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



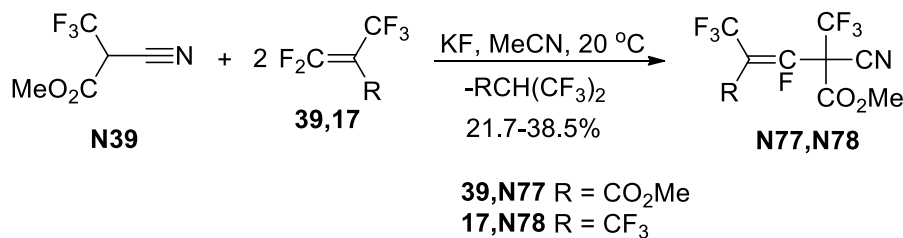
Scheme 40. Synthesis of bis-(α -carbomethoxy- α -cyanotrifluoroethyl)disulfide (**N74**).

R^{F} -nitriles **N39** and **N41**, in the presence of a mild dehydrofluorinating reagent $\text{Et}_3\text{N} \cdot \text{BF}_3$, at -10 °C quantitatively convert into CF_3 -dinitriles **N75** and **N76**, respectively (Scheme 41).⁵⁸



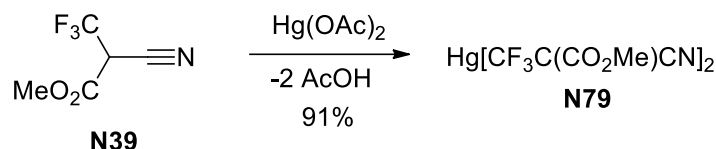
Scheme 41. Synthesis of CF_3 -dinitriles **N75** and **N76**.

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**.

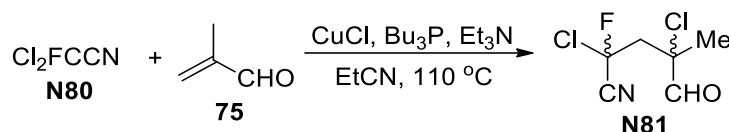
Mercurated CF_3 -nitrile **N79** (91%) was prepared from **N39** and mercuric acetate (Scheme 43).⁵⁸



Scheme 43. Synthesis of mercurated CF₃-nitrile **N79**.

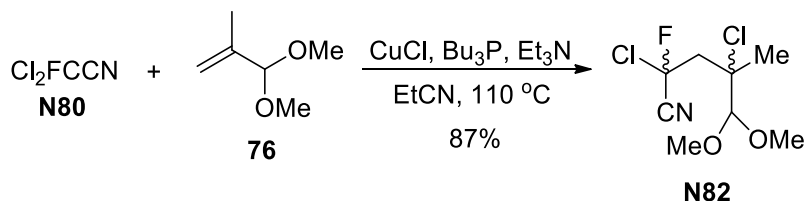
2.12. Addition of dichlorofluoroacetonitrile to alkenes

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**.

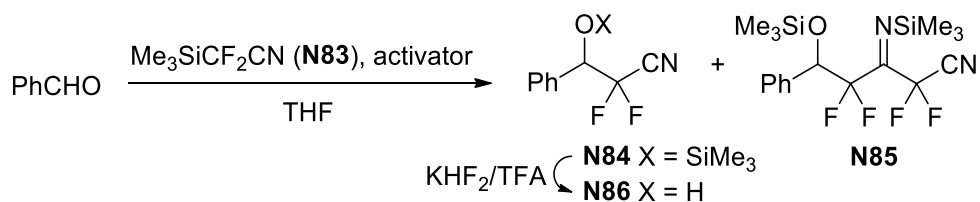
The addition of dichlorofluoroacetonitrile (**N80**) to methacrolein dimethyl acetal (**76**) resulted in a functionalized α-fluoronitrile, 2,4-dichloro-2-fluoro-4-methyl-5,5-dimethoxypentmenitrile (**N82**), which was obtained as a mixture of diastereomers in 87% yield (Scheme 45).³⁷



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

2.13. Fluoroalkylation of aldehydes, imines, and enamines

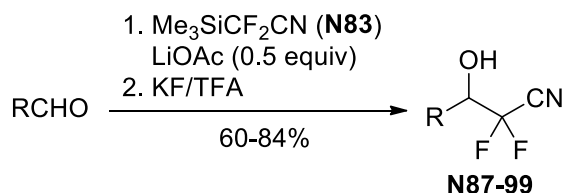
Fluoroalkylation of benzaldehyde with difluoro(trimethylsilyl)acetonitrile (**N83**) (its preparation is considered in paragraph 2.16, Scheme 51) in the presence of an activator gave difluoronitrile **N84** as the major product and some amounts of **N85** as the by-product, which is likely produced from the nucleophilic addition of **N83** to primary product **N84** (Table 4).⁶⁶ After desilylative workup with KHF₂/CF₃CO₂H 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 ₄ NOAc, 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

^aDMF as solvent. ^bIsolated 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

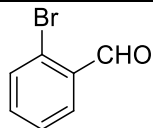
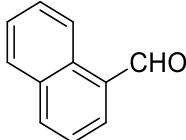
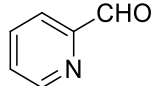
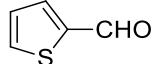
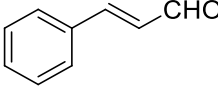
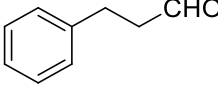
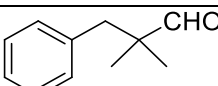
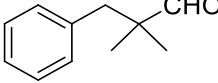

Table 5. Reaction of aldehydes with Me₃SiCF₂CN **N83**⁶⁶

Method A: **N83** (2.0 equiv), rt, 18 h

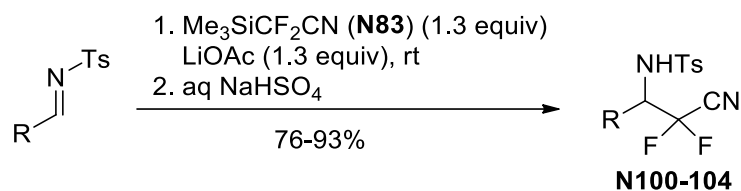
Method B: **N83** (1.05 equiv), 50 °C, 3 h

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

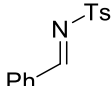
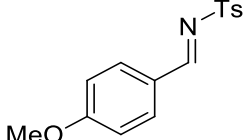
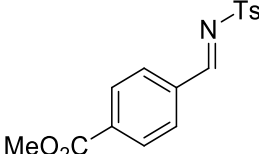
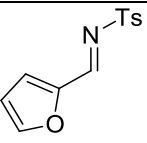
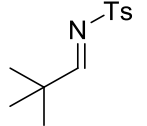
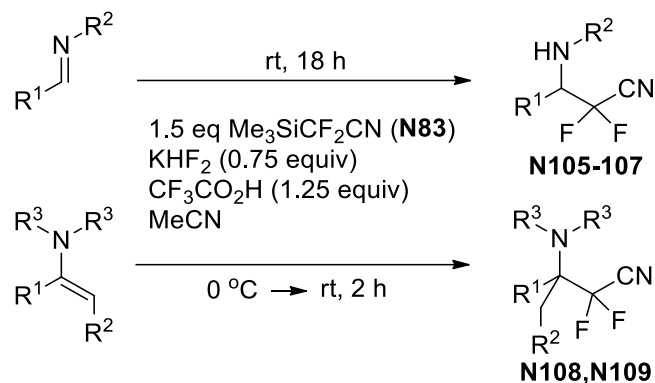
Entry	Imine	Time, h	Product	Yield of product, %
1		18	N100	93
2		48	N101	78
3		18	N102	91

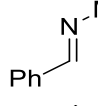
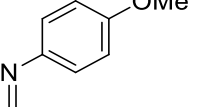
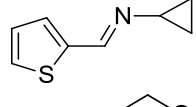
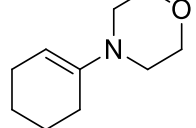
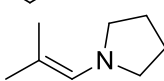
Table 6. Continued

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

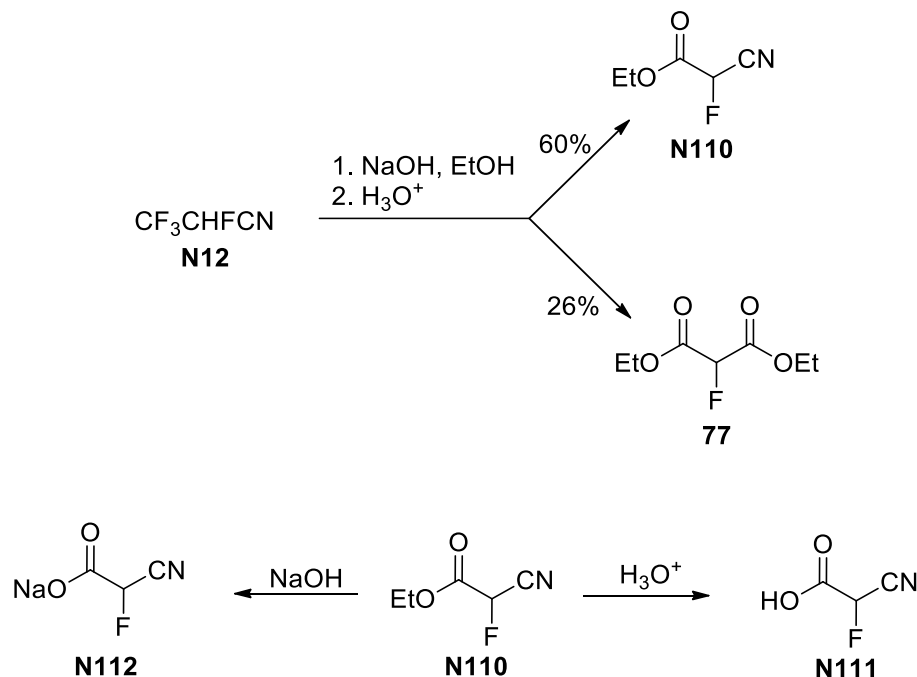
Table 7. Preparation of *N*-monosubstituted (**N105-107**) and *N,N*-disubstituted (**N108** and **N109**) α,α -difluorinated β -aminonitriles⁶⁶



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



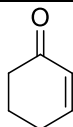
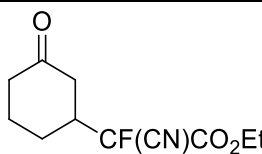
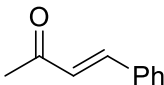
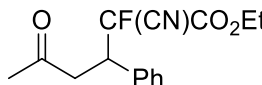
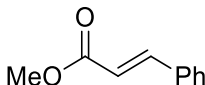
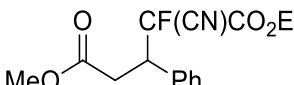
Scheme 46. Synthesis of ethyl α -fluorocyanoacetate (**N110**), and α -fluorocyanoacetic acid (**N111**).

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 reaction⁶⁷

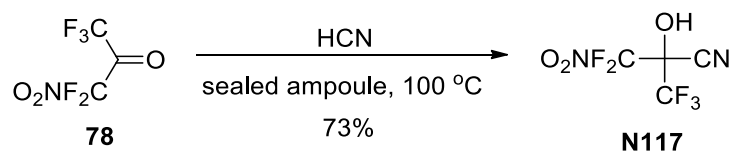
Entry	Michael acceptor	Reaction time	Product	^{19}F NMR yield
1		10 min	 N111	79
2		2 h	 N112	95
3		2 h	 N113	94

Table 8. Continued

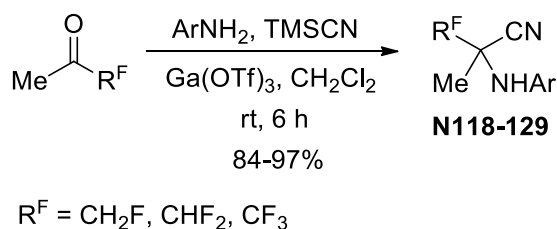
Entry	Michael acceptor	Reaction time	Product	19F NMR yield
4		10 min	 N114	99
5		10 min	 N115	93
6		15 h	 N116	92

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 -CF₃-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 -CF₃-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

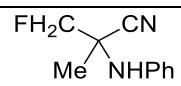
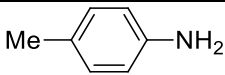
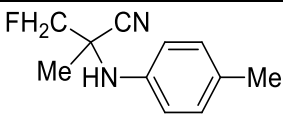
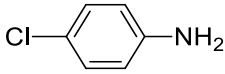
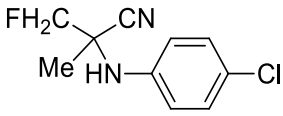
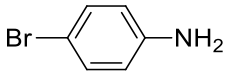
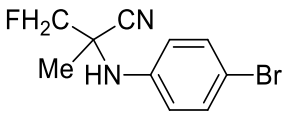
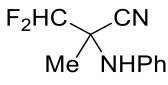
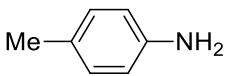
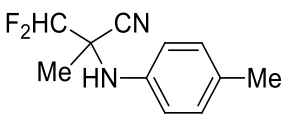
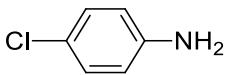
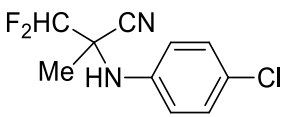
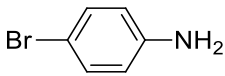
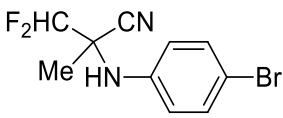
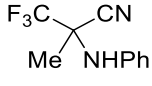
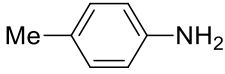
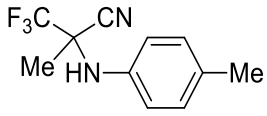
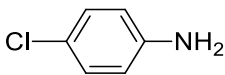
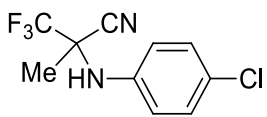
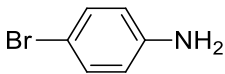
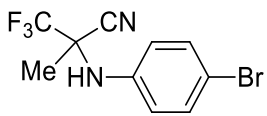
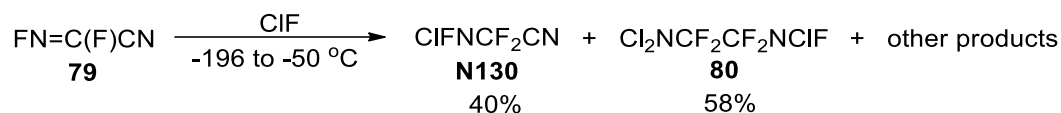
Entry	R^F	Amine	Product	Yield of product, %
1	CH ₂ F	PhNH ₂	 N118	97

Table 9. Continued

Entry	RF	Amine	Product	Yield of product, %
2	CH ₂ F		 N119	96
3	CH ₂ F		 N120	92
4	CH ₂ F		 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

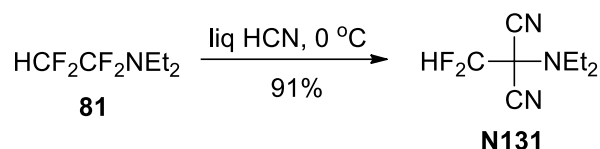
2.16. Other methods

Reaction of *N*-fluoro-1-cyano-1-fluoromethanimine (**79**) with ClF resulted in the formation of difluoroacetonitrile derivative, nitrile ClFNCF₂CN **N130** (40%), together with Cl₂NCF₂CF₂NCIF **80** (58%) and other products (Scheme 48).⁷⁰



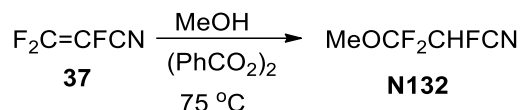
Scheme 48. Synthesis of ClFNCF₂CN **N130**.

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



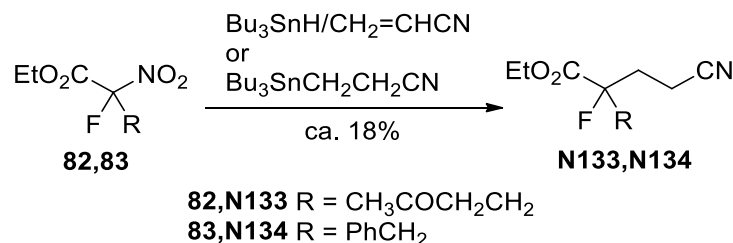
Scheme 49. Synthesis of 2-(diethylamino)-2-(difluoromethyl)malononitrile (**N131**).

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



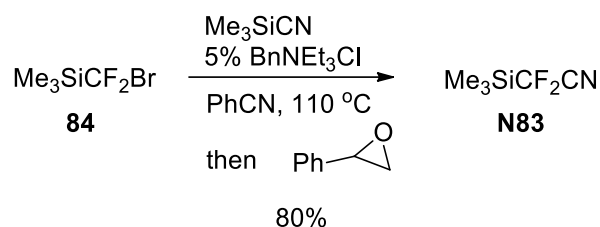
Scheme 50. Synthesis of 2,3,3-trifluoro-3-methoxypropanenitrile (**N132**).

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 Bu₃SnH/CH₂=CHCN gave γ -fluoronitriles **N133** and **N134**, respectively, in ca. 18% yield.⁷² Alternatively, Bu₃SnCH₂CH₂CN can be used as the source of the CH₂CH₂CN group.⁷² Similarly, α -bromo- α -fluoroesters can also be utilized in the synthesis of γ -fluoronitriles (Scheme 51).⁷²



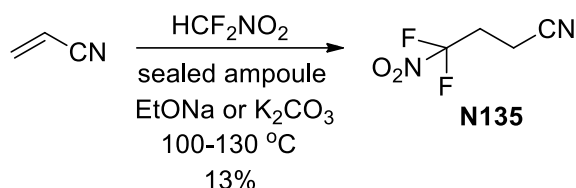
Scheme 51. Synthesis of γ -fluoronitriles **N133** and **N134**.

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}



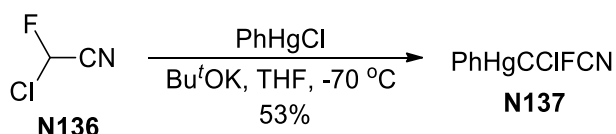
Scheme 52. Synthesis of α -silylated α -fluoronitrile **N83**.

Acrylonitrile was used as the Michael acceptor in the reaction with difluoronitromethane (100-130 $^\circ\text{C}$, sealed ampoule, EtONa or K_2CO_3 as a base), and 4,4-difluoro-4-nitrobutyronitrile (**N135**) was obtained as the desired R^{F} -nitrile in 13% yield (Scheme 53).⁷⁴



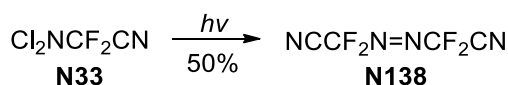
Scheme 53. Synthesis of 4,4-difluoro-4-nitrobutyronitrile (**N135**).

Phenylmercurated chloro(fluoro)acetonitrile **N137** was prepared in 53% yield through the reaction of chlorofluoroacetonitrile (**N136**) and Bu^tOK with PhHgCl in THF at $-70 ^\circ\text{C}$ (Scheme 54).⁷⁵



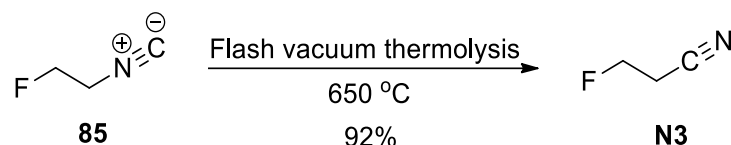
Scheme 54. Synthesis of phenylmercurated chloro(fluoro)acetonitrile **N137**.

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



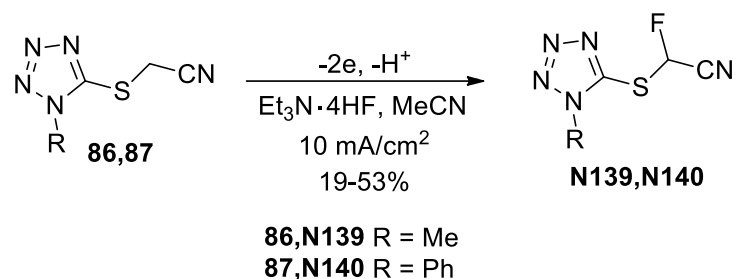
Scheme 55. Photolysis of nitrile **N33**.

3-Fluoropropionitrile (**N3**) was prepared on a half-gram scale in a 92% yield by flash vacuum thermolysis of the 2-fluoroethylisocyanide (**85**) at $650 ^\circ\text{C}$. The product was collected in pure form in a U-trap equipped with stopcocks and immersed in a $-90 ^\circ\text{C}$ 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 Et₃N·4HF resulted in monofluorinated nitriles **N139** and **N140**, respectively, in 19-53% yield (Scheme 57).⁷⁷

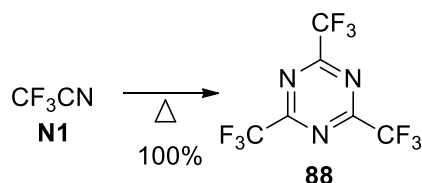


Scheme 57. Anodic monofluorination of nitriles **86** and **87**.

3. Chemical properties of fluoroalkyl cyanides

3.1. Trimerization

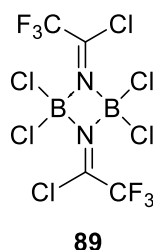
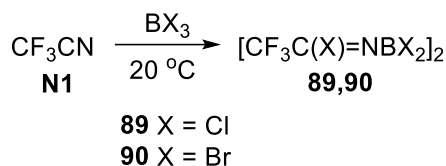
Heating trifluoroacetonitrile (**N1**) in the presence of other compounds often leads to trimerization and the formation of 2,4,6-tris(trifluoromethyl)-1,3,5-triazine (**88**).^{78,79} Therefore, heating CF₃CN in the presence of reagents less reactive towards CF₃CN can cause the formation of some amounts of **88**. Thus, CF₃CN doesn't react with tetrafluorohydrazine, N₂F₄, 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(CF₂)₂CN gives some amounts of the corresponding HCF₂CF₂-triazine as a by-product (see paragraph 3.3.3, Scheme 102).⁷⁹



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

3.2. Reactions with electrophiles

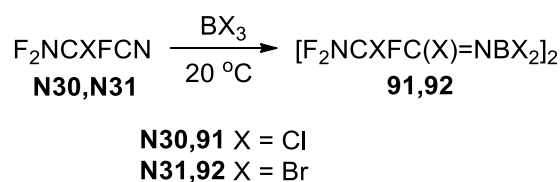
3.2.1 Reactions with boron(III) and titanium(III) Lewis acids. CF₃CN is a weaker donor than MeCN, and in contrast to the last, it forms no stable coordination compound with SnCl₄ or TiCl₄, and with the boron trihalides the insertion reaction occurs, giving dimeric ethylideneaminoboranes **89** and **90** (Scheme 59).⁸⁰



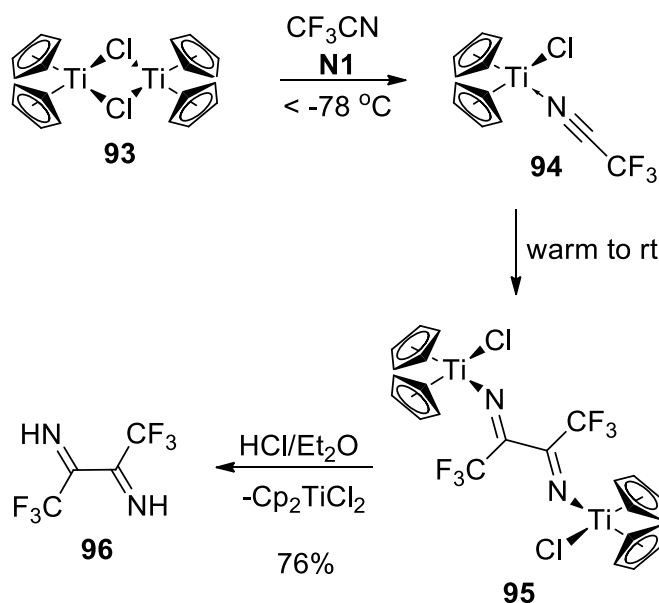
Scheme 59. Formation of dimeric ethyldeneaminoboranes **89** and **90**.

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

The reaction of F₂NCClFCN **N30** and F₂NCBrFCN **N31** with BCl₃ and BBr₃ also leads to the formation of the corresponding dimeric products **91** and **92** (Scheme 60).⁵⁴



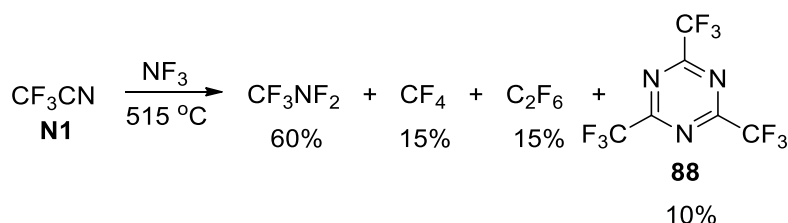
Scheme 60. Formation of dimeric products **91** and **92** from F₂NCClFCN **N30** and F₂NCBrFCN **N31**.



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/Et₂O liberated the free diimine, 1,1,1,4,4,4-hexafluoro-2,3-butanediimine (**96**) in 76% yield (Scheme 61).⁸³

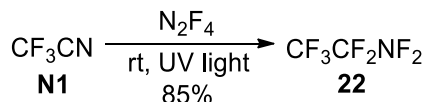
3.2.2 Reactions with NF₃ and N₂F₄. Reaction of trifluoroacetonitrile (**N1**) with NF₃ at 515 °C gave a mixture of CF₃NF₂ (60%), CF₄ (15%), C₂F₆ (15%), and triazine **88** (10%). The reaction doesn't proceed at 480 °C or lower temperatures (Scheme 62).⁷⁸



Scheme 62. Reaction of trifluoroacetonitrile (**N1**) with NF₃ 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 F₃C·, NC·, F·, F₂N·, 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 CF₃CN with N₂F₄ at room temperature under UV light produces for 48 hours C₂F₅NF₂ **22** in 85% yield (Scheme 63).⁷⁸

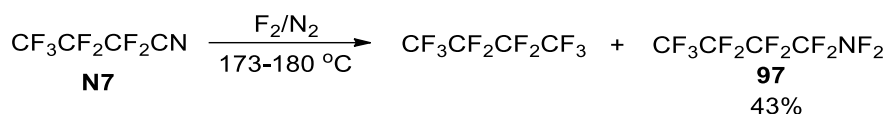


Scheme 63. Synthesis of *N,N*-difluoro(perfluoroethyl)amine **22** from CF₃CN **N1** and N₂F₄.

3.2.3 Reactions with halogens. The first direct fluorination of R^F-nitriles was published in 1959.⁸⁴ Fluorination of CF₃CN and C₂F₅CN with F₂ diluted with helium resulted in the formation of a mixture of products. The fluorination of CF₃CN at 275 °C yielded a mixture of CF₄, C₂F₆, CF₃CF₂NF₂, and, probably, CF₂=NF. The fluorination of CF₃CN under milder conditions (30-47 °C) gave C₂F₆, F₅C₂N=NC₂F₅, and unreacted CF₃CN. The fluorination of C₂F₅CN at 275 °C yielded a mixture of CF₄, C₂F₆, C₃F₈, and CF₃CF₂CF₂NF₂. The fluorination of C₂F₅CN under milder conditions (54-65 °C) gave F₇C₃N=NC₃F₇ and unreacted C₂F₅CN.⁸⁴

Direct fluorination of trifluoroacetonitrile with F₂/N₂ at 140 °C gave a mixture of CF₄, C₂F₆, C₂F₅NF₂, CF₃CF=NF, CF₃N=NC₂F₅, and C₂F₅N=NC₂F₅. The CF₃CF=NF was obtained pure by analytical chromatography.⁸⁵ Direct fluorination of CClF₂CN with F₂/N₂ at 140 °C yielded a crude product, which was rectified, and thus pure samples of CClF₂CF₂NF₂, CClF₂CF₂N=NCF₃, and CClF₂CF=NF were obtained.⁸⁵ The fluorination of CClF₂CN at 175 °C yielded a product, which contained CF₄, NF₃, CClF₃, C₂F₅Cl, and trace amounts of CF₃N=NCF₃, and CClF₂CF₂NF₂.⁸⁵

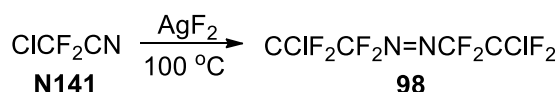
Direct fluorination of perfluorobutyronitrile (**N7**) with F_2/N_2 at 173-180 °C gave a mixture of perfluorobutane and *N,N*-difluoro(perfluorobutyl)amine (**97**) (43%) (Scheme 64).⁴⁰



Scheme 64. Direct fluorination of $\text{CF}_3\text{CF}_2\text{CF}_2\text{CN}$ **N7**.

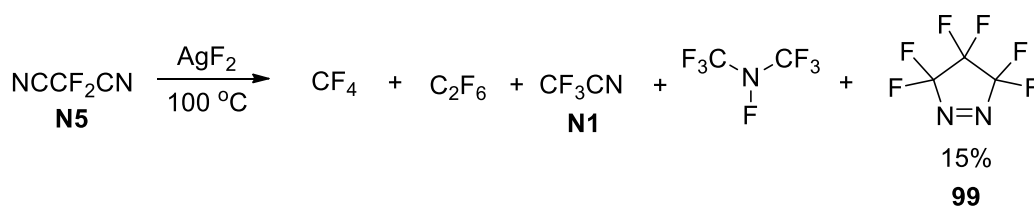
Direct fluorination of difluoromalononitrile, tetrafluoroscuccinonitrile, and hexafluoroglutaronitrile with F_2/N_2 gives complex mixtures of fluorinated products. By the fluorination of tetrafluoroscuccinonitrile, perfluoropyrrolidine was found as one of the products.⁴⁰

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



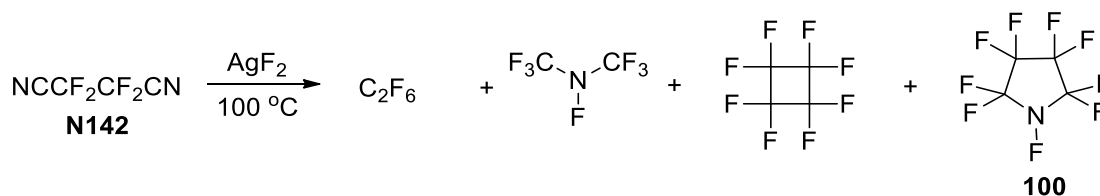
Scheme 65. Fluorination of ClCF_2CN **N141** with AgF_2 .

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 , $(\text{CF}_3)_2\text{NF}$, and hexafluoro-1-pyrazoline (**99**) (15%) (Scheme 66).⁸⁶



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

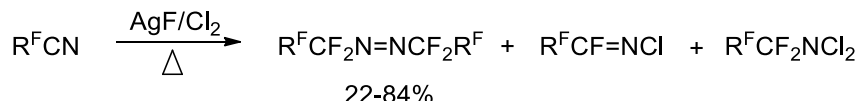
The fluorination of tetrafluorosuccinonitrile (**N142**) with AgF_2 at 100 °C gave a mixture of products such as C_2F_6 , $(\text{CF}_3)_2\text{NF}$, perfluorocyclobutane, and perfluoropyrrolidine (**100**) (Scheme 67).⁸⁶



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 $(\text{CF}_3)_2\text{NF}$ as major components, and some $(\text{CF}_3)_2\text{NH}$.⁸⁶

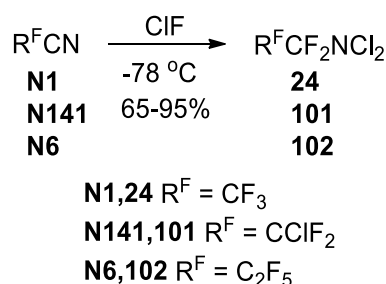
Treatment of $\text{R}^{\text{F}}\text{-nitriles}$ with AgF and Cl_2 gave the corresponding polyfluoroazoalkanes (22-84%), however, other products frequently formed such as *N*-chlorofluoroalkylidenimines and *N,N*-dichlorofluoroalkylamines (Scheme 68).⁸⁷



Scheme 68. Chlorination of $\text{R}^{\text{F}}\text{-nitriles}$ with Cl_2 in the presence AgF .

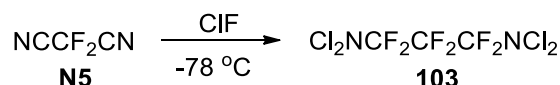
Photolytically induced reaction of CF_3CN with Cl_2 produced $\text{CF}_3\text{CCl}=\text{NCl}$, $\text{CF}_3\text{CCl}=\text{N}=\text{N}=\text{CClCF}_3$, and CF_3CCl_3 as well as minor quantities of $\text{CF}_3\text{C}(\text{Cl})=\text{N}-\text{CCl}_2\text{CF}_3$, $\text{CF}_3\text{CCl}_2\text{C}(\text{CF}_3)=\text{N}=\text{N}=\text{C}(\text{Cl})\text{CF}_3$, $\text{CF}_3\text{CCl}_2-\text{N}=\text{N}-\text{CCl}_2\text{CF}_3$, $\text{CF}_3\text{CCl}_2\text{C}(\text{CF}_3)=\text{N}-\text{CCl}_2\text{CF}_3$, and $\text{CF}_3\text{CCl}_2\text{C}(\text{CF}_3)=\text{N}=\text{N}=\text{C}(\text{CF}_3)\text{CCl}_2\text{CF}_3$.⁸⁸

Reaction of $\text{R}^{\text{F}}\text{CN}$ with ClF at -78 °C resulted in the formation of fluorinated aliphatic dichloramines $\text{R}^{\text{F}}\text{CF}_2\text{NCl}_2$ in 65-95% yield (Scheme 69).⁸⁹



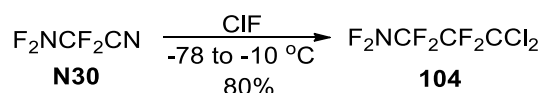
Scheme 69. Reaction of $\text{R}^{\text{F}}\text{CN}$ with ClF .

Similarly, fluorinated tetrachlorodiamine $\text{Cl}_2\text{NCF}_2\text{CF}_2\text{CF}_2\text{NCl}_2$ **103** was synthesized from difluoromalononitrile (**N5**) and ClF (Scheme 70).⁸⁹



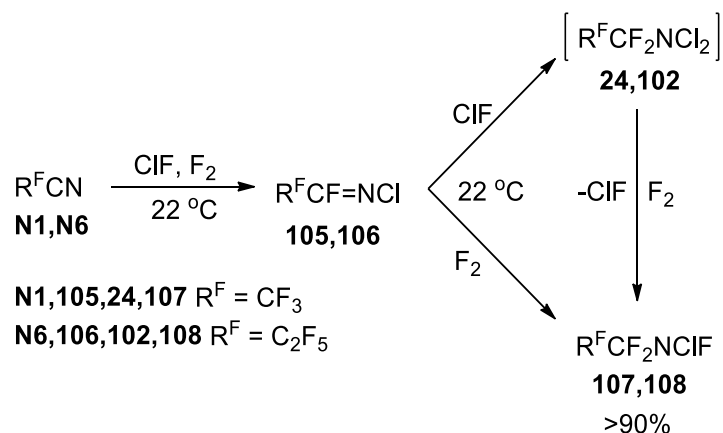
Scheme 70. Reaction of difluoromalononitrile (**N5**) with ClF .

The reaction of $\text{F}_2\text{NCF}_2\text{CN}$ **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



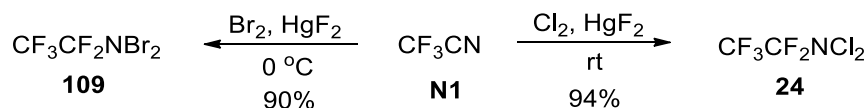
Scheme 71. Reaction of $\text{F}_2\text{NCF}_2\text{CN}$ **N30** with ClF .

Treatment of R^F -nitriles with ClF/F_2 produced *N*-chloro-*N*-fluorofluoroalkylamines R^FCF_2NCIF **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_2NCIF **107** and **108**.

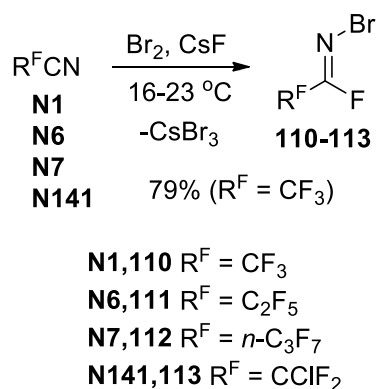
Chlorination and bromination of trifluoroacetonitrile (**N1**) in the presence of HgF_2 gave $C_2F_5NCl_2$ **24** (94%) and $C_2F_5NBr_2$ **109** (90%), respectively (Scheme 73).^{92,93}



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

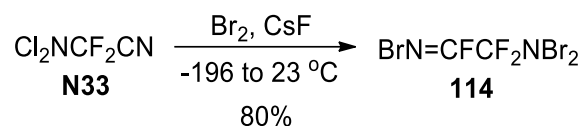
Bromination of CF_3CN at 22 °C in the presence of CsF can produce in different proportions, dependently on the amount of Br_2 , $CF_3CF=NBr$ and $F_5C_2N=NC_2F_5$.⁹⁴

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



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

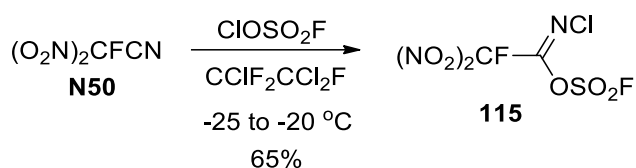
Cesium fluoride-promoted bromination of α,α -difluoronitrile $\text{Cl}_2\text{NCF}_2\text{CN}$ **N33** with excess Br_2 (1.5:10 mol. ratio) at -196 to 23 °C yielded *N*-brominated imidoyl fluoride **114**, $\text{BrN}=\text{CFCF}_2\text{NBr}_2$, in 80% yield (Scheme 75).⁵⁶



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: $(\text{BrN}=\text{CF})_2$, $(\text{CIN}=\text{CF})_2$, $\text{CIN}=\text{CFCF}_2\text{NCl}_2$, $\text{CIN}=\text{CFCF}=\text{NBr}$, $\text{BrN}=\text{CFCF}_2\text{NCl}_2$, $\text{BrN}=\text{CFCF}_2\text{NBrCl}$, $\text{CIN}=\text{CFCF}_2\text{NBrCl}$, and $\text{CIN}=\text{CFCF}_2\text{NBr}_2$.⁵⁶

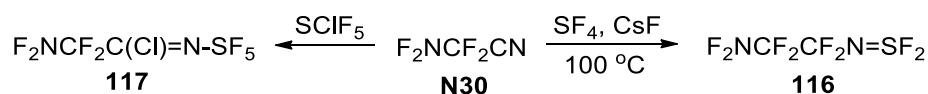
3.2.4 Reactions with chlorine fluorosulfate (ClOSO_2F), SF_4 and SClF_5 . Reaction of fluorodinitroacetonitrile (**N50**) with chlorine fluorosulfate in 1,1,2-trichlorotrifluoroethane (the solvent) at -25 to -20 °C resulted in *N*-chloroiminoflorodinitroacetyl fluorosulfate (**115**) (65%) (Scheme 76).⁹⁷



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

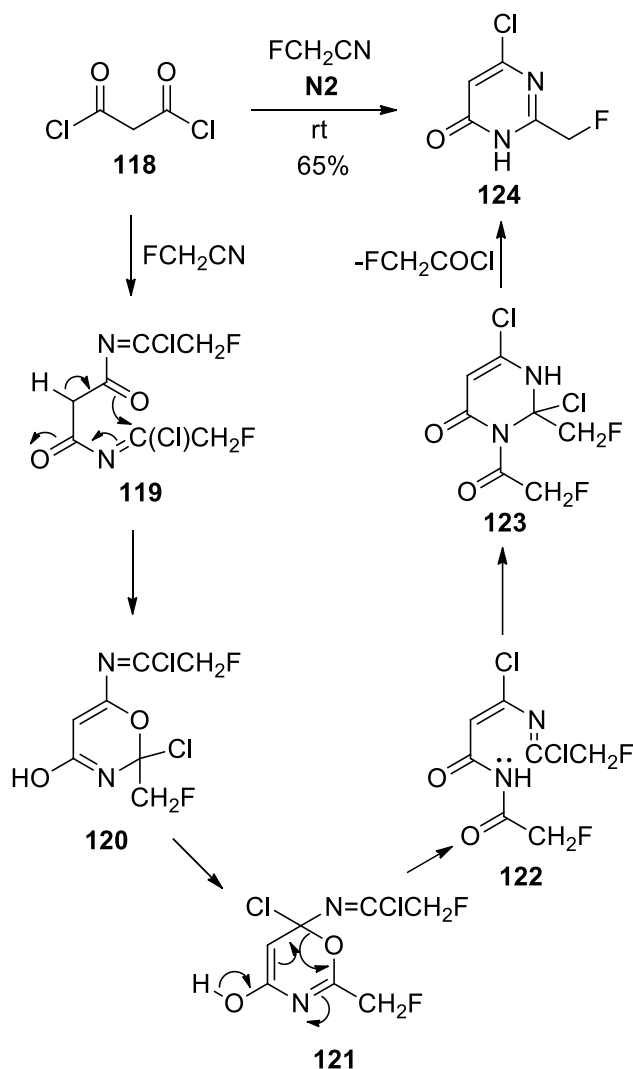
Similarly, other R^{F} -*N*-chloroiminofluorosulfates were synthesized from CF_3CN , $\text{CF}_3\text{OCF}_2\text{CN}$, $\text{CF}_3(\text{CF}_2)_2\text{CN}$, $\text{CF}_3(\text{CF}_2)_3\text{CN}$, and $\text{O}_2\text{NCF}_2\text{CN}$.⁹⁸

Reactions of $\text{F}_2\text{NCF}_2\text{CN}$ **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 $\text{F}_2\text{NCF}_2\text{CN}$ **N30** with SF_4/CsF and SF_5Cl .

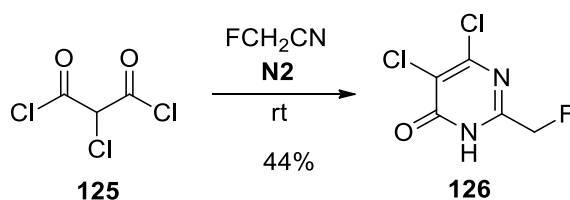
3.2.5 Reactions with C-electrophiles. The reaction of fluoroacetonitrile (**N2**) with malonyl chloride gave 4-chloro-2-fluoromethyl-6-pyrimidone (**124**) in 65% yield. The suggested plausible mechanism involves the formation of diimidoyl chloride **119** and the subsequent cyclic transformations with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



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

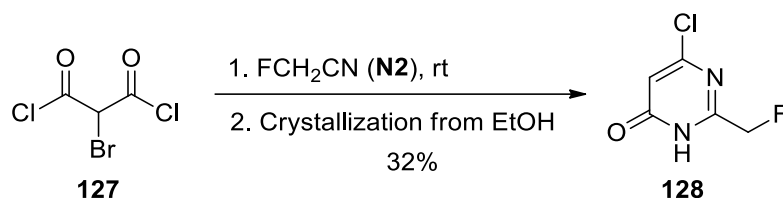
No solid product was isolated when a mixture of cyanoacetyl chloride and **N2** was kept at room temperature for several days.⁹⁹

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



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

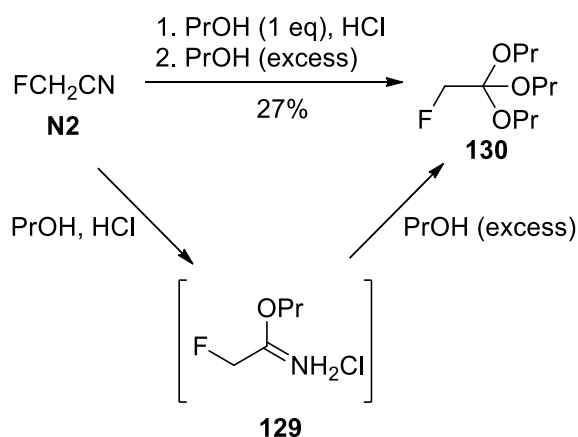
The reaction of **N2** with bromomalonyl chloride (**127**) gave a solid, which was crystallized from EtOH. The crystallized product was 4-chloro-2-fluoromethyl-6-pyrimidinone (**128**) (32%) (Scheme 80).⁹⁹ Most likely, EtOH in this case plays the role of a reducing agent (debromination).



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

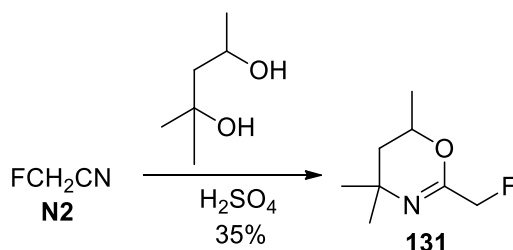
3.3. Reactions with nucleophiles

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.

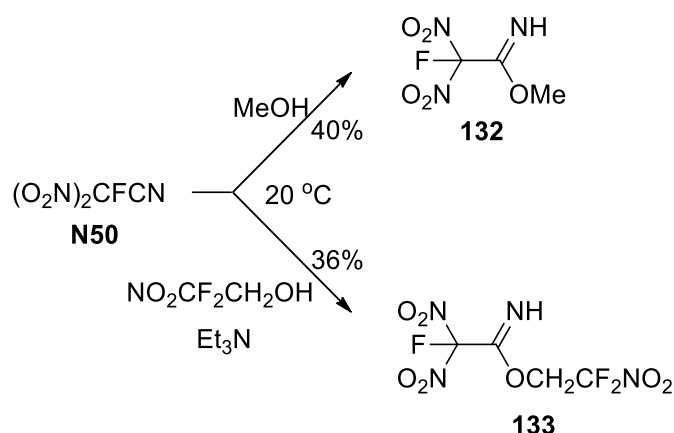
Cyclic iminoester **131** was synthesized in 35% yield from **N2** and 2-methyl-1,3-pentanediol in H_2SO_4 at -5 to 0°C (Scheme 82).¹⁰¹ Oxazine **131** can be α -metalated rapidly at -78°C by *n*-butyllithium, *tert*-butyllithium, or *n*-butyllithium/HMPA, and, moreover, **131** and its α -alkylated 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**).

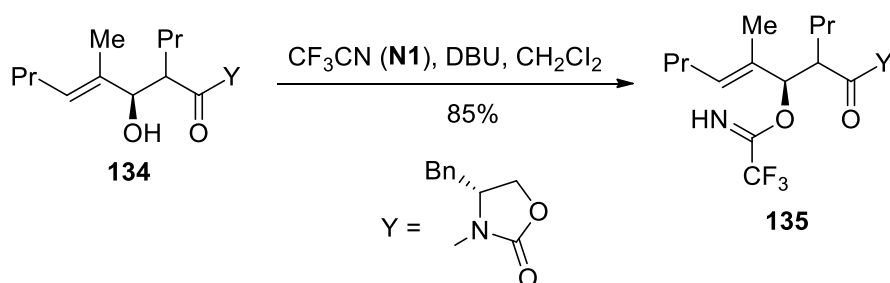
The reaction of fluorodinitroacetonitrile (**N50**) with MeOH proceeds at 20°C without any catalyst, whereas the corresponding reaction with less reactive 2,2-difluoro-2-nitroethanol was carried out in the

presence of Et₃N as a catalyst. In both cases, the corresponding imino esters **132** and **133** were isolated in 40% and 36% yield, respectively (Scheme 83).¹⁰²



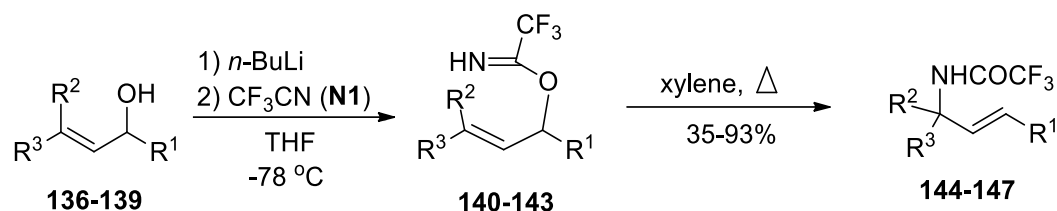
Scheme 83. Reaction of fluorodinitroacetonitrile (**N50**) with MeOH and 2,2-difluoro-2-nitroethanol.

The reaction of highly functionalized alcohol **134** with CF₃CN 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 $\text{R}^1 = \text{R}^2 = \text{H}$, $\text{R}^3 = \text{Ph}$

137,141,145 $\text{R}^1 = \text{H}$, $\text{R}^2 = \text{Me}$, $\text{R}^3 = (\text{CH}_2)_2\text{CHC}(\text{CH}_3)_2$

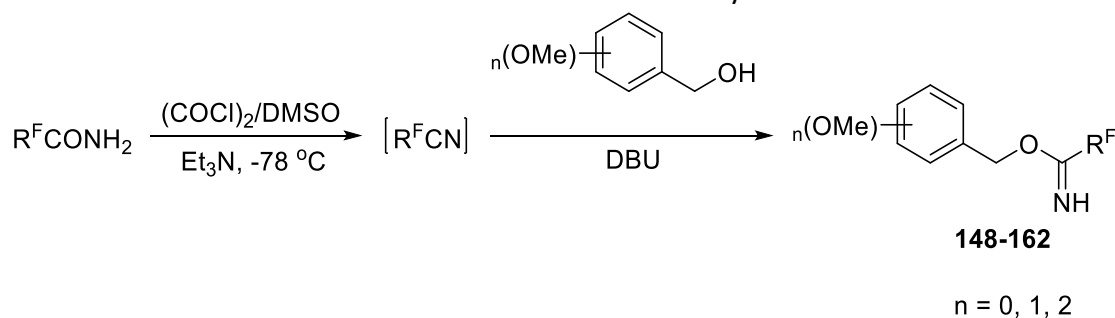
138,142,146 $\text{R}^1 = \text{R}^2 = \text{H}$, $\text{R}^3 = \text{CHCHMe}$

139,143,147 $\text{R}^1 = \text{Me}$, $\text{R}^2 = \text{H}$, $\text{R}^3 = \text{C}_3\text{H}_5\text{O}_2$

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

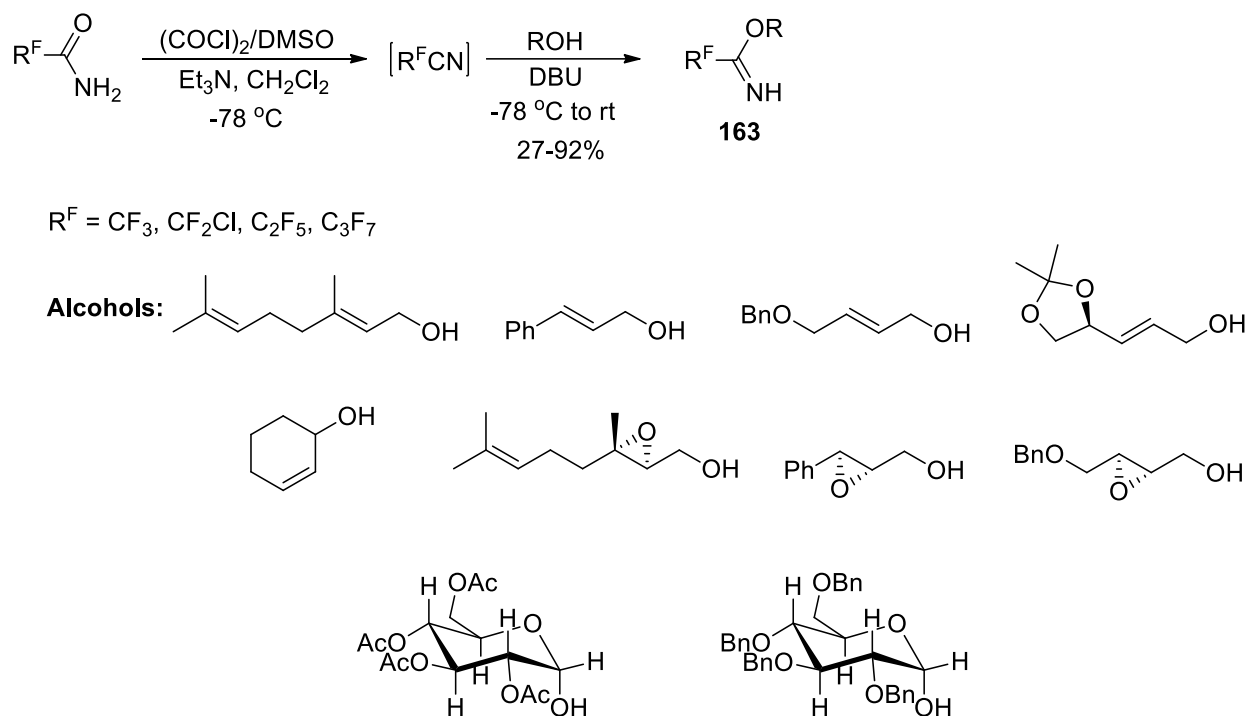
Table 10. Synthesis of R^{F} -imidates **148-162** from R^{F} -nitriles and benzyl alcohols¹⁰⁵



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

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

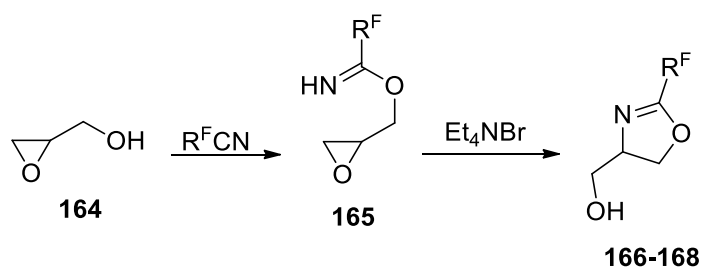
Similarly, treatment of R^F -nitriles with $(\text{COCl})_2/\text{DMSO}$ in the presence of Et_3N at -78°C , and the subsequent treatment of the reaction mixtures with an alcohol in the presence of DBU resulted in the formation of various perfluoroimidates **163** in 27-92% yield (Scheme 86).¹⁰⁶



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). $\text{BF}_3 \cdot \text{Et}_2\text{O}$ can also be used as a catalyst to synthesize R^F -isoxazolines.¹⁰⁷

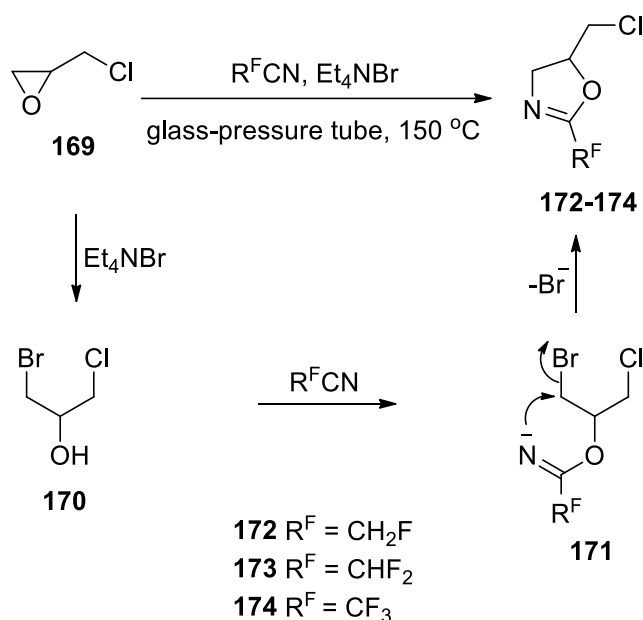
Table 11. 2- R^F -4-(hydroxymethyl)oxazolines **166-168**¹⁰⁷



Entry	R^F	Reaction temperature, $^\circ\text{C}$	Product	Yield of product, %
1	CH_2F	70	166	93
2	CHF_2	150	167	56
3	CF_3	150	168	46

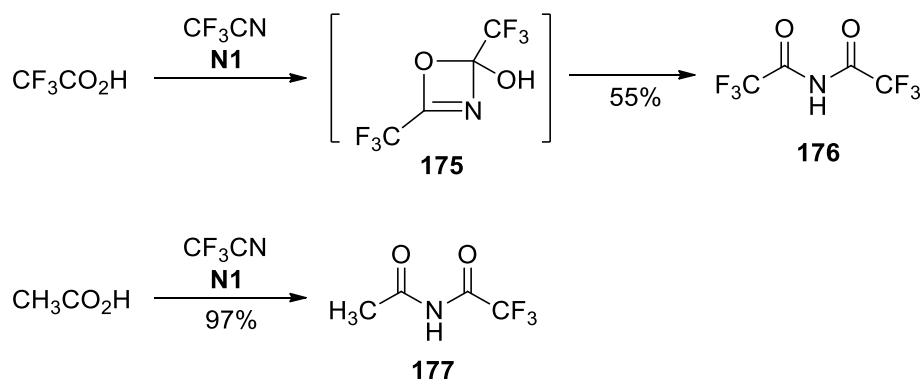
The above R^F -isoxazolines **166-168** can be used in the synthesis of fluorine-containing analogues of 2-methyl-5-dimethylaminomethyl-2-oxazoline methiodide, which is the 2-oxazoline analogue of Fourbeau's dioxolane that equals acetylcholine in potency and belongs to the highly active cholinomimetics.¹⁰⁸

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^F CN and subsequent cyclization of anion **171** to give **172-174** (Scheme 87).¹⁰⁹



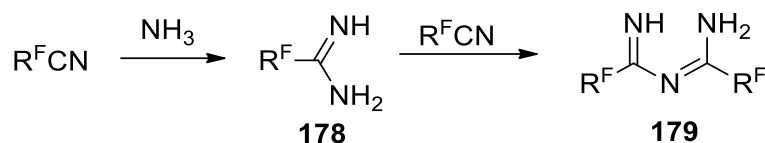
Scheme 87. Reaction of 1-chloro-2,3-epoxypropane (**169**) with R^F -nitriles.

The reaction of trifluoroacetonitrile (**N1**) with carboxylic acids was reported in 1963.¹¹⁰ Analytically pure imides: trifluoroacetyltrifluoroacetimide, $(\text{CF}_3\text{CO})_2\text{NH}$ (**176**) and acetyltrifluoroacetimide, $\text{CH}_3\text{CONHCOCF}_3$ (**177**), were synthesized from trifluoroacetonitrile (**N1**) and the corresponding carboxylic acids. The authors believe that the reaction of $\text{CF}_3\text{CO}_2\text{H}$ 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 $\text{CF}_3\text{CO}_2\text{H}$ and MeCN (Scheme 88).¹¹¹



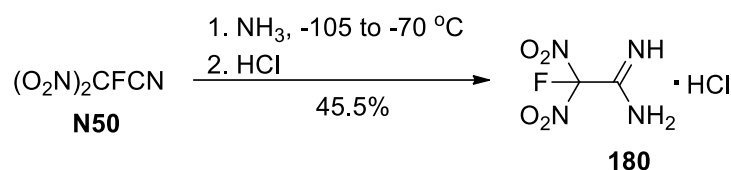
Scheme 88. Reaction of CF_3CN with $\text{CF}_3\text{CO}_2\text{H}$ and AcOH.

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^F CN in the reaction mixture to give products **179** (Scheme 89).¹¹²



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

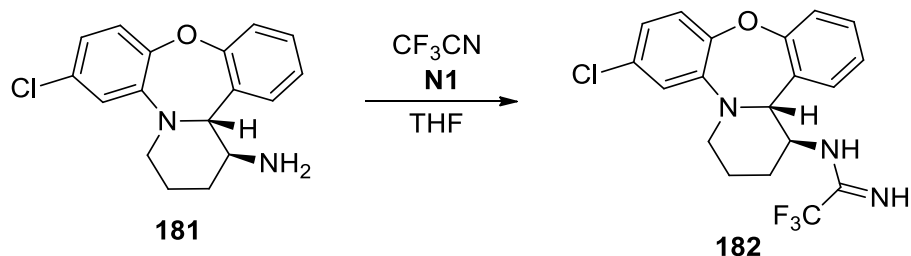
The reaction of fluorodinitroacetoneitrile (**N50**) with NH_3 , and subsequent treatment of the reaction mixture with HCl gave the corresponding amidine hydrochloride **180** in 45.5% yield (Scheme 90).¹⁰²



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

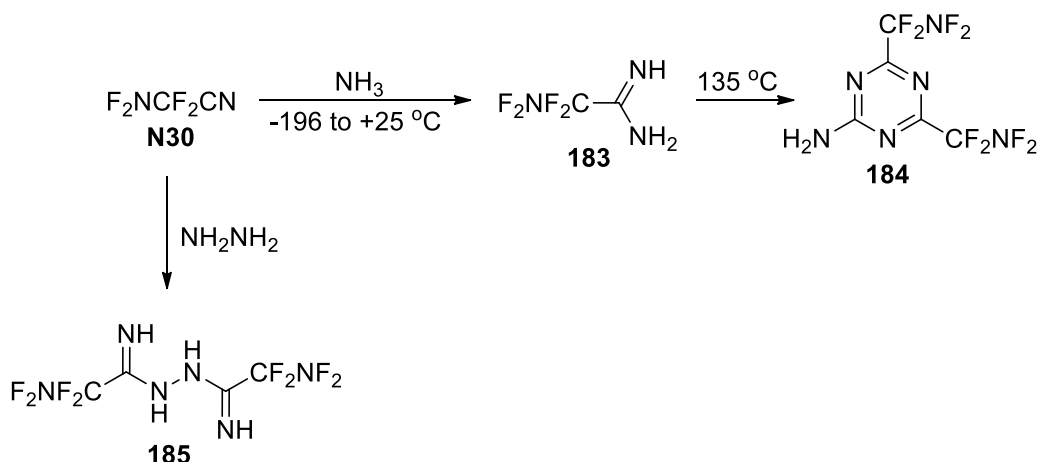
Similarly, difluoronitroacetamidine, $O_2NCF_2C(NH_2)=NH$ (63%) was synthesized from O_2NCF_2CN and ammonia.¹¹³

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



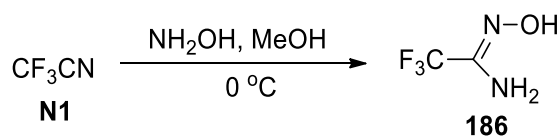
Scheme 91. Preparation of amidine **182**.

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 imidohydrazone **185** (Scheme 92).¹¹⁵



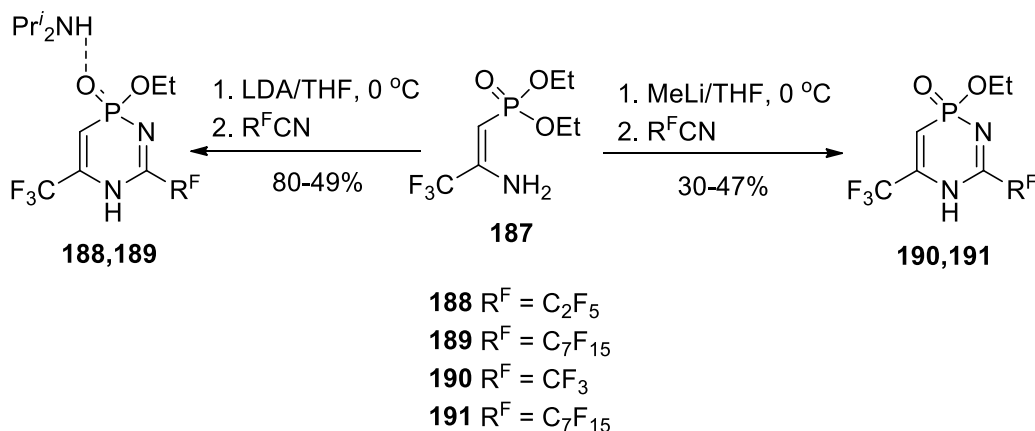
Scheme 92. Reactions of $\text{F}_2\text{NCF}_2\text{CN}$ **N30** with ammonia and hydrazine.

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



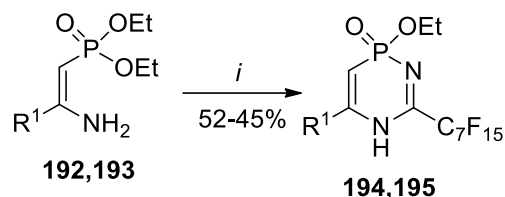
Scheme 93. Synthesis of trifluoroacetamide oxime (**186**).

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



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

Aromatic (**192**) and heteroaromatic (**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



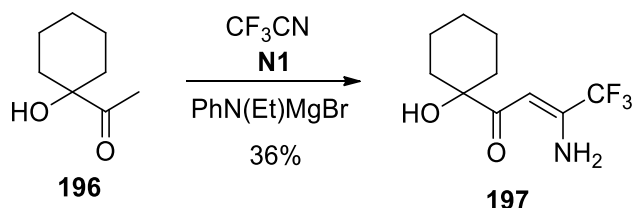
i: 1. BuLi/THF, 0 °C; 2. C₇F₁₅CN, 0 °C to rt; 3. H₂O

192,194 R¹ = Ph

193,195 R¹ = 2-Furyl

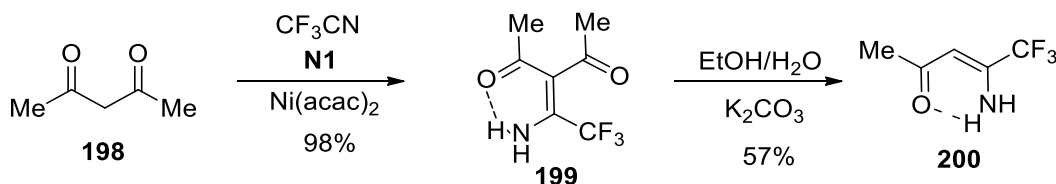
Scheme 95. Reaction of β -enaminophosphonates **192** and **193** with perfluorooctanenitrile.

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 -hydroxyoxoamine **197** (36 %) (Scheme 96).¹¹⁸



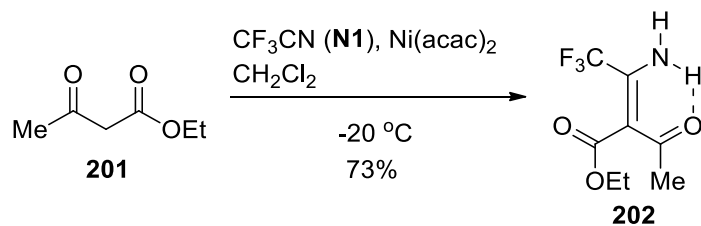
Scheme 96. Synthesis of α -hydroxyoxoamine **197**.

Acetylacetone (**198**) adds smoothly to the C \equiv 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 K₂CO₃ in aqueous EtOH, **199** is deacetylated to give enaminone **200**, which was isolated by sublimation in vacuum (Scheme 97).¹¹⁹



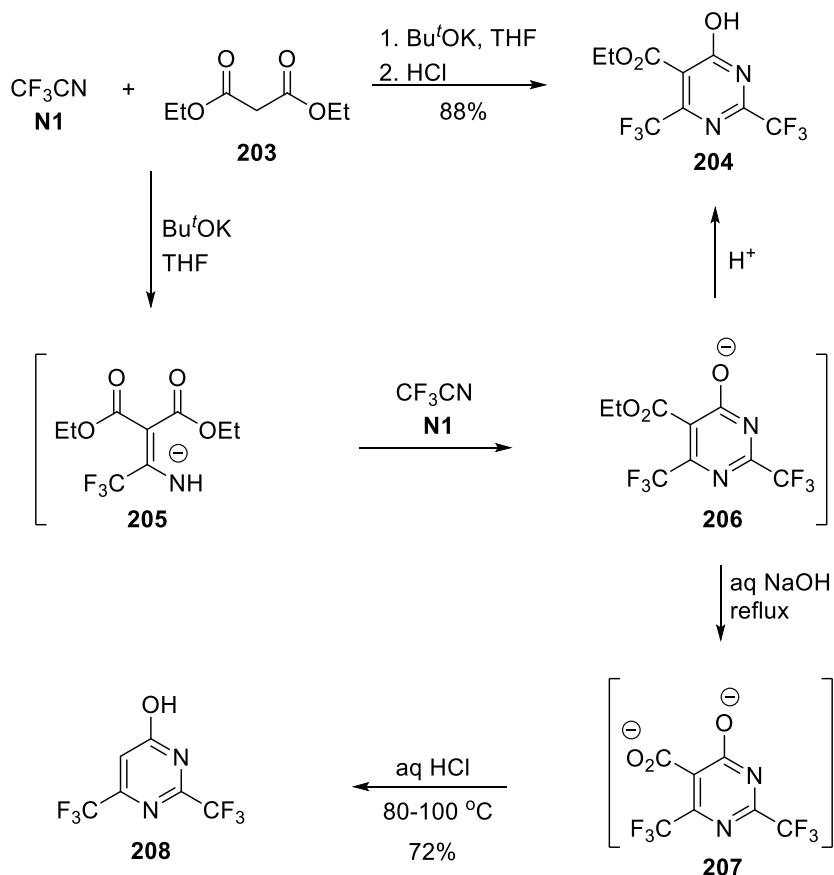
Scheme 97. Reaction of acetylacetone with CF₃CN in the presence of Ni(acac)₂.

Ethyl acetoacetate (**201**) readily reacts with CF₃CN in the presence of 1 mol.% of Ni(acac)₂ to give ethyl 2-acetyl-3-amino-4,4,4-trifluoro-2-buten-1-olate (**202**) in 73% yield. The reaction occurs more slowly than in the case of acetylacetone (Scheme 98).¹²⁰



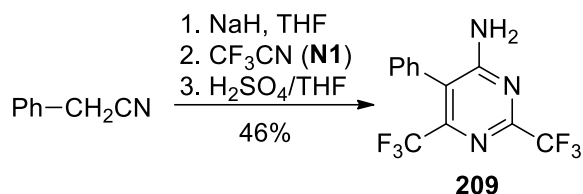
Scheme 98. Reaction of ethyl acetoacetate with CF_3CN .

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



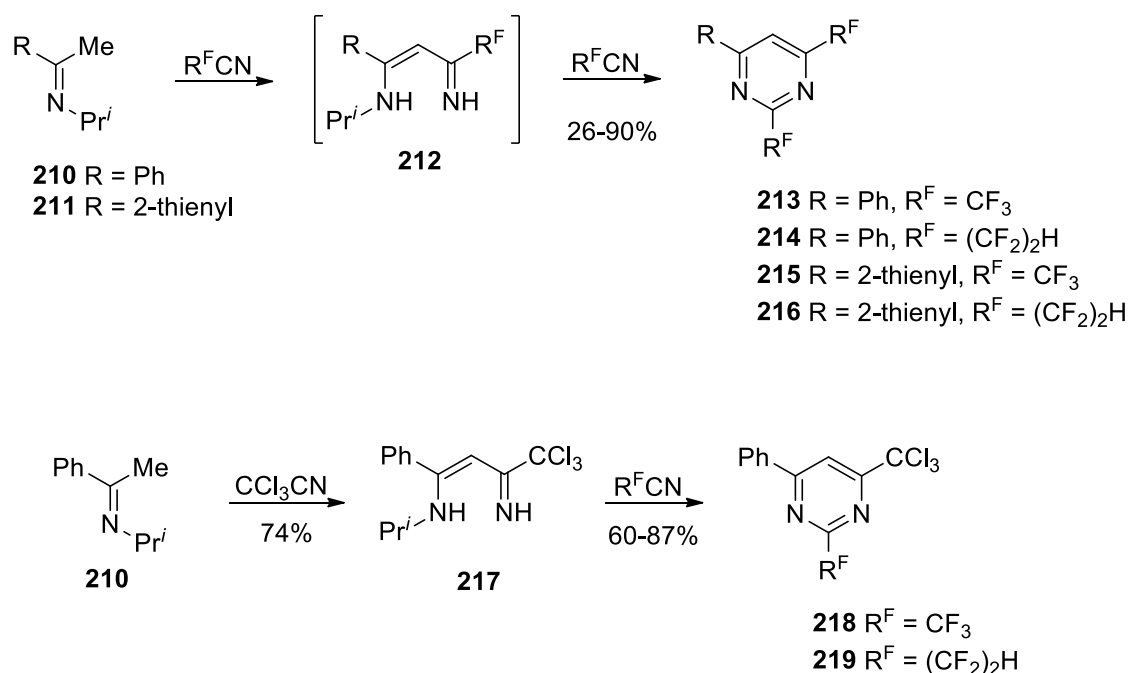
Scheme 99. Synthesis of CF_3 -pyrimidines **204** and **208**.

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



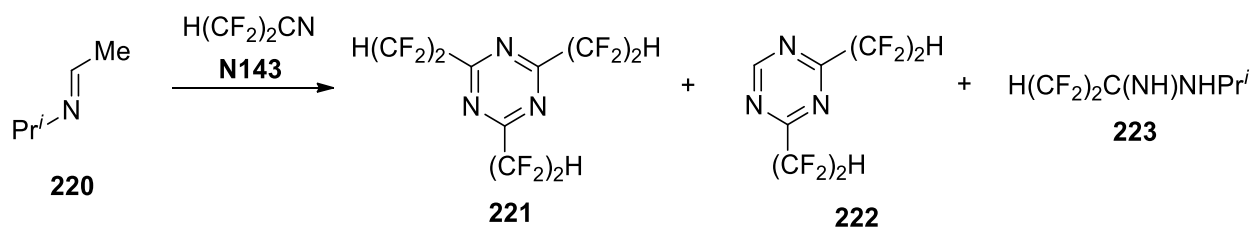
Scheme 100. Cyclotrimerization of CF_3CN and phenylacetonitrile in the presence of NaH.

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 $\text{R}^{\text{F}}\text{CN}$ gave CCl_3 -bearing R^{F} -pyrimidines **218** and **219** in 60-87% yield (Scheme 101).⁷⁹



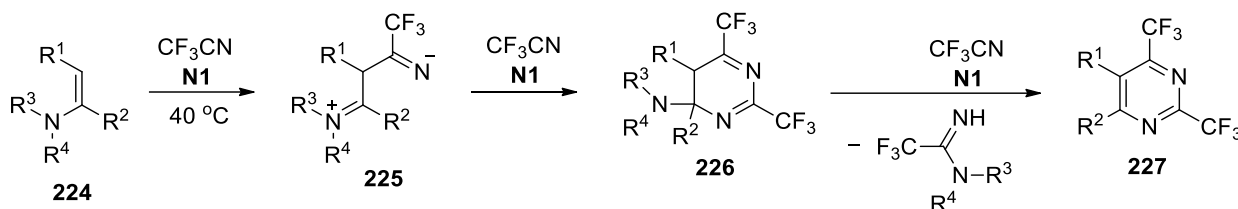
Scheme 101. Synthesis of R^{F} -pyrimidines from aromatic methyl ketimines and R^{F} -nitriles.

Reaction of aldimine **220** with $\text{H}(\text{CF}_2)_2\text{CN}$ **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



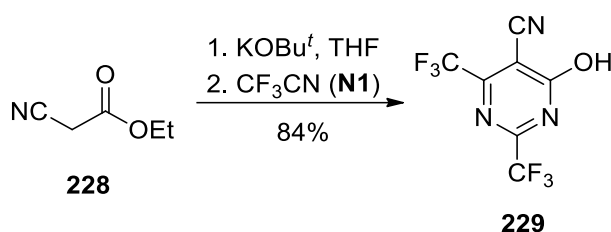
Scheme 102. Reaction of aldimine **220** with $\text{H}(\text{CF}_2)_2\text{CN}$.

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}



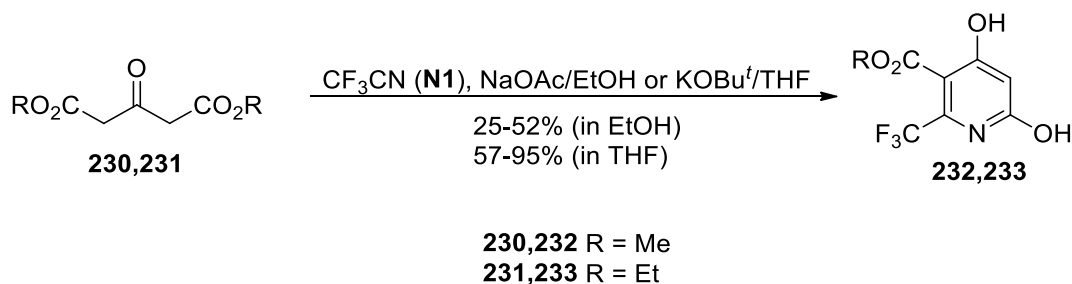
Scheme 103. Reaction of CF_3CN with enamines **224**.

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



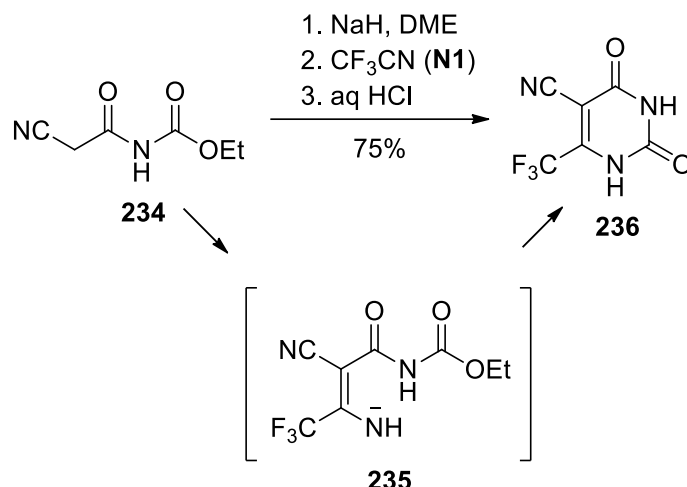
Scheme 104. Synthesis of CF_3 -pyrimidinol **229**.

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



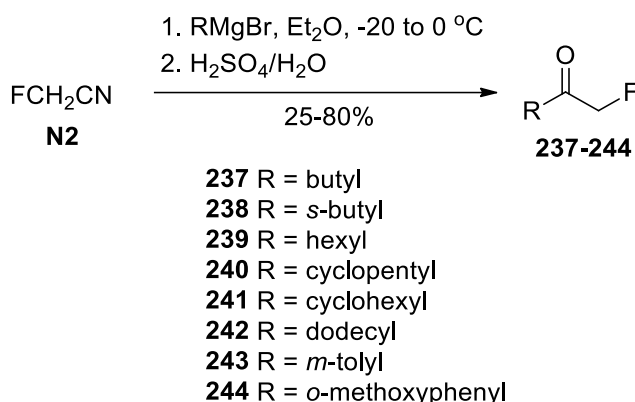
Scheme 105. Synthesis of CF_3 -pyridinediols **232** and **233**.

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



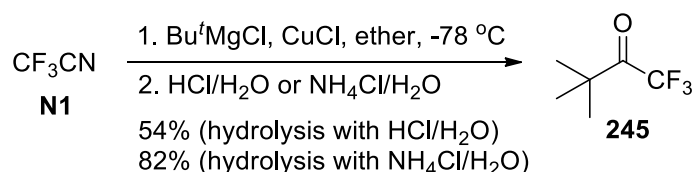
Scheme 106. 5-cyano-6-(trifluoromethyl)uracil (**236**).

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 FCH₂CN.

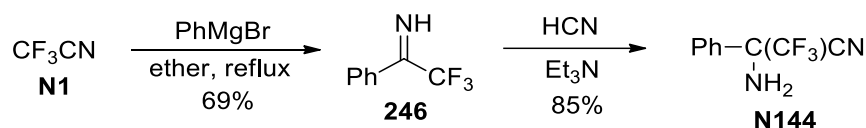
tert-Butyl trifluoromethyl ketone **245** (54-82%) was synthesized through the reaction between trifluoroacetonitrile (**N1**) and *tert*-butylmagnesium chloride in the presence of CuCl (Scheme 108).¹²⁸



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

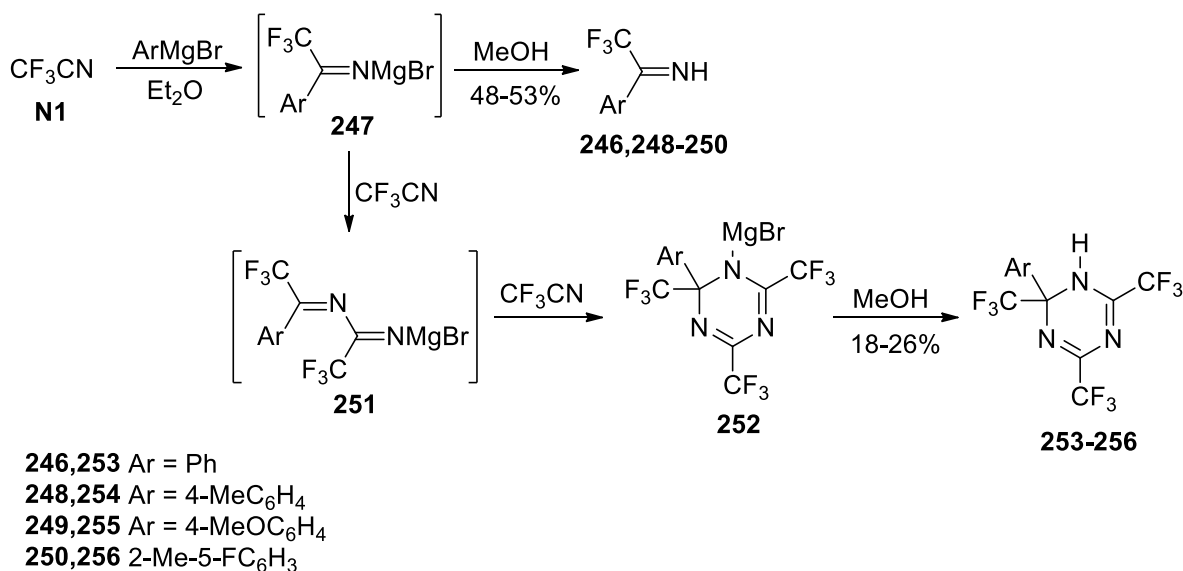
The reaction of trifluoroacetonitrile (**N1**) with PhMgBr resulted in the formation of phenyl trifluoromethyl ketimine **246** in 69%.¹⁰² Imine **246** was used for the preparation of α -amino- α -(trifluoromethyl)phenylacetonitrile (**N144**), which is a good precursor for the synthesis of some

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



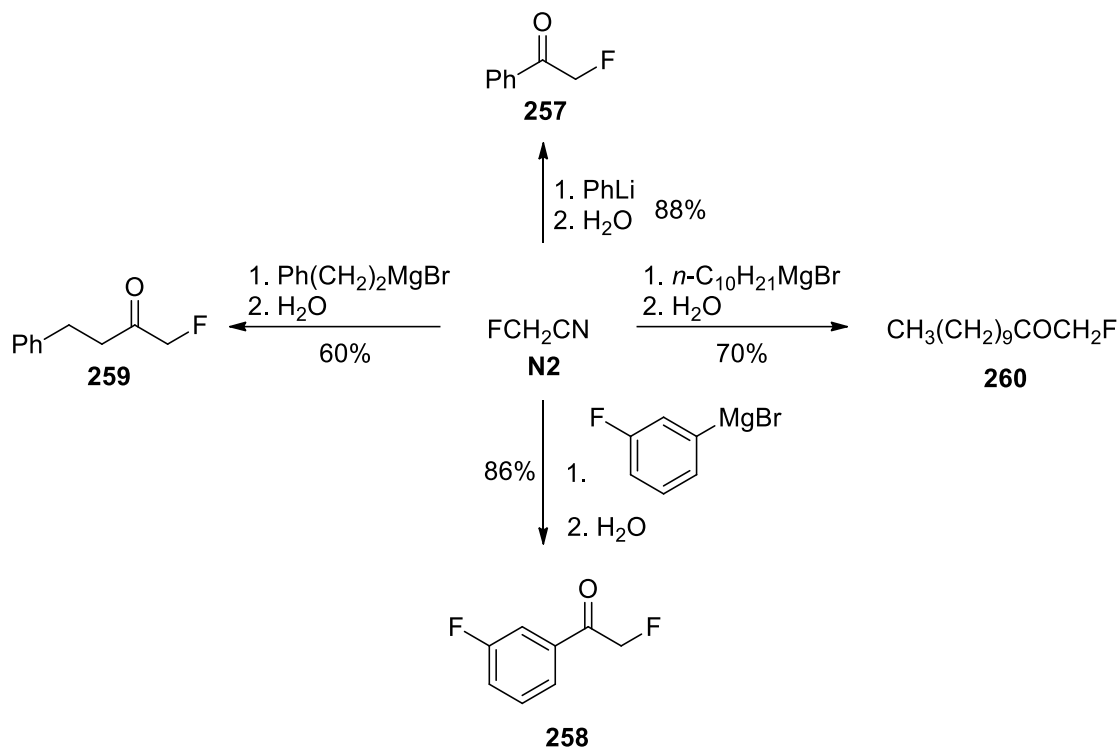
Scheme 109. Reaction of CF₃CN with PhMgBr and subsequent synthesis of R^F-nitrile **N144**.

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 CF₃CN with arylmagnesium bromides, due to the reaction of intermediate imine salt **247** with CF₃CN (Scheme 110).¹²⁹ Excess CF₃CN increases the yield of dihydrotriazine **254** up to 66%.¹²⁹



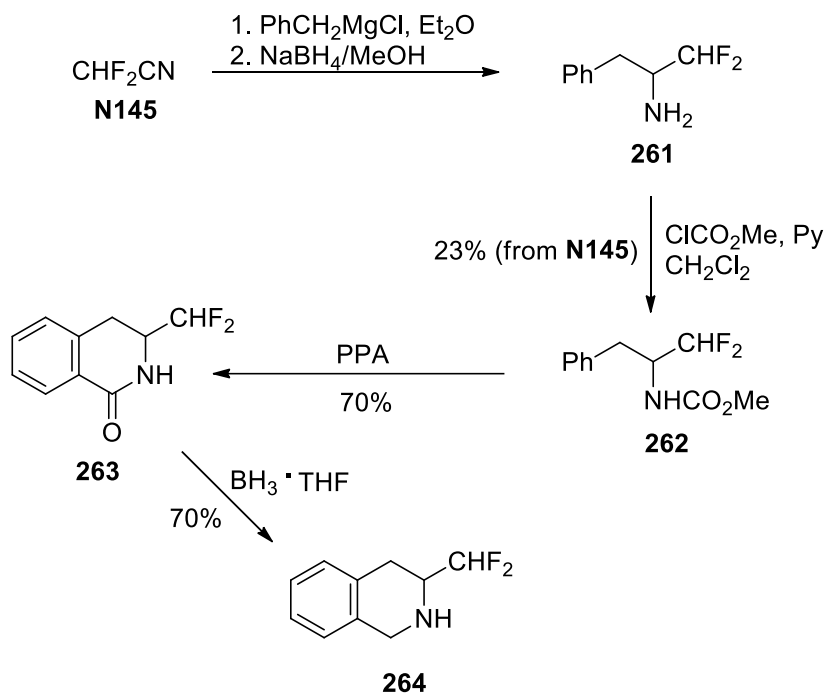
Scheme 110. Synthesis of CF₃-imines **246,248-250** and dihydrotriazines **253-256**.

Phenyllithium and 3-fluorophenylmagnesium bromide provided α-fluoroacetophenones **257** and **258** (88-86%) in the reaction with FCH₂CN **N2**. Aliphatic Grignard reagents gave the fluorinated ketones **259** and **260** in good yields (60-70%) (Scheme 111).¹³⁰



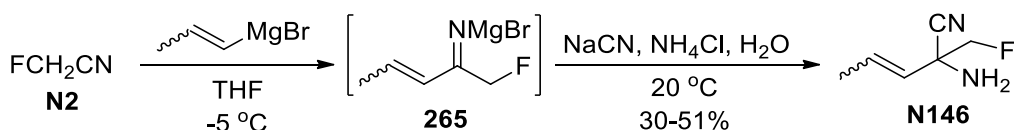
Scheme 111. Reactions of FCH₂CN with PhLi and Grignard reagents.

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 CH₂Cl₂ 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 BH₃·THF gave 3-(difluoromethyl)-1,2,3,4-tetrahydroisoquinoline (**264**) (70%) (Scheme 112).³⁰



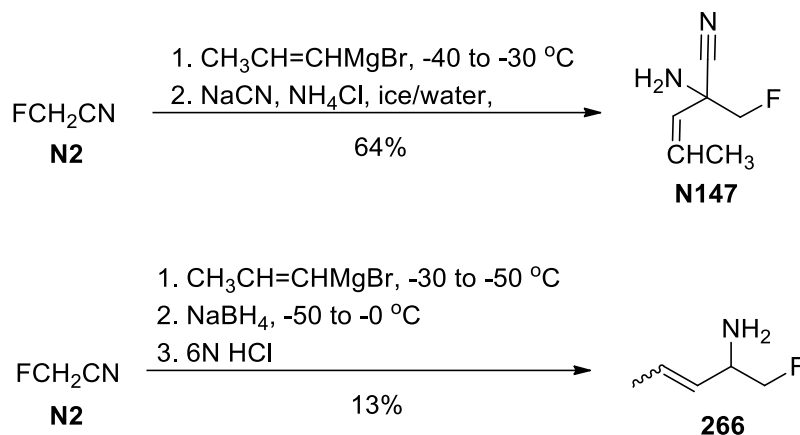
Scheme 112. 1,1-Difluoro-3-phenylpropan-2-amine (**261**) and 3-(difluoromethyl)-1,2,3,4-tetrahydroisoquinoline (**264**).

Synthesis of 2-amino-2-fluoromethyl-3-pentenitrile (**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



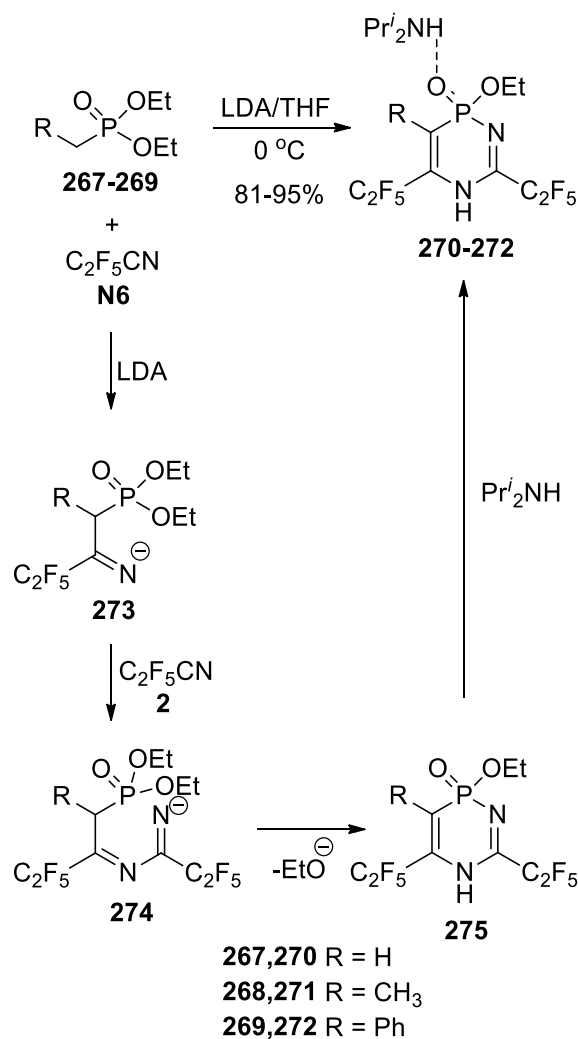
Scheme 113. Synthesis of α -fluoromethylated α -aminonitrile **N146**.

2-Amino-2-(fluoromethyl)-3-pentenitrile (**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



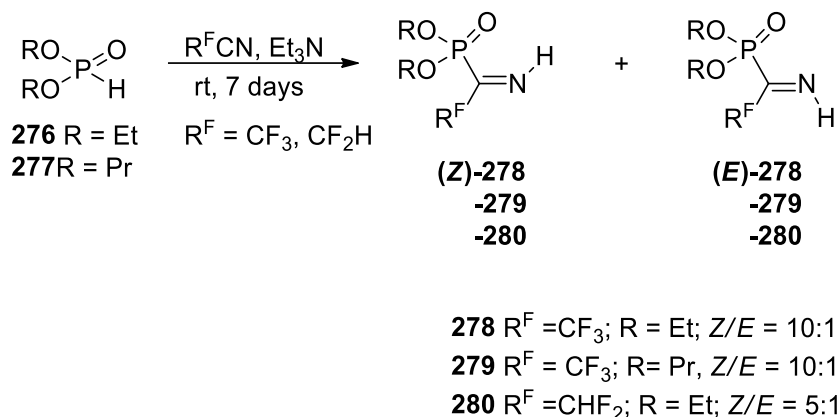
Scheme 114. Synthesis of monofluorinated α -aminonitrile **N147** and fluoroamine **266**.

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



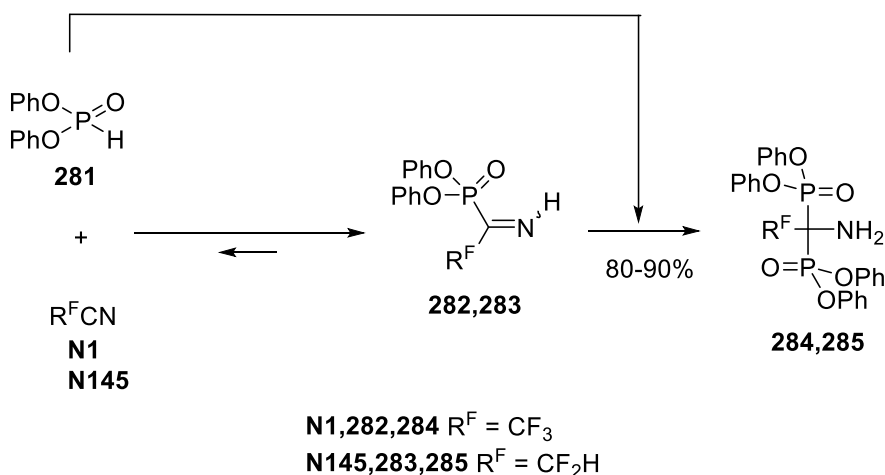
Scheme 115. Synthesis of C_2F_5 -substituted diisopropylamine-2,5-dihydro-1,5,2-diazaphosphinines adducts **270-272**.

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



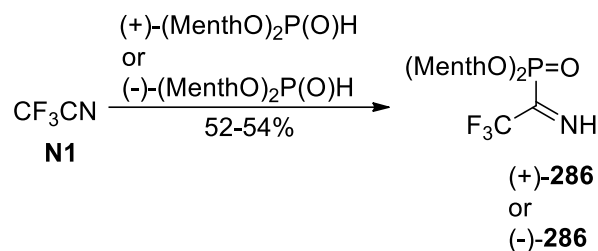
Scheme 116. Synthesis of imidoyl phosphonates **278-280**.

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



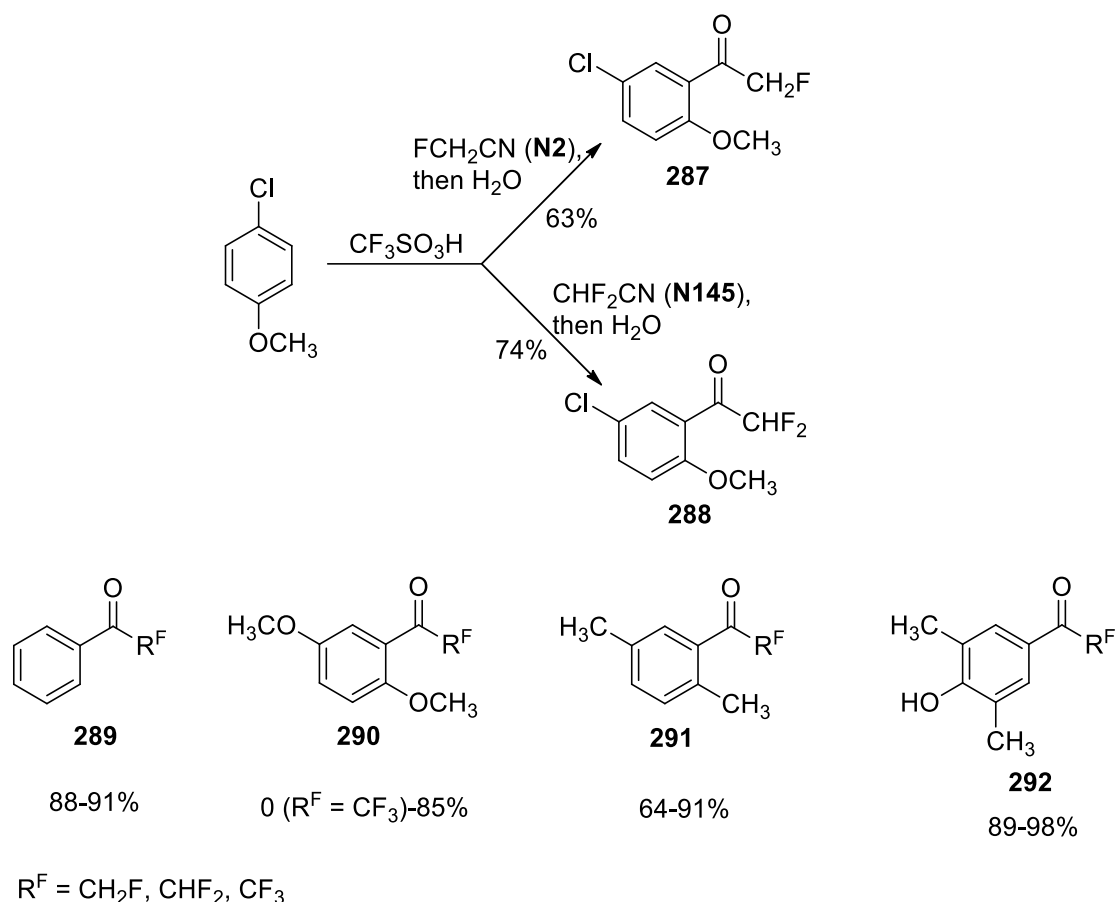
Scheme 117. Formation of imidoyl phosphonates **282** and **283**, and geminal bisphosphonates **284** and **285**.

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



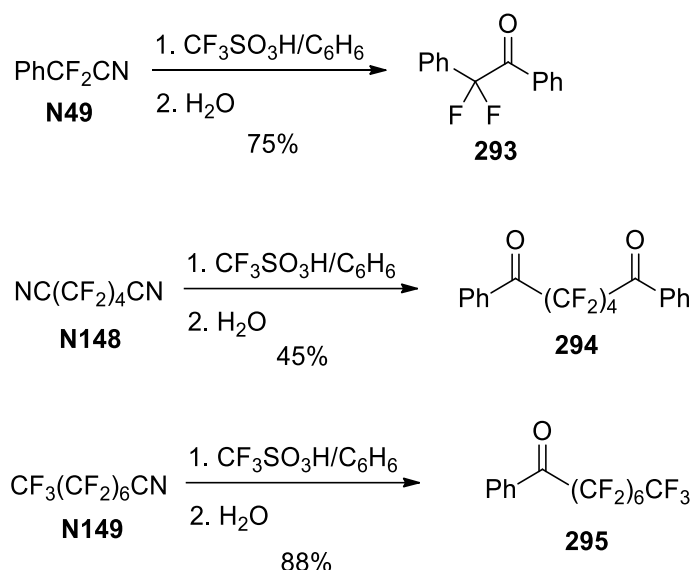
Scheme 118. Synthesis of optically pure CF₃-bearing dimethyl iminophosphonates (+)-**286** and (-)-**286**.

R^F-nitriles undergo the Houben–Hoesch reaction with arenes in CF₃SO₃H 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, FCH₂CN and F₂CHCN 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 CH₂F, CHF₂ and CF₃ groups **289-292** were also synthesized in up to 98% yield by using of the corresponding aromatic substrates, CH₂FCN, CHF₂CN and CF₃CN (Scheme 119).¹³⁰



Scheme 119. Houben–Hoesch reaction of R^FCN with arenes in CF₃SO₃H.

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

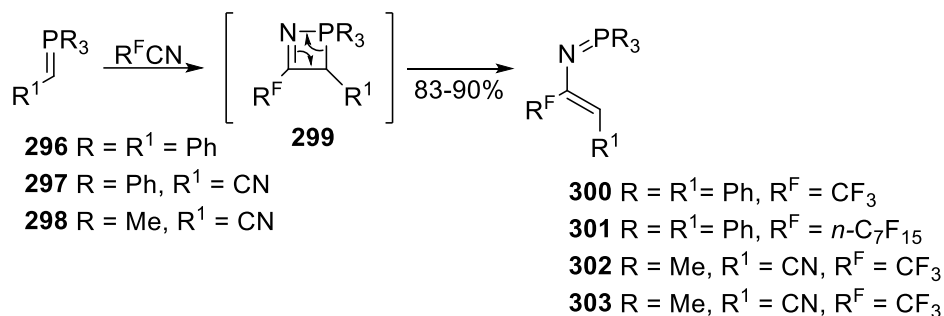


Scheme 120. Houben–Hoesch reaction of R^{F} -nitriles with benzene in $\text{CF}_3\text{SO}_3\text{H}$.

3.4. Cycloadditions

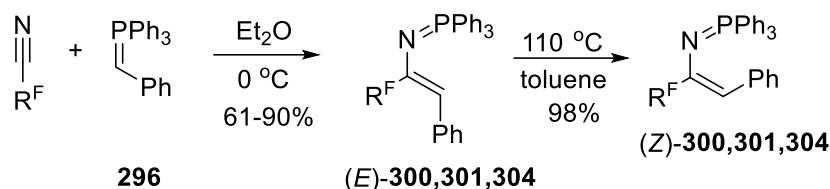
Due to the presence in molecules of R^{F} -nitriles the highly polarized triple bond that belongs to the highly electron-deficient $\text{C}\equiv\text{N}$ group, these compounds are reactive enophiles, dienophiles and dipolarophiles: they can undergo cycloadditions with isolated double bonds (including 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



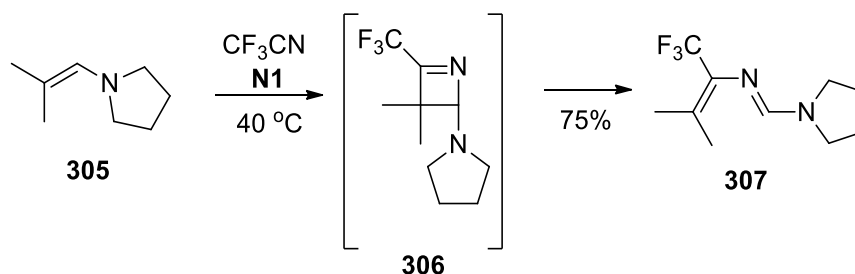
Scheme 121. Synthesis of R^{F} -phosphazenes **300–303**.

In accordance with an improved procedure, gaseous CF_3CN and $\text{CF}_3\text{CF}_2\text{CN}$ were bubbled through a cooled ($0\text{ }^{\circ}\text{C}$) 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 $110\text{ }^{\circ}\text{C}$ in toluene leads to their isomerization, producing the *Z*-isomers, (*Z*)-**300,301,304**, which were isolated in 98% yield (Table 12).¹³⁷

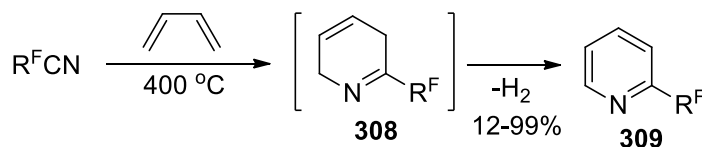
Table 12. Synthesis of R^F-phosphazenes **300,301,304**¹³⁷

Entry	R ^F	Product	Yield, %
1	CF ₃	(E)- 300	90
2	CF ₃	(Z)- 300	98
5	<i>n</i> -C ₇ F ₁₅	(E)- 301	83
6	<i>n</i> -C ₇ F ₁₅	(Z)- 301	98
3	C ₂ F ₅	(E)- 304	61
4	C ₂ F ₅	(Z)- 304	98

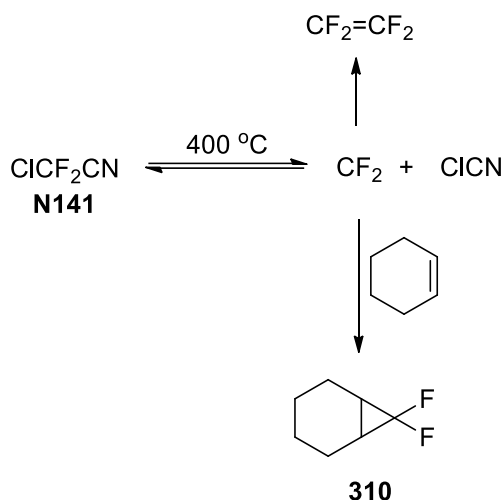
β,β-Disubstituted enamine **305** reacted with CF₃CN at 40 °C to give 2-aza-1,3-pentadiene derivative **307** (75%). The authors noted that most likely, the reaction proceeds via the formation of 1-azetidine intermediate **306** (Scheme 122).¹²³

**Scheme 122.** Reaction of β,β-disubstituted enamine **305** with CF₃CN.

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 = CF₃, C₂F₅, CF₃CF₂CF₂) and 12% yield (R^F = CClF₂) (Scheme 123).¹³⁸

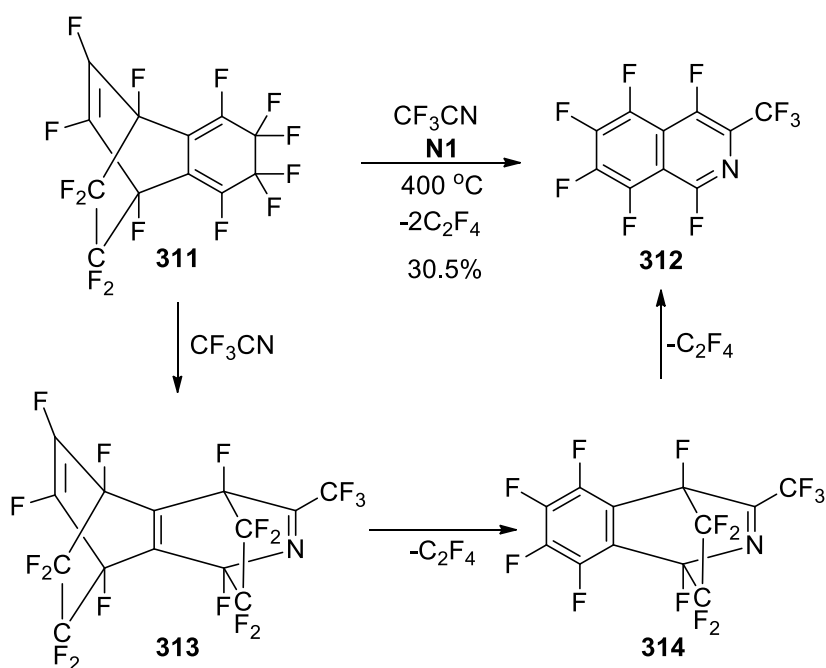
**Scheme 123.** Diels-Alder cycloaddition of R^F-nitriles and 1,2-butadiene.

The low yield in the case of ClCF₂CN **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 CF₂ addition product **310** (Scheme 124).¹³⁹



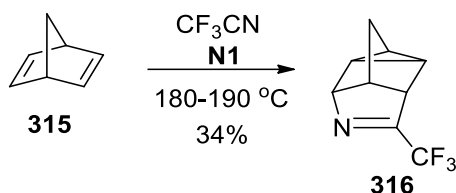
Scheme 124. Dissociation of ClCF_2CN **N141** at 400 °C and formation of tetrafluoroethylene, and CF_2 addition product **310**.

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



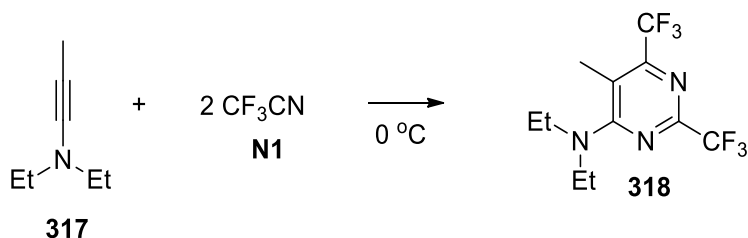
Scheme 125. Synthesis of 1,4,5,6,7,8-hexafluoro-3-(trifluoromethyl)isoquinoline (**312**).

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



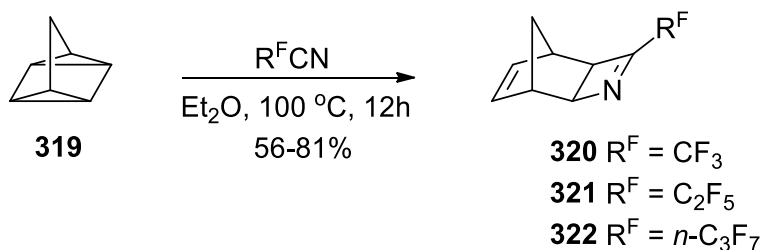
Scheme 126. Cycloaddition of CF_3CN and norbornadiene.

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



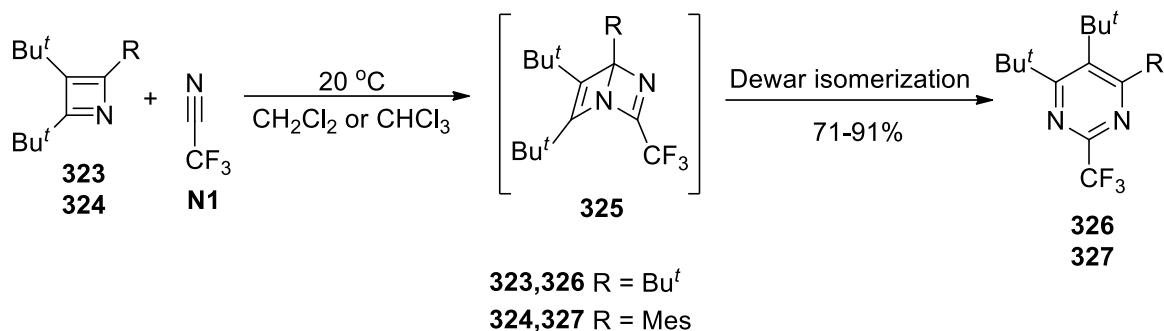
Scheme 127. [2+2+2]-Cycloaddition of ynamine **317** and CF_3CN .

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 , $\text{C}_2\text{F}_5\text{CN}$, and $n\text{-C}_3\text{F}_7\text{CN}$ 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



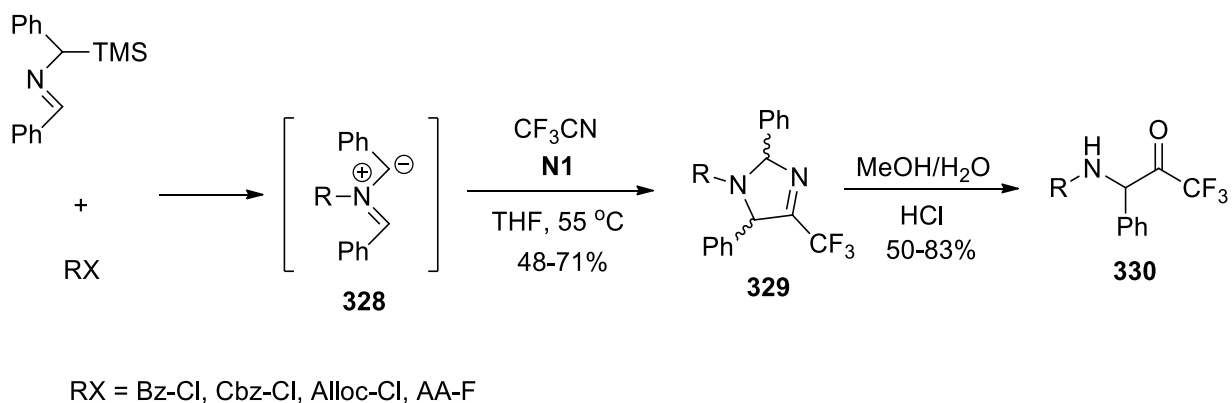
Scheme 128. Cycloaddition of quadricyclane (**319**) and R^{F} -nitriles.

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



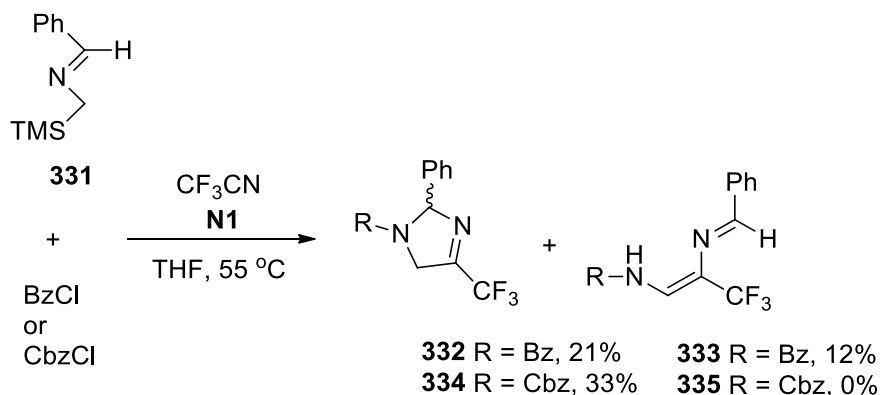
Scheme 129. [4 + 2] cycloaddition of azetes **323** and **324**, and CF_3CN at 20°C , and subsequent Dewar isomerization to CF_3 -pyrimidines **326** and **327**.

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



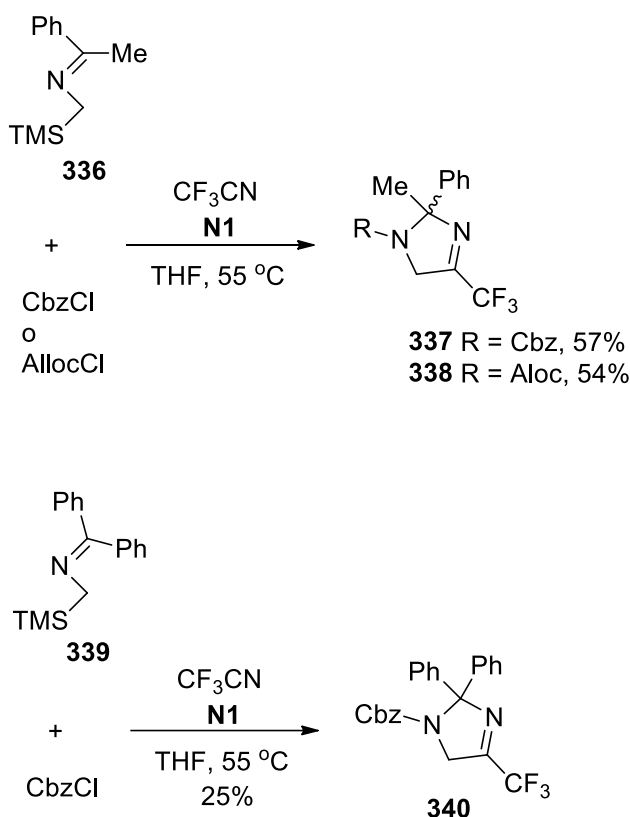
Scheme 130. 1,3-Dipolar cycloaddition of intermediate azomethine ylide **328** and CF_3CN .

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



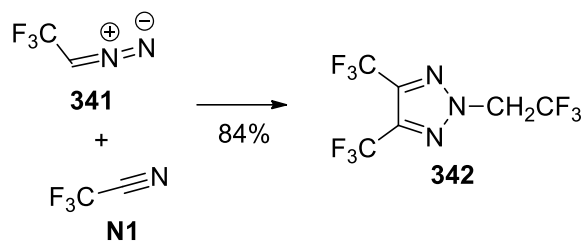
Scheme 131. Reaction of imine **331** with CF_3CN in the presence of either BzCl or CbzCl.

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



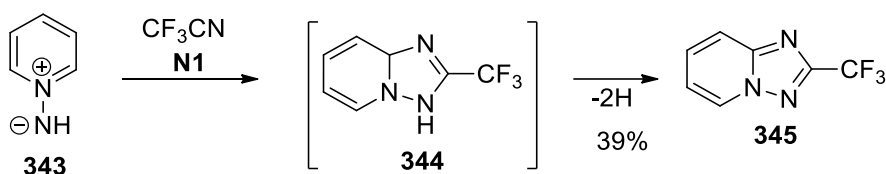
Scheme 132. Synthesis of CF_3 -imidazolines **337**, **338**, and **340**.

2,2,2-Trifluorodiazaoethane (**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



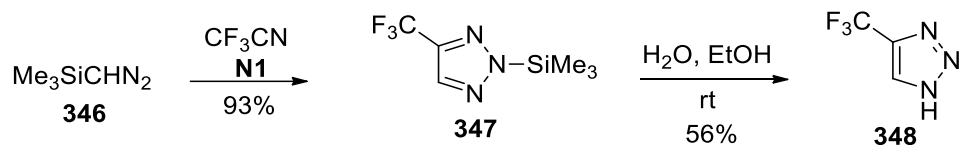
Scheme 133. Synthesis of triazole **342**.

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



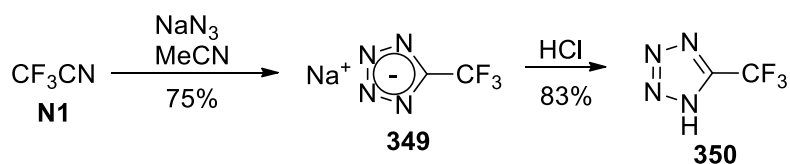
Scheme 134. Synthesis of 2-(trifluoromethyl)-*s*-triazolo[1,5-*a*]pyridine (**345**).

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



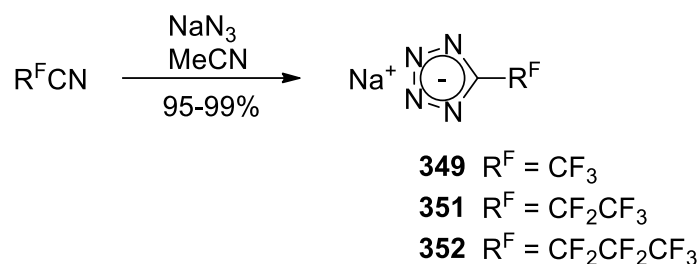
Scheme 135. Synthesis of 4- CF_3 -1,2,3-triazoles **347** and **348**

The reactions of $\text{R}^{\text{F}}\text{CN}$ 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**).

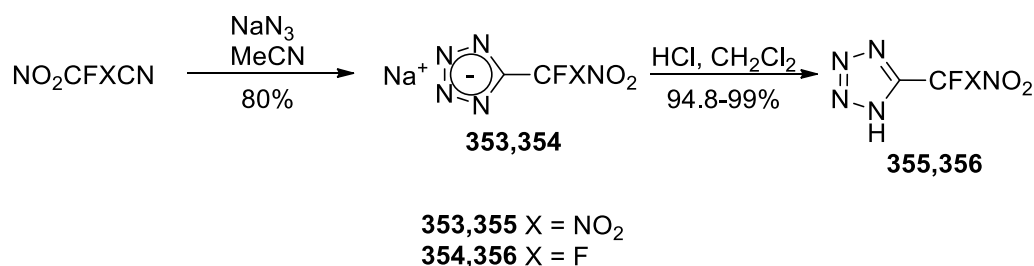
Furthermore, besides the reaction of CF_3CN with NaN_3 , the reactions of the $\text{CF}_3\text{CF}_2\text{CN}$ and $\text{CF}_3\text{CF}_2\text{CF}_2\text{CN}$ with NaN_3 in MeCN forming sodio-5- R^{F} -tetrazoles **351** and **352**, were undertaken (Scheme 137).⁴³



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

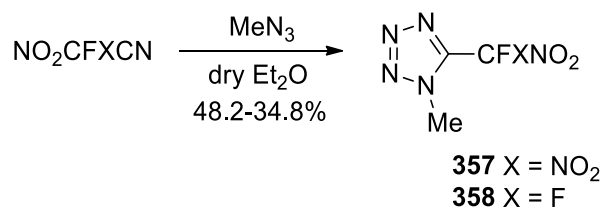
A similar approach for the synthesis of sodio-5-(trifluoromethyl)tetrazole **349** (40%) through bubbling CF_3CN into a solution of NaN_3 in MeCN at 25 °C was described.⁴⁴

The reaction of $(\text{O}_2\text{N})_2\text{CFCN}$ and $\text{O}_2\text{NCF}_2\text{CN}$ 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



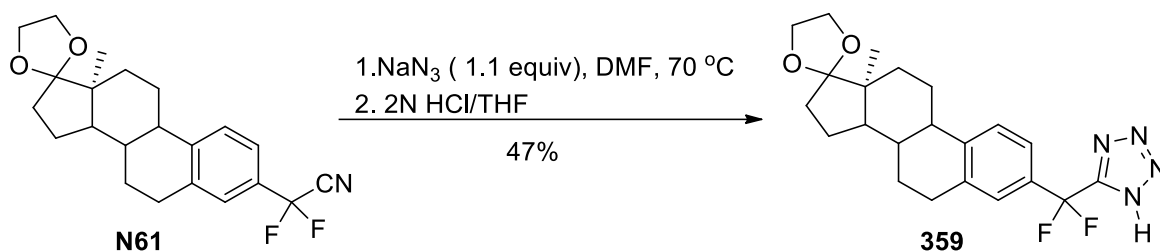
Scheme 138. Synthesis of R^{F} -tetrazoles **355** and **356**.

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



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

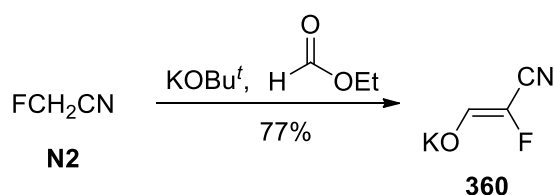
Tetrazole **359**, a fluorine-containing estrone derivative, was prepared in 47% yield through the reaction of difluoronitrile **N61** with NaN_3 (Scheme 140).⁶³



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

3.5. R^{F} -nitriles as active methylene compounds

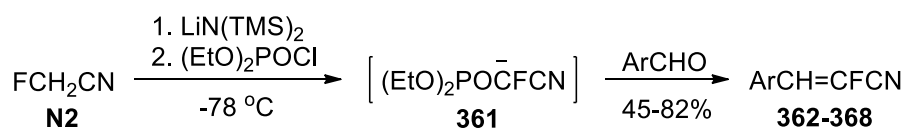
Fluoroacetonitrile and its α -monosubstituted derivatives are active methylene compounds, which can be used in various synthetic strategies for the preparation of fluorine-containing substances. Thus, the reaction of fluoroacetonitrile with ethyl formate in the presence of KOBU^t gave potassium (Z)-2-cyano-2-fluoroethenolate (**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 , NaOAm^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**).

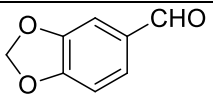
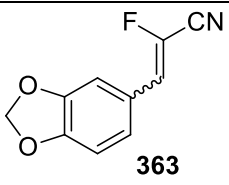
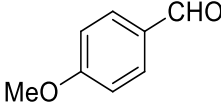
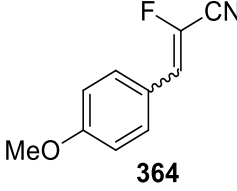
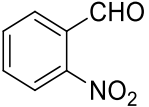
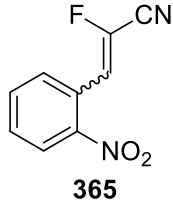
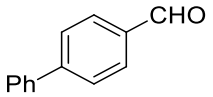
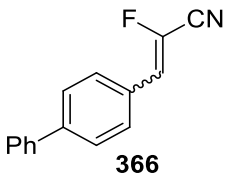
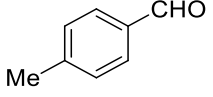
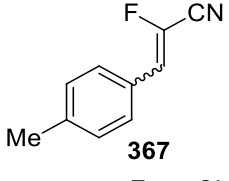
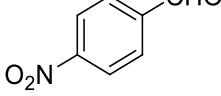
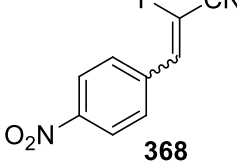
The reaction of FCH_2CN with diethylchlorophosphate at $-78\text{ }^\circ\text{C}$, in the presence of $\text{LiN}(\text{TMS})_2$, and the subsequent treatment of the reaction mixture (intermediate anion **361**) with aromatic aldehydes, gave 1-cyano-1-fluoroalkenes **362-368** in 45-82% yield.¹⁵² Aliphatic 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

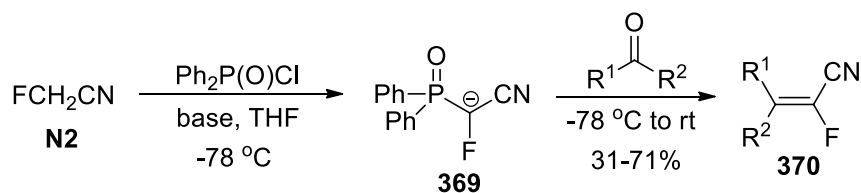


Entry	Aldehyde	Product	Yield, %
1		<p style="text-align: center;">362</p>	46

Table 13. Continued

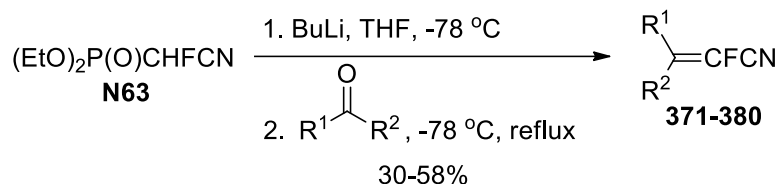
Entry	Aldehyde	Product	Yield, %
2		 363	45
3		 364	52
4		 365	62
5		 366	82
6		 367	51
7		 368	45

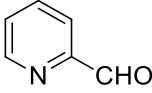
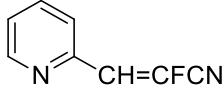
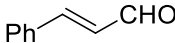
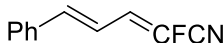
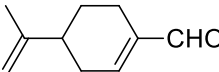
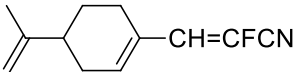
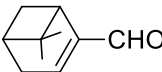
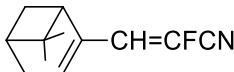
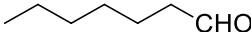
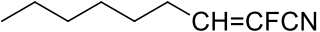

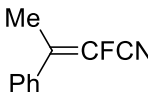
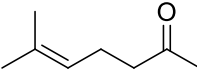
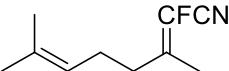
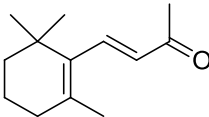
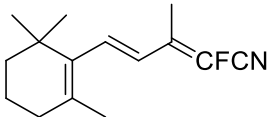
The use of fluoroacetonitrile in the Horner–Wittig reaction allows preparation of α -fluoro acrylonitriles. The reaction of FCH_2CN with $\text{Ph}_2\text{P}(\text{O})\text{Cl}$ leads to the formation of nucleophilic anions **369**, which then react with aldehydes and ketones to give α -fluoro- α,β -unsaturated nitriles **370**, which were isolated in 31–73% yield (Scheme 142).¹⁵³

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

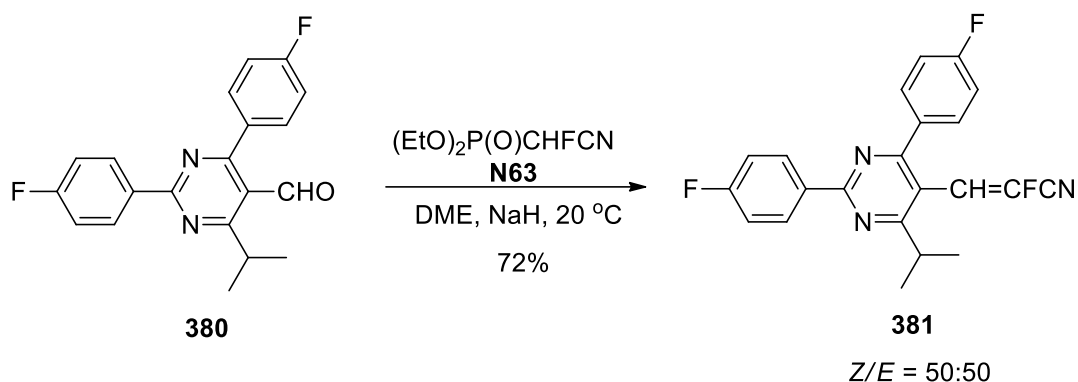
The Wittig-Horner reaction of diethyl cyanofluoromethanephosphonate (**N63**), an α -fluorinated nitrile, with aldehydes and ketones yielded various α -fluoro- α,β -unsaturated nitriles **371-380** as *Z:E* mixtures in 30-58% yield (Table 14).⁶⁴

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



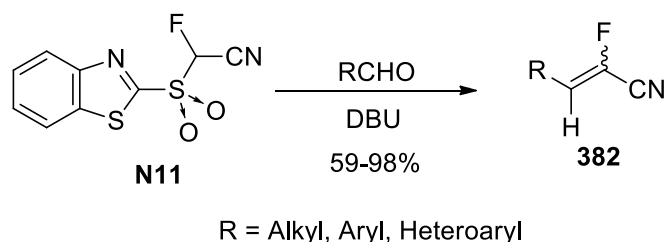
Entry	Carbonyl compound	Product	Yield of product, %	<i>Z:E</i>
1	PhCHO	PhCH=CFCN (371)	54	1:2
2		 372	53	2:3
3		 373	38	2:3
4		 374	42	1:2
5		 375	54	1:2
6		 376	30	7:3
7		 377	58	1:1
8		 378	40	1:1
9		 379	46	1:2
10	PhCH ₂ CHO	PhCH ₂ CH=CFCN (380)	50	3:2

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



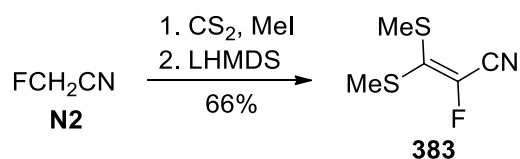
Scheme 143. Synthesis of α,β -unsaturated α -fluoronitrile **381**.

α -Fluoronitrile **N11** was used as a building-block to synthesize various 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



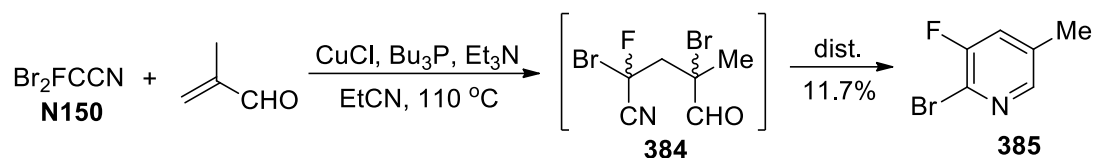
Scheme 144. Synthesis of α,β -unsaturated α -fluoronitriles **382**.

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



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 $\text{Bu}_3\text{P}/\text{Et}_3\text{N}$ 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



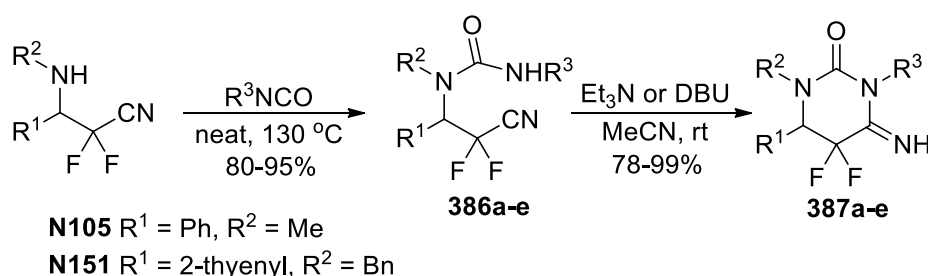
Scheme 146. Reaction of dibromofluoroacetonitrile (**N150**) with methacrolein in the presence of CuCl/Bu₃P/Et₃N.

No pyridine products were found during the distillation of the adducts formed from Cl₂FCCN **N80** and methacrolein: all pyrolytic attempts at ring closure resulted in the formation of tars and multiple reactions products.³⁷

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

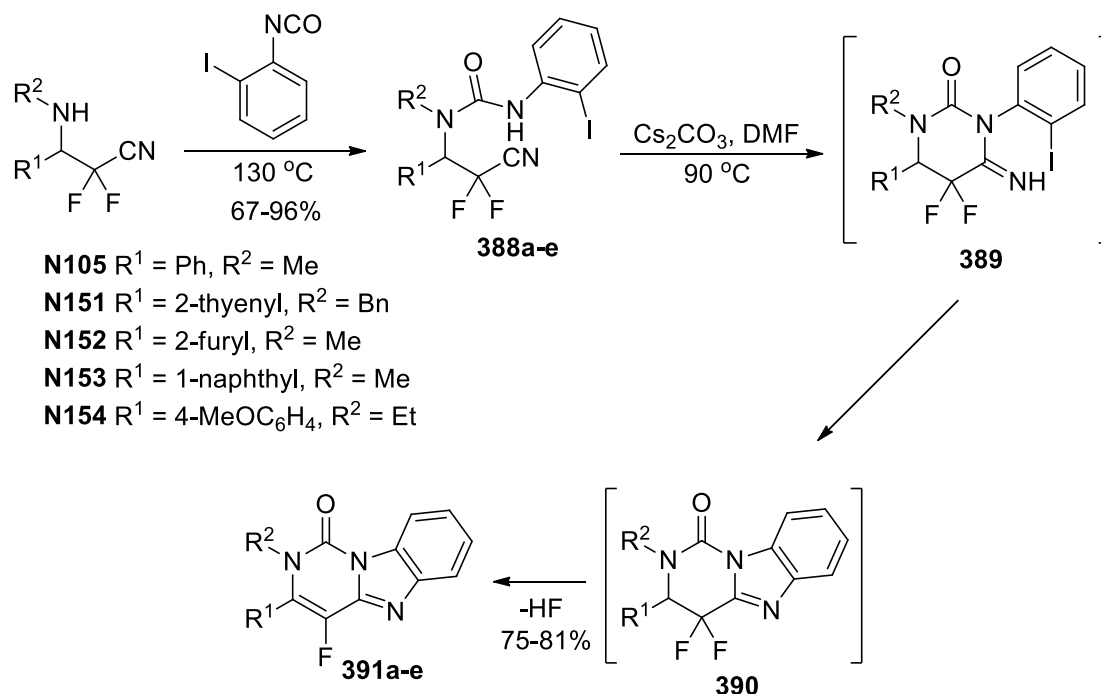
Reaction of 3-amino-2,2-difluoropropanenitriles **N105** and **N151** with isocyanates at 130 °C, and the subsequent treatment of intermediates **386** with either Et₃N or DBU in MeCN at rt yielded iminopyrimidones **387** in 78-99% yield. Intermediate substances **386** were also isolated (80-95%) and characterized (Table 15).¹⁵⁶

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



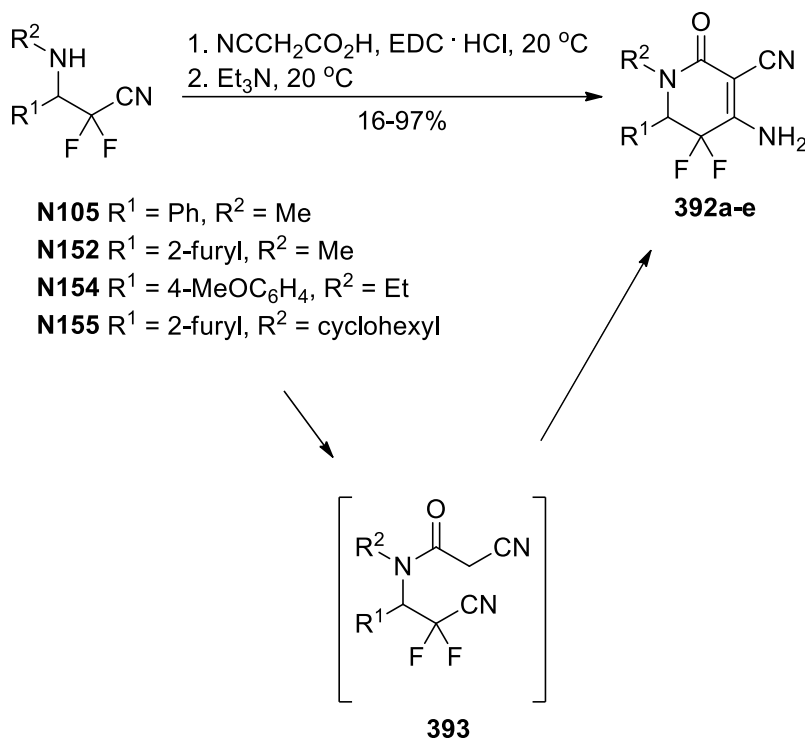
Entry	R ¹	R ²	R ³	386	Yield of 386 , %	387	Base	Yield of 387 , %
1	Ph	Me	Ph	386a	95	387a	Et ₃ N	95
2	Ph	Me	4-ClC ₆ H ₄	386b	95	387b	Et ₃ N	97
3	2-thienyl	Bn	Ph	386c	83	387c	Et ₃ N	98
4	2-thienyl	Bn	4-ClC ₆ H ₄	386d	80	387d	Et ₃ N	99
5	Ph	Me	Pr	386e	93	387e	DBU	78

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 ₆ H ₄	Et	388e	92	391e	75

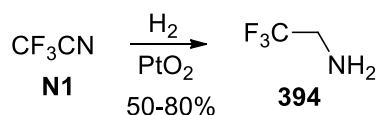
Fluorinated 4-amino-5,6-dihydropyridin-2(1*H*)-ones **392** (16-97%) were synthesized from α,α-difluoronitriles **N105**, **N152**, **N154** and **N155** and cyanoacetic acid in the presence of EDC·HCl.¹⁵⁷ The plausible mechanism involves the formation intermediates **393** formed in the acylation step, 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

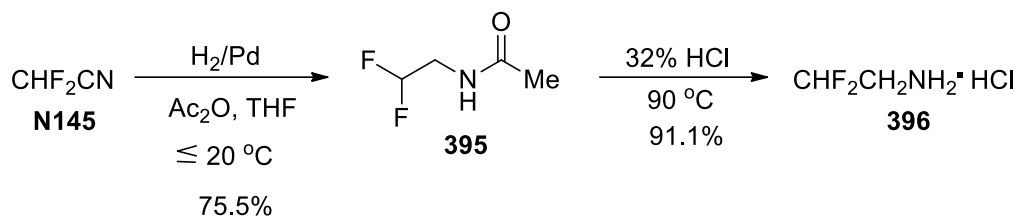
Entry	R ¹	R ²	Product 392	Yield of 392 , %
1	Ph	Me	392a	95
2	2-furyl	Me	392b	97
3	4-MeOC ₆ H ₄	Et	392c	93
4	2-thienyl	Bn	392d	43
5	2-furyl	cyclohexyl	392e	16

3.7. Reduction

It was shown, that CF₃CN can be reduced to 2,2,2-trifluoroethylamine (**394**) (50-80%) by hydrogenation in the presence of PtO₂ (Scheme 147).²⁹

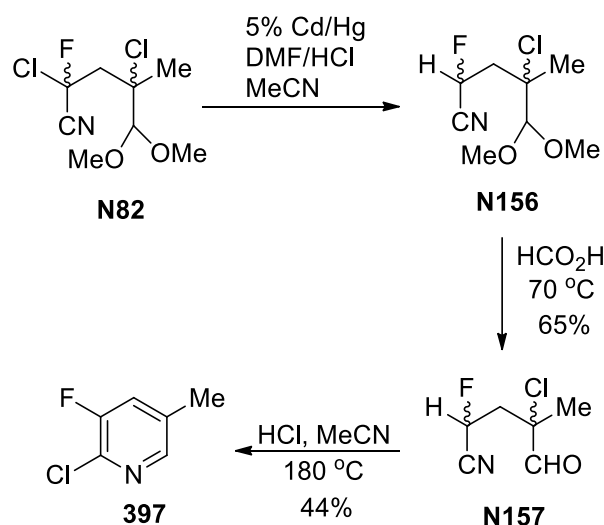
**Scheme 147.** Synthesis of 2,2,2-trifluoroethylamine.

2,2-Difluoroethylamine hydrochloride (**396**) (91.1%) was prepared in 69% overall yield via the reduction of CHF₂CN with H₂/Pd in Ac₂O/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**).

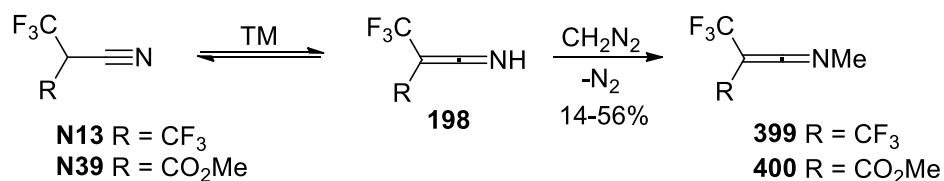
The α -chlorine atom can selectively be removed from a molecule of α -chloro- α -fluoronitriles by reduction. Thus, the reduction of α -fluoronitrile (**N82**) with 5% Cd/Hg α -dechlorinated α -fluoronitrile **N156**, which was hydrolyzed with formic acid to afford functionalized α -fluoronitriles **N157** 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^{-1} in the region normally assigned to the C=N stretching frequency.¹⁵⁹ Another product, isolated from the reaction of CF_3CN and $\text{Pt}(\text{PPh}_3)_4$, for which chemical analysis shows the molecular formula $(\text{PPh}_3)_2\text{Pt}(\text{CF}_3\text{CX})_2\text{N}$ **402**, was subjected to a single-crystal X-ray diffraction structure determination (Figure 1).¹⁵⁹

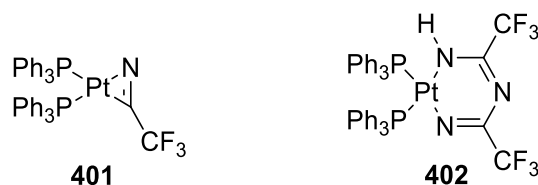


Figure 1. Formation of platinum complexes **401** and **402**.

Kinetics and mechanism of free-radical addition of CF_3CN to ethylene at $350\text{--}450\text{ }^\circ\text{C}$ 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 $\text{C}\equiv\text{N}$ 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	<i>N</i> -fluorobenzenesulfonimide
PPA	polyphosphoric acid
R ^F	fluoroalkyl
rt	room temperature
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TM	tautomerism
TMS	trimethylsilyl
TMSCN	trimethylsilyl cyanide

References

- Reddy, V. P. *Organofluorine compounds in biology and medicine*, 1st ed., Elsevier, **2015**.
<https://www.elsevier.com/books/organofluorine-compounds-in-biology-and-medicine/reddy/978-0-444-53748-5>
- Kirsch, P. *Modern fluoroorganic chemistry*, 2nd ed., Wiley-VCH, Weinheim, **2013**.
<https://www.wiley.com/en-us/Modern+Fluoroorganic+Chemistry%3A+Synthesis%2C+Reactivity%2C+Applications%2C+2nd%2C+Completely+Revised+and+Enlarged+Edition-p-9783527331666>
- Gouverneur, V.; Müller, K. *Fluorine in pharmaceutical and medicinal chemistry*, Imperial College Press, London, **2012**.
- Usachev, B. I. *J. Fluorine Chem.* **2016**, 185, 118–167.
<https://www.sciencedirect.com/science/article/abs/pii/S0022113916300458>
- Usachev, B. I. *J. Fluorine Chem.* **2015**, 175, 36–46.
<https://www.sciencedirect.com/science/article/abs/pii/S0022113915000548>
- Usachev, B. I. *J. Fluorine Chem.* **2015**, 172, 80–91.
<https://www.sciencedirect.com/science/article/abs/pii/S0022113915000354>
- Foreman, P. B.; Chien, K. R.; Williams, J. R.; Kukolich, S. G. *J. Mol. Spectrosc.* **1974**, 52, 251–255.
<https://www.sciencedirect.com/science/article/abs/pii/0022285274901167>
- Walker, L. C.; Sinke, G. C.; Perettie, D. J.; Janz, G. J. *J. Am. Chem. Soc.* **1970**, 92, 4525–4526.
<https://pubs.acs.org/doi/10.1021/ja00718a006>
- Edgell, W. F.; Potter, R. M. *J. Chem. Phys.* **1956**, 24, 80–85.
<https://aip.scitation.org/doi/10.1063/1.1700875>
- Mousa, A.H.N. *J. Fluorine Chem.* **1975**, 6, 221–226.
<https://www.sciencedirect.com/science/article/abs/pii/S0022113900830018>
- Pace, E. L.; Bobka, R. J. *J. Chem. Phys.* **1961**, 35, 454–457.
<https://aip.scitation.org/doi/10.1063/1.1731951>
- Fantran, J.A.; Shurvell, H.F. *Spectrochim. Acta, A*, **1970**, 26, 1459–1467.
<https://www.sciencedirect.com/science/article/abs/pii/0584853970802070>
- Sheridan, J.; Gordy, W. *J. Chem. Phys.* **1952**, 20, 591–595.

- <https://aip.scitation.org/doi/10.1063/1.1700499>
14. Sheridan, J.; Gordy, W. *Phys. Rev.* **1950**, 77, 292–293.
<https://journals.aps.org/pr/abstract/10.1103/PhysRev.77.292>
 15. Whittle, M. J.; Baker, J. G.; Corbelli, G. J. *Mol. Spectrosc.* **1971**, 40, 388–396.
<https://www.sciencedirect.com/science/article/abs/pii/0022285271901639>
 16. Burrus, C. A.; Gordy, W. J. *Chem. Phys.* **1957**, 26, 391–394.
<https://aip.scitation.org/doi/abs/10.1063/1.1743304>
 17. Friedrich, A.; Gerke, C.; Harder, H.; Mäder, H.; Cosléau, J.; Wlodarczak, G.; Demaison, J. *Mol. Phys.* **1997**, 91, 697–714.
<https://www.tandfonline.com/doi/abs/10.1080/002689797171193?journalCode=tmph20>
 18. Seo, P. J.; Carpenter, J. H.; Smith, J. G. J. *Mol. Spectrosc.* **1997**, 184, 362–370.
<https://www.sciencedirect.com/science/article/abs/pii/S0022285297973380>
 19. Cox, A. P.; Ellis, M. C.; Legon, A. C.; Wallwork, A. J. *Chem. Soc., Faraday Trans.* **1993**, 89, 2937–2944.
<https://pubs.rsc.org/en/content/articlelanding/1993/ft/ft9938902937/unauth#!divAbstract>
 20. Motamedi, M.; Haseli, A. J. *Mol. Spectrosc.* **2006**, 236, 91–96.
<https://www.sciencedirect.com/science/article/abs/pii/S0022285205003140>
 21. Carpenter, J. H.; Motamedi, M.; Smith, J. G. J. *Mol. Spectrosc.* **1995**, 171, 468–480.
<https://www.sciencedirect.com/science/article/abs/pii/S0022285285711332>
 22. Ai, X.; Tu, Y.; Zhang, Y.; Chen, G.; Yuan, Z.; Wang, C.; Yan, X.; Liu, W. *Electrical Power and Energy Systems* **2020**, 118, 105751.
<https://www.sciencedirect.com/science/article/abs/pii/S0142061519309299>
 23. Su, T.; Hammond, G. B.; Morris, R. A.; Viggiano, A. A.; Paulson, J. F.; Liebman, J. F.; Su, A. C. L. *J. Fluorine Chem.* **1995**, 74, 149–157.
<https://www.sciencedirect.com/science/article/abs/pii/002211399503266G>
 24. Lin, W.; Novick, S. E. *J. Mol. Spectrosc.* **2007**, 243, 32–36.
<https://www.sciencedirect.com/science/article/abs/pii/S0022285207000914>
 25. Lin, W.; Wu, A.; Lu, X.; Tang, X.; Obenchain, D. A.; Novick, S. E.; *Phys. Chem. Chem. Phys.* **2015**, 17, 17266–17270.
<https://pubs.rsc.org/en/content/articlelanding/2015/cp/c5cp01550b#!divAbstract>
 26. Larson, J. W.; McMahon, T. B. *J. Am. Chem. Soc.* **1985**, 107, 766–773.
<https://pubs.acs.org/doi/10.1021/ja00290a005>
 27. Sass, V. P.; Voronkov, A. N.; Nadervel', T. A.; Stolyarov, V. P.; Sokolov, S. V.; Fokin, A. V. *Russ. Chem. Bull.* **1979**, 28, 2175–2177.
<https://link.springer.com/article/10.1007%2F00947575>
 28. Swarts, F. *Bull. Acad. R. Belg. Classe Sci.* **1922**, 8, 343.
 29. Gilman, H.; Jones, R. G. *J. Am. Chem. Soc.* **1943**, 65, 1458–1460.
<https://pubs.acs.org/doi/10.1021/ja01248a005>
 30. Grunewald, G. L.; Seim, M. R.; Lu, J.; Makboul, M.; Criscione, K. R. *J. Med. Chem.* **2006**, 49, 2939–2952.
<https://pubs.acs.org/doi/10.1021/jm051262k>
 31. Swarts, F. *Bull. Soc. Chim. Belg.* **1922**, 31, 364–365.
 32. Buckle, F. J.; Heap, R.; Saunders, B. C. *J. Chem. Soc.* **1949**, 912–916.
<https://pubs.rsc.org/en/content/articlelanding/1949/jr/jr9490000912/unauth#!divAbstract>
 33. Gryszkiewicz-Trochimowski, E.; Sporzynski, A.; Wnuk, J. *Rec. Frau. Chim.* **1947**, 66, 419, cited in Pattison, F. L. M.; Cott, W. J.; Howell, W. C.; White, R. S. V. *J. Am. Chem. Soc.* **1956**, 78, 3484–3487 (ref.³⁴).

34. Pattison, F. L. M.; Cott, W. J.; Howell, W. C.; White, R. S. V. *J. Am. Chem. Soc.* **1956**, *78*, 3484–3487.
<https://pubs.acs.org/doi/abs/10.1021/ja01595a058>
35. Dietz, J.-P.; Derstine, B. P.; Ferenc, D.; Crawford, E. T.; Arduengo III, A. J.; Gupton, B. F.; McQuade, D. T.; Opatz, T. *Eur. J. Org. Chem.* **2019**, 5519–5526.
<https://chemistry-europe.onlinelibrary.wiley.com/doi/abs/10.1002/ejoc.201900629>
36. Young, J.A.; Tarrant, P. *J. Am. Chem. Soc.* **1949**, *71*, 2432–2433.
<https://pubs.acs.org/doi/pdf/10.1021/ja01175a055>
37. Pews, R. G.; Lysenko, Z. *J. Org. Chem.* **1985**, *50*, 5115–5119.
<https://pubs.acs.org/doi/pdfplus/10.1021/jo00225a027>
38. Dakkouri, M. Grunvogel-Hurst, A.; Guirgis, G. A.; Yu, Z.; Jin, Y.; Durig, J. R. *Spectrochim. Acta, A*, **1997**, *53*, 2001–2012.
<https://www.sciencedirect.com/science/article/abs/pii/S1386142597001194>
39. Atavin, E. G.; Dakkouri, M.; Khristenko, L. V.; Vilkov, L. V. *Spectrochim. Acta, A*, **2005**, *61*, 1671–1674.
<https://www.sciencedirect.com/science/article/abs/pii/S1386142504006675>
40. Bishop, B. C.; Hynes, J. B.; Bigelow, L. A. *J. Am. Chem. Soc.* **1963**, *85*, 1606–1608.
<https://pubs.acs.org/doi/abs/10.1021/ja00894a015>
41. McBee, E.; Wiseman, P.; Bachman, G. *Ind. Eng. Chem.* **1947**, *39*, 415–417.
<https://pubs.acs.org/doi/10.1021/ie50447a639>
42. Parker, M. H. *Synth. Commun.* **2004**, *34*, 903–907.
<https://www.tandfonline.com/doi/abs/10.1081/SCC-120028363>
43. Crawford, M.-J.; Klapötke, T. M.; Radies, H. *J. Fluorine Chem.* **2008**, *129*, 1199–1205.
<https://www.sciencedirect.com/science/article/abs/pii/S002211390800290X>
44. Karri, P.; Pabba, J.; Gurjar, B. L.; Klausener, A. G. M. WO **2020**/049436 A1, assigned by Pi Industries Ltd.
45. Geraschenko, O. V.; Solomin, V. V.; Vashchenko, B. V.; Khodakivskiy, P.; Tolmachev, A. A.; Grygorenko, O. *J. Fluorine Chem.* **2020**, *229*, 109407.
<https://www.sciencedirect.com/science/article/pii/S0022113919303045>
46. del Solar, M.; Ghosh, A. K.; Zajc, B. *J. Org. Chem.* **2008**, *73*, 8206–8211.
<https://pubs.acs.org/doi/10.1021/jo801235x>
47. Knunyants, I. L.; German, L. S.; Dyatkin, B. L. *Russ. Chem. Bull.* **1956**, *5*, 1387–1394.
<https://link.springer.com/article/10.1007/BF01177704>
48. Bumgardner, C. L.; Lawton, E. L. *J. Org. Chem.* **1972**, *37*, 410–412.
<https://pubs.acs.org/doi/pdf/10.1021/jo00968a018>
49. Mitsch, R. A.; Neuvar, E. W. *J. Org. Chem.* **1968**, *33*, 3675–3678.
<https://pubs.acs.org/doi/pdf/10.1021/jo01273a085>
50. Kumar, R.C.; Shreeve, J. M. *J. Am. Chem. Soc.* **1980**, *102*, 4958–4959.
<https://pubs.acs.org/doi/abs/10.1021/ja00535a022>
51. Doyle, M.P.; Whitefleet, J. L.; Zaleta, M. A. *Tetrahedron. Lett.* **1975**, *16*, 4201–4204.
<https://www.sciencedirect.com/science/article/abs/pii/S0040403900911481>
52. Doyle, M. P.; Whitefleet, J. L.; Bosch, R. J. *J. Org. Chem.* **1979**, *44*, 2923–2929.
<https://pubs.acs.org/doi/abs/10.1021/jo01330a021>
53. Marsden, H. M.; Shreeve, J. M. *Inorg. Chem.* **1987**, *26*, 169–172.
<https://pubs.acs.org/doi/abs/10.1021/ic00248a033>
54. John, E. O.; Kirchmeier, R. L.; Shreeve, J. M. *J. Fluorine Chem.* **1992**, *56*, 335–340.
<https://www.sciencedirect.com/science/article/abs/pii/S0022113900811823>

55. Emel  us, H. J.; Shreeve, J. M.; Verma, R. D. *Adv. Inorg. Chem.* **1989**, *33*, 139–196.
<https://www.sciencedirect.com/science/article/abs/pii/S0898883808601956>
56. Mir, Q.-C.; DesMarteau, D. D. *Inorg. Chem.* **1991**, *30*, 535–538.
<https://pubs.acs.org/doi/10.1021/ic00003a036>
57. LaZerte, J. D.; Rausch, D. A.; Koshar, R. J.; Park, J. D.; Pearlson, W. H.; Lacher, J. R. *J. Am. Chem. Soc.* **1956**, *78*, 5639–5641.
<https://pubs.acs.org/doi/abs/10.1021/ja01602a047>
58. Sizov, A. Yu.; Kolomiets, A. F.; Fokin, A. V. *Russ. Chem. Bull.* **1987**, *36*, 2095–2099.
<https://link.springer.com/article/10.1007/BF00961994>
59. Bartmann, E.; Krause, J. J. *Fluorine Chem.* **1993**, *61*, 117–122.
<https://www.sciencedirect.com/science/article/abs/pii/S0022113900804212>
60. H  gele, G.; Haas, A. J. *Fluorine Chem.* **1996**, *76*, 15–19.
<https://www.sciencedirect.com/science/article/abs/pii/0022113995033467>
61. Fokin, A. V.; Galakhov, V. S.; Uzun, A. T.; Radchenko, V. P.; Stotyarov, V. P. *Russ. Chem. Bull.* **1974**, *23*, 425–427.
<https://link.springer.com/article/10.1007/BF00924706>
62. Kotoris, C. C.; Chen, M.-J.; Taylor, S. D. *J. Org. Chem.* **1998**, *63*, 8052–8057.
<https://pubs.acs.org/doi/abs/10.1021/jo981163x>
63. Chen, M.-J.; Taylor, S. D. *Tetrahedron Lett.* **1999**, *40*, 4149–4152.
<https://www.sciencedirect.com/science/article/abs/pii/S0040403999007327>
64. Xu, Z.-Q.; DesMarteau, D. D. *J. Chem. Soc., Perkin Trans. 1* **1992**, 313–315.
<https://pubs.rsc.org/en/content/articlelanding/1992/p1/p19920000313/unauth#!divAbstract>
65. Gershon, H.; Schulman, S. G.; Spevack, A. D. *J. Med. Chem.* **1967**, *10*, 536–541.
<https://pubs.acs.org/doi/10.1021/jm00316a008>
66. Kosobokov, M. D.; Dilman, A. D.; Levin, V. V.; Struchkova, M. I. *J. Org. Chem.* **2012**, *77*, 5850–5855.
<https://pubs.acs.org/doi/10.1021/jo301094b>
67. Ishikawa, N.; Takaoka, A. EP **1986**/0167179 A1, assigned by Daikin Kogyo Co., Ltd.
68. Knunyants, I. L.; Fokin, A. V.; Komarov, V. A. *Russ. Chem. Bull.* **1966**, *15*, 437–442.
<https://link.springer.com/article/10.1007/BF00846100>
69. Prakash, G. K. S.; Mathew, T.; Panja, C.; Alconcel, S.; Vaghoo, H.; Do, C.; Olah, G. A. *PNAS* **2007**, *104*, 3703–3706.
<https://www.pnas.org/content/104/10/3703>
70. Mir, Q.-C.; Desmarteau, D. D. *J. Fluorine Chem.* **1990**, *48*, 367–377.
<https://www.sciencedirect.com/science/article/abs/pii/S0022113900802225>
71. England, D. C.; Melby, L. R.; Dietrich, M. A.; Lindsey, R. V., Jr. *J. Am. Chem. Soc.* **1960**, *82*, 5116–5122.
<https://pubs.acs.org/doi/abs/10.1021/ja01504a026>
72. Takeuchi, Y.; Kanada, A.; Kawahara, S.; Koizumi, T. *J. Org. Chem.* **1993**, *58*, 3483–3485.
<https://pubs.acs.org/doi/pdf/10.1021/jo00065a005>
73. Dilman, A. D.; Levin, V. V. *Mendeleev Commun.* **2015**, *25*, 239–244.
<https://www.sciencedirect.com/science/article/abs/pii/S0959943615001182>
74. Fokin, A. V.; Voronkov, A. N. *Russ. Chem. Bull.* **1979**, *28*, 1775.
<https://link.springer.com/article/10.1007/BF00951025>
75. Tronchet, J. M. J.; Martin, O. R.; *Helv. Chim. Acta* **1977**, *60*, 585–589.
<https://onlinelibrary.wiley.com/doi/abs/10.1002/hlca.19770600231>

76. Møllendal, H.; Samdal, S.; Guillemin, J.-C. *J. Phys. Chem., A*, **2012**, *116*, 1015–1022.
<https://pubs.acs.org/doi/10.1021/jp210932k>
77. Zagipa, B.; Nagura, H.; Fuchigami, T. *J. Fluorine Chem.* **2007**, *128*, 1168–1173.
<https://www.sciencedirect.com/science/article/abs/pii/S0022113907002631>
78. Biermann, U.; Glemser, O.; Knaak, J. *Chem. Ber.* **1967**, *100*, 3789–3794.
<https://chemistry-europe.onlinelibrary.wiley.com/doi/abs/10.1002/cber.19671001137>
79. Sosnovskikh, V. Y.; Usachev, B. I.; Röschenhalter, G.-V. *Tetrahedron* **2002**, *58*, 1375–1379.
<https://www.sciencedirect.com/science/article/abs/pii/S0040402001012315>
80. Chatt, J.; Richards, R. L.; Newman, D. J. *J. Chem. Soc., A* **1968**, 126–128.
<https://pubs.rsc.org/en/content/articlelanding/1968/j1/j19680000126/unauth#!divAbstract>
81. Meller, A.; Ossko, A. *Monatshefte für Chemie* **1969**, *100*, 1187–1194.
<https://link.springer.com/article/10.1007/BF00903450>
82. Meller, A.; Maringgele, W. *Monatshefte für Chemie* **1970**, *101*, 753–761.
<https://link.springer.com/article/10.1007/BF00909894>
83. Diel, B. N.; Deardorff, P. J.; Zelenski, C. M.; Incarvito, C.; Liable-Sands, L.; Rheingold, A. M. *Inorg. Chim. Acta* **2004**, *357*, 3902–3910.
<https://www.sciencedirect.com/science/article/abs/pii/S0020169304004888>
84. Attaway, J. A.; Growth, R. H.; Bigelow, L. A. *J. Am. Chem. Soc.* **1959**, *81*, 3599–3603.
<https://pubs.acs.org/doi/abs/10.1021/ja01523a031>
85. Bishop, B.C.; Hynes, J. B.; Bigelow, L. A. *J. Am. Chem. Soc.* **1964**, *86*, 1827–1830.
<https://pubs.acs.org/doi/abs/10.1021/ja01063a034>
86. Hynes, J.B.; Bishop, B.C.; Bigelow, L.A. *J. Org. Chem.* **1963**, *28*, 2811–2814.
<https://pubs.acs.org/doi/abs/10.1021/jo01045a078>
87. Chambers, W. J.; Tullock, C. W.; Coffman, D. D. *J. Am. Chem. Soc.* **1962**, *84*, 2337–2343.
<https://pubs.acs.org/doi/abs/10.1021/ja00871a014>
88. de Vohringer, C. M.; de Staricco, E. R.; Staricco, E. H. *J. Fluorine Chem.* **1987**, *37*, 29–40.
<https://www.sciencedirect.com/science/article/abs/pii/S0022113900830833>
89. Hynes, J. B.; Austin, T. E. *Inorg. Chem.* **1966**, *5*, 488–489.
<https://pubs.acs.org/doi/abs/10.1021/ic50037a038>
90. Sekiya, A.; DesMarteau, D. D. *J. Am. Chem. Soc.* **1979**, *101*, 7640–7641.
<https://pubs.acs.org/doi/abs/10.1021/ja00519a041>
91. Sekiya, A.; DesMarteau, D. D. *Inorg. Chem.* **1981**, *20*, 1–3.
<https://pubs.acs.org/doi/pdf/10.1021/ic50215a001>
92. Waterfeld, A.; Mews, R. *J. Chem. Soc., Chem. Commun.* **1982**, 839–840.
<https://pubs.rsc.org/en/content/articlelanding/1982/C3/C39820000839#!divAbstract>
93. Waterfeld, A.; Geisel, M.; Mews, R. *J. Fluorine Chem.* **1982**, *21*, 58.
<https://www.sciencedirect.com/science/article/abs/pii/S0022113900854226>
94. Chang, S. C.; DesMarteau, D. D. *Inorg. Chem.* **1983**, *22*, 805–809.
<https://pubs.acs.org/doi/abs/10.1021/ic00147a020>
95. O'Brien, B. A.; DesMarteau, D. D. *J. Org. Chem.* **1984**, *49*, 1469–1471.
<https://doi.org/10.1021/jo00182a040>
96. Bauknight, C.W.; DesMarteau, D. D., Jr. *J. Am. Chem. Soc.* **1990**, *112*, 728–733.
<https://pubs.acs.org/doi/pdfplus/10.1021/ja00158a035>

97. Fokin, A. V.; Studnev, Yu. N.; Rapkin, A. I.; Kuznetsova, L. D.; Komarov, V. A. *Russ. Chem. Bull.* **1976**, *25*, 472–475.
98. Fokin, A. V.; Studnev, Yu. N.; Rapkin, A. I.; Krotovich, I. N.; Verenikin, O. V. *Russ. Chem. Bull.* **1981**, *30*, 1953–1955.
<https://link.springer.com/article/10.1007/BF00963434>
99. Elvidge, J. A.; Zaidi, N. A. *J. Chem. Soc., C* **1968**, 2188–2198.
<https://pubs.rsc.org/en/content/articlelanding/1968/j3/j39680002188/unauth#!divAbstract>
100. Elworthy, T. R.; Morgans D. J., Jr.; Palmer, W. S.; Repke, D. B.; Smith, D. B.; Waltos, A. M. *Tetrahedron Lett.* **1994**, *35*, 4951–6954.
<https://www.sciencedirect.com/science/article/abs/pii/S0040403900732904>
101. Patrick, T. B.; Hosseini, S.; Bains, S. *Tetrahedron Lett.* **1990**, *31*, 179–182.
<https://www.sciencedirect.com/science/article/abs/pii/S0040403900943648>
102. Koos, M.; Mosher, H. S. *Tetrahedron* **1993**, *49*, 1541–1546.
<https://www.sciencedirect.com/science/article/abs/pii/S0040402001803410>
103. Wai, J. S.; Fisher, T. E.; Embrey, M.W. *Tetrahedron Lett.* **1995**, *36*, 3461–3464.
<https://www.sciencedirect.com/science/article/abs/pii/004040399500635P>
104. Chen, A.; Savage, I.; Thomas, E. J.; Wilson, P. D. *Tetrahedron lett.* **1993**, *34*, 6769–6772.
<https://www.sciencedirect.com/science/article/abs/pii/S0040403900616970>
105. Nakajima, N.; Saito, M.; Ubukata, M. *Tetrahedron Lett.* **1998**, *39*, 5565–5568.
<https://www.sciencedirect.com/science/article/abs/pii/S0040403998011216>
106. Nakajima, N.; Saito, M.; Kudo, M.; Ubukata, M. *Tetrahedron* **2002**, *58*, 3579–3588.
<https://www.sciencedirect.com/science/article/abs/pii/S0040402002003058>
107. Fotadar, U.; Becu, C.; Borremans, F. A. M.; Anteunis, M. J. O. *Tetrahedron* **1978**, *34*, 3537–3544.
<https://www.sciencedirect.com/science/article/abs/pii/0040402078884294>
108. Triggle, D. J.; Belleau, B. *Can. J. Chem.* **1962**, *40*, 1201–1215.
<https://www.nrcresearchpress.com/doi/pdf/10.1139/v62-183>
109. Nerdel, F.; Buddrus, J.; Scherowsky, G.; Klamann, D.; Fligge, M. *Liebigs. Ann.* **1967**, *710*, 85–89.
<https://chemistry-europe.onlinelibrary.wiley.com/doi/abs/10.1002/jlac.19677100110>
110. Durrell, W. S.; Young, J. A.; Dresdner, R. D. *J. Org. Chem.* **1963**, *28*, 831–833.
<https://pubs.acs.org/doi/abs/10.1021/jo01038a060>
111. Narula, P. M.; Day, C. S.; Powers, B. A.; Odian, M. A.; Lachgar, A.; Pennington, W. T.; Nofle, R. E. *Polyhedron* **1999**, *18*, 1751–1759.
<https://www.sciencedirect.com/science/article/abs/pii/S0277538799000558>
112. Brown, H. C.; Schum, P. D. *J. Org. Chem.* **1963**, *28*, 1122–1127.
<https://pubs.acs.org/doi/abs/10.1021/jo01039a064>
113. Bissell, E. R. *J. Org. Chem.* **1963**, *28*, 1717–1720.
<https://pubs.acs.org/doi/abs/10.1021/jo01041a516>
114. Dols, P. P. M. A.; Folmer, B. J. B.; Hamersma, H.; Kuil, C. W.; Lucas, H.; Ollero, L.; Rewinkel, J. B. M.; Hermkens P. H. H. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 1461–1467.
<https://www.sciencedirect.com/science/article/abs/pii/S0960894X07015247>
115. John, E. O.; Shreeve, J. M. Private communication, cited in Emeléus, H. J.; Shreeve, J. M.; Verma, R. D. *Adv. Inorg. Chem.* **1989**, *33*, 139–196.
<https://www.sciencedirect.com/science/article/abs/pii/S0898883808601956>
116. Goldberg, K.; Clarke, D. S.; Scott, J. S. *Tetrahedron Lett.* **2014**, *55*, 4433–4436.

- <https://www.sciencedirect.com/science/article/abs/pii/S0040403914009988>
117. Palacios, F.; Ochoa de Retana, A. M.; Pascual, S.; López de Munain, R.; Oyarzabal, J.; Ezpeleta, J. M. *Tetrahedron* **2005**, *61*, 1087–1094.
<https://www.sciencedirect.com/science/article/abs/pii/S0040402004019775>
118. Sosnovskikh, V. Y.; Mel'nikov, M. Y.; Kutsenko, V. A. *Russ. Chem. Bull.* **1996**, *45*, 1777–1778.
119. Dorokhov, V. A.; Komkov, A. V.; Vasil'ev, L. S.; Azarevich, O. G.; Gordeev, M. F. *Russ. Chem. Bull.* **1991**, *40*, 2311–2313.
<https://link.springer.com/article/10.1007/BF00961059>
120. Dorokhov, V. A.; Vasil'ev, L. S.; Surzhikov, F. E.; Bogdanov, V. S. *Russ. Chem. Bull.* **1995**, *44*, 1283–1285.
<https://link.springer.com/article/10.1007/BF00700905>
121. Sing, Y. L.; Lee, L. F. *J. Heterocyclic Chem.* **1989**, *26*, 7–9.
<https://onlinelibrary.wiley.com/doi/abs/10.1002/jhet.5570260102>
122. Aisikowitsch, A. J.; Saripolva, F. F. *Zh. Org. Khim.* **1984**, *22*, 1564, cited in Carreira, E. M. *et al.* (Ed.), *Product Class 12: Pyrimidines. Science of Synthesis: Knowledge Updates 2011/1*, 1st Edition, Thieme, **2011**.
<https://www.thieme-connect.de/products/ebooks/lookinside/10.1055/sos-SD-116-00063>
123. Burger, K.; Hein, F.; Wassmuth, U.; Krist, H. *Synthesis* **1981**, 904–905.
<https://www.thieme-connect.com/products/ejournals/abstract/10.1055/s-1981-29643>
124. Burger, K.; Waßmuth, U.; Hein, F.; Rottegger S. *Liebigs Ann. Chem.* **1984**, 991–1002.
<https://chemistry-europe.onlinelibrary.wiley.com/doi/abs/10.1002/ilac.198419840517>
125. Lee, L. F.; Normansell, J. E. *J. Org. Chem.* **1990**, *55*, 2964–2967.
<https://pubs.acs.org/doi/10.1021/jo00296a077>
126. Sing, Y. L.; Lee, L. F. *J. Org. Chem.* **1985**, *50*, 4642.
<https://pubs.acs.org/doi/abs/10.1021/jo00223a045>
127. Bergmann, E. D.; Cohen, S.; Hoffman, E.; Rand-Meir, Z. *J. Chem. Soc.* **1961** 3452–3457.
<https://pubs.rsc.org/en/content/articlelanding/1961/jr/jr9610003452#!divAbstract>
128. Feigl, D. M.; Mosher, H. S. *J. Org. Chem.* **1968**, *33*, 4242–4245.
<https://pubs.acs.org/doi/abs/10.1021/jo01275a047>
129. Vovk, M. V.; Bol'but, A. V.; Lebed', P. S.; Mel'nichenko, N. V. *Russ. J. Org. Chem.* **2007**, *43*, 928–929.
<https://link.springer.com/article/10.1134/S1070428007060231>
130. Raja, E. K.; Klumpp, D. A. *Tetrahedron Lett.* **2011**, *52*, 5170–5172.
<https://www.sciencedirect.com/science/article/abs/pii/S0040403911012639>
131. Gerhart, F.; François, J.-P.; Kolb, M.; Laskovics, M.; Le Borgne J.-F. *J. Fluorine Chem.* **1990**, *50*, 243–249.
<https://www.sciencedirect.com/science/article/abs/pii/S0022113900804996>
132. Bey, P.; Gerhart, F.; Van Dorsselaer, V.; Danzin, C. *J. Med. Chem.* **1983**, *26*, 1551–1556.
<https://pubs.acs.org/doi/abs/10.1021/jm00365a002>
133. Rassukana, Y. V.; Yelenich, I. P.; Synytsya, A. D.; Onys'ko, P. P. *Tetrahedron* **2014**, *70*, 2928–2937.
<https://www.sciencedirect.com/science/article/abs/pii/S0040402014003500>
134. Rassukana, Y. V.; Yelenich, I. P.; Bezdudny, A. V.; Mironov, V. F.; Onys'ko, P. P. *Tetrahedron Lett.* **2014**, *55*, 4771–4773.
<https://www.sciencedirect.com/science/article/abs/pii/S0040403914011587>
135. Rassukana, Y. V.; Stanko, O. V.; Onys'ko, P. P. *J. Fluorine Chem.* **2019**, *219*, 123–128.
<https://www.sciencedirect.com/science/article/abs/pii/S0022113918305013>
136. Palacios, F. Alonso, C. Rubiales, G. Villegas M. *Tetrahedron Lett.* **2004**, *45*, 4031–4034.

- <https://www.sciencedirect.com/science/article/abs/pii/S0040403904007336>
137. Palacios, F.; Alonso, C.; Rodríguez, M. de Marigorta, E.M.; Rubiales, G. *Eur. J. Org. Chem.* **2005** 1795–1804.
<https://chemistry-europe.onlinelibrary.wiley.com/doi/abs/10.1002/ejoc.200400770>
138. Janz, G. J.; Monahan, A. R. *J. Org. Chem.* **1964**, 29, 569–571.
<https://pubs.acs.org/doi/abs/10.1021/jo01026a011>
139. Monahan, A. R.; Perettie, D. J.; Janz, G. J. *Tetrahedron Lett.* **1968**, 9, 3955–3958.
<https://www.sciencedirect.com/science/article/abs/pii/S0040403900723756>
140. Feast, W. J.; Hughes, R. R.; Musgrave, W. K. R. *J. Fluorine Chem.* **1977**, 9, 271–278.
<https://www.sciencedirect.com/science/article/abs/pii/S0022113900825440>
141. Vasil'ev, N. V.; Truskanova, T. D.; Buzaev, A. V.; Romanov, D. V.; Zatonskii, G. V. *Russ. Chem. Bull.* **2005**, 54, 1038–1040.
<https://link.springer.com/article/10.1007/s11172-005-0353-x>
142. Petrov, V. A.; Davidson, F.; Marshall, W. J. *Fluorine Chem.* **2004**, 125, 1621–1628.
<https://www.sciencedirect.com/science/article/abs/pii/S0022113904002337>
143. Petrov, V. A.; Vasil'ev, N. V. *Curr. Org. Synth.* **2006**, 3, 215–259.
<https://www.eurekaselect.com/56955/article/synthetic-chemistry-quadricyclane>
144. Hees, U.; Ledermann, M.; Regitz, M. *Synlett* **1990**, 401–403.
<https://www.thieme-connect.com/products/ejournals/abstract/10.1055/s-1990-21106>
145. Derstine, C. W.; Smith, D. N.; Katzenellenbogen, J. A. *Tetrahedron Lett.* **1997**, 38, 4359–4362.
<https://www.sciencedirect.com/science/article/abs/pii/S0040403997009349>
146. Fields, R.; Tomlinson, J. P. *J. Fluorine Chem.* **1979**, 13, 19–28.
<https://www.sciencedirect.com/science/article/abs/pii/S0022113900829899>
147. Banks, R. E.; Hitchen, S. M. *J. Fluorine Chem.* **1982**, 20, 373–384.
<https://www.sciencedirect.com/science/article/abs/pii/S0022113900822307>
148. Crossman, J. M.; Haszeldine, R. N.; Tipping A. E. *J. Chem. Soc., Dalton Trans.* **1973**, 483–486.
<https://pubs.rsc.org/en/content/articlelanding/1973/dt/dt9730000483#!divAbstract>
149. Norris, W. P. *J. Org. Chem.* **1962**, 27, 3248–3251.
<https://pubs.acs.org/doi/10.1021/jo01056a062>
150. Fokin, A.V.; Studnev, Yu.N.; Rapkin, A.I.; Komarov, V.A.; Verenikin O.V.; Potarina, T. M. *Russ. Chem. Bull.* **1981**, 30, 1285–1288.
<https://link.springer.com/article/10.1007%2F01417990>
151. Lucas, T.; Dietz, J.-P.; Opatz, T. *Beilstein J. Org. Chem.* **2020**, 16, 445–450.
<https://www.beilstein-journals.org/bjoc/content/pdf/1860-5397-16-41.pdf>
152. Patrick, T.B.; Nadj, S. *J. Fluorine Chem.* **1990**, 49, 147–150.
<https://www.sciencedirect.com/science/article/abs/pii/S0022113900803711>
153. van Steenis, J. H.; van den Nieuwendijk A. M. C. H.; van der Gen, A. J. *Fluorine Chem.* **2004**, 125, 107–117.
<https://www.sciencedirect.com/science/article/abs/pii/S0022113903003117>
154. Baader, E.; Bartmann, W.; Beck, G.; Below, P.; Bergmann, A.; Jendralla, H.; Keßeler, K.; Wess, G. *Tetrahedron Lett.* **1989**, 30, 5115–5118.
<https://www.sciencedirect.com/science/article/abs/pii/S0040403901934628>
155. Pirrung, M. C.; Rowley, E. G.; Holmes, C. P. *J. Org. Chem.* **1993**, 58, 5683–5689.
<https://pubs.acs.org/doi/abs/10.1021/jo00073a029>

156. Kosobokov, M. D.; Struchkova, M. I.; Arkhipov, D. E.; Korlyukov, A. A.; Dilman, A. D. *J. Fluorine Chem.* **2013**, *154*, 73–79.
<https://www.sciencedirect.com/science/article/abs/pii/S0022113913002455>
157. Kosobokov, M. D.; Struchkova, M. I.; Dilman, A. D. *Russ. Chem. Bull.* **2014**, *63*, 549–551.
<https://link.springer.com/article/10.1007/s11172-014-0468-z>
158. Odenthal, N. L.; Leverkusen, A.; Monheim, A. M. US **2012**/8242311 B2, assigned by Bayer Cropscience AG.
159. Bland, W. J.; Kemmitt, R. D. W.; Nowell, I. W.; Russell, D. R. *Chem. Commun.* **1968**, 1065–1066.
<https://pubs.rsc.org/en/Content/ArticleLanding/1968/C1/C19680001065#!divAbstract>
160. Gac, N. A.; Janz, G. J. *Phys. Inorg. Chem.* **1964**, *86*, 5059–5063.
<https://pubs.acs.org/doi/pdf/10.1021/ja01077a001>
161. Flannery, J. B.; Janz, G. J. *J. Am. Chem. Soc.* **1966**, *88*, 5097–5103.
<https://pubs.acs.org/doi/abs/10.1021/ja00974a009>

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.

This paper is an open access article distributed under the terms of the Creative Commons Attribution (CC BY) license (<http://creativecommons.org/licenses/by/4.0/>)