**Univerzita Karlova**

**Přírodovědecká fakulta**

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# Azidoperfluoroalkany: Syntéza a Aplikace
# Azidoperfluoroalkanes: Synthesis and Application

Disertační práce

Školitel: Ing. Petr Beier, Ph.D.

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**Charles University**

**Faculty of Science**

Study programme: Organic Chemistry


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Doctoral thesis

Supervisor: Ing. Petr Beier, Ph.D.

Prague, 2019

**Prohlášení:**

Prohlašuji, že jsem závěrečnou práci zpracovala samostatně a že jsem uvedla všechny použité informační zdroje a literaturu. Tato práce ani její podstatná část nebyla předložena k získání jiného nebo stejného akademického titulu.

V Praze, 08.01.2019.

Podpis

Ask and it will be given to you;
seek and you will find;
knock and the door will be opened to you.
(Matthew 7:7)

# Acknowledgements

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# Abstract

The incorporation of the trifluoromethyl and perfluoroalkyl motifs into organic compounds has been a hot topic in synthetic organofluorine chemistry. There is a plethora of methods for the introduction of the $CF_3$ moiety at carbon, oxygen and sulfur centers. In sharp contrast, methods for synthesizing N-trifluoromethyl and N-perfluoroalkyl compounds are very limited and new approaches are highly sought-after. The scarcity of these compounds prompted us to develop reagents capable of transferring the perfluoroalkyl unit to nitrogen atom. To fulfil this purpose, we have regarded azidoperfluoroalkanes as ideal reagents, therefore, this thesis is concerned with the synthesis and applications of these azides.

The first part describes the preparation of azidoperfluoroalkanes. Upon activation by cesium fluoride, $TMSCF_3$ transfers the trifluoromethyl group to an electrophilic azide to produce the desired azidotrifluoromethane. Longer carbon chain azidoperfluoroalkanes were prepared in a similar way, starting from the corresponding organosilane. A different synthetic strategy was applied for the preparation of azidopentafluoroethane where the perfluoroalkyl anion was generated from pentafluoroethane with $^{n}$BuLi, followed by the addition of tosyl azide. The isolation of these fluorinated azides was accomplished by distillation with a suitable solvent.

The second part showcases the synthetic potential of azidoperfluoroalkanes through various transformations. The azides exhibited good reactivity in the copper(I)-catalyzed azide-alkyne cycloaddition and in the organocatalytic azide-ketone cycloaddition to furnish diverse 1,2,3-triazoles bearing the N-perfluoroalkyl group. At last, protonation of azidotrifluoromethane in superacid is demonstrated. The protonated azide was characterized by low-temperature NMR spectroscopy and the experimental results were validated by computational studies.

# Abstrakt

Zavedení trifluormethylové a perfluoralkylové skupiny do organických molekul představuje jedno z hlavních témat syntetické organofluorové chemie. Existuje řada metod pro zavedení $CF_3$ skupiny na atom uhlíku, kyslíku a síry. Naopak metody pro syntézu N-trifluor-methylovaných a N-perfluoralkylovaných sloučenin jsou velmi omezené a vývoj nových přístupů k jejich syntéze je vysoce žádaný. Nedostatek těchto sloučenin nás vedl k vývoji činidel schopných přenosu perfluoralkylové skupiny na atom dusíku, kde jsme jako vhodná činidla zvolili azidoperfluoralkany. Tato práce se zabývá syntézou a aplikací perfluoralkylazidů.

První část popisuje přípravu azidoperfluoralkanů. Po aktivaci fluoridem cesným může $TMSCF_3$ přenést trifluormethylovou skupinu na elektrofilní azid za vzniku žádaného azidotrifluormethanu. Azidoperfluoralkany s delším uhlíkatým řetězcem byly připraveny podobným způsobem vycházejícím z příslušného organosilanu. Rozdílný syntetický přístup byl použit pro přípravu azidoperfluorethanu, kde byl při reakci pentafluorethanu s $^{n}$BuLi generován perfluorethylový anion, k němuž byl následně přidán tosylazid. Fluorované azidy byly izolovány pomocí destilace s vhodným rozpouštědlem.

Druhá část se zabývá syntetickým potenciálem azidoperfluoralkanů. Tyto azidy vykazovaly velkou reaktivitu v azido-alkynových cykloadicích katalyzovaných měď´nými solemi a v organokatalyzovaných azido-keton cykloadicích za vzniku různých 1,2,3-triazolů nesoucích N-perfluoralkylové skupiny. Závěrečná část práce popisuje protonaci azidotrifluormethanu v superkyselině. Protonovaný azid byl charakterizován pomocí nízkoteplotní NMR spektroskopie a experimentální výsledky byly validovány pomocí výpočetních studií.

# List of publications

**Part of the work described in this thesis has been published or is in preparation**

*Azidoperfluoroalkanes: Synthesis and Application in Copper(I)-Catalyzed Azide–Alkyne Cycloaddition*
Z. E. Blastik, S. Voltrová, V. Matoušek, B. Jurásek, D. W. Manley, B. Klepetářová, P. Beier, *Angew. Chem., Int. Ed.* **2017**, *56*, 346-349.

*Enamine-Mediated Azide-Ketone [3 + 2] Cycloaddition of Azidoperfluoroalkanes*
Z. E. Blastik, B. Klepetářová, P. Beier, *ChemistrySelect* **2018**, *3*, 7045-7048.

*Protonation of Azidomethane and Azidotrifluoromethane in Superacids: Syntheses, Characterization and Structural Studies*
Z. E. Blastik, A. Nirmalchandar, R. Haiges, G. Rasul, T. Saal, A. F. Baxter, G. K. S. Prakash, P. Beier *in preparation*

**Previous work**

*Expanding the Scope of Hypervalent Iodine Reagents for Perfluoroalkylation: From Trifluoromethyl to Functionalized Perfluoroethyl*
V. Matoušek, J. Václavík, P. Hájek, J. Charpentier, Z. E. Blastik, E. Pietrasiak, A. Budinská, A. Togni, P. Beier, *Chem. Eur. J.* **2016**, *22*: 417-424.

**Contributions in form of an oral presentation**

*Azidoperfluoroalkanes: Synthesis and application*
International Symposium on Synthesis and Catalysis (ISySyCat2017), September 2017, University of Évora, Portugal

*Azidoperfluoroalkanes: Synthesis and application*
53rd Advances in Organic, Bioorganic and Pharmaceutical Chemistry (Liblice 2018), November 2018, Hotel Tree of Life, Lázně Bělohrad, Czech Republic

# Abbreviations

| | |
|---|---|
| Å | Ångström |
| APT | attached proton test |
| Ar | aryl |
| br | broad |
| Bn | benzyl |
| Bu | butyl |
| CCDC | Cambridge Crystallographic Data Centre |
| COSY | homonuclear correlation spectroscopy |
| CuAAC | copper-catalyzed azide-alkyne cycloaddition |
| CuMeSal | copper(I) 3-methylsalicylate |
| DBH | 1,3-dibromo-5,5-dimethylhydantoin |
| DBU | 1,8-diazabicyclo(5.4.0)undec-7-ene |
| DCM | dichloromethane |
| Deoxo-Fluor | bis(2-methoxyethyl)aminosulfur trifluoride |
| DFT | density functional theory |
| DIPEA | *N*,*N*-diisopropylethylamine |
| DMF | *N*,*N*-dimethylformamide |
| DMSO | dimethylsulfoxide |
| EI | electron impact ionization |
| equiv | equivalent(s) |
| ESI | electrospray ionization |
| ESR | electron spin resonance spectroscopy |
| Et | ethyl |
| *et al.* | et alii (Latin), and others |
| EtOAc | ethyl acetate |
| HMBC | heteronuclear multiple bond correlation spectroscopy |
| HMDS | bis(trimethylsilyl)amine |
| HRMS | high-resolution mass spectrometry |

| | |
|---|---|
| HSQC | heteronuclear single quantum correlation spectroscopy |
| GIAO-CCSD(T) | gauge invariant atomic orbitals, coupled-cluster singles and doubles |
| LDA | lithium diisopropylamide |
| MCPBA | 3-chloroperbenzoic acid |
| Me | methyl |
| m.p. | melting point |
| MP2 | Møller-Plesset perturbation theory of the second order |
| NBS | *N*-bromosuccinimide |
| Nf | nonafluorobutanesulfonyl, nonaflyl |
| NHC | N-heterocyclic carbene |
| NIS | *N*-iodosuccinimide |
| NMR | nuclear magnetic resonance |
| ORTEP | Oak Ridge thermal ellipsoid plot |
| Ph | phenyl |
| Pr | propyl |
| $R_f$ | retention factor |
| rt | room temperature |
| RuAAC | ruthenium-catalyzed azide-alkyne cycloaddition |
| SSA | silica sulfuric acid |
| SPAAC | strain-promoted azide-alkyne cycloaddition |
| TBAA | tetrabutylammonium acetate |
| TBAF | tetrabutylammonium fluoride |
| TBAT | tetrabutylammonium difluorotriphenylsilicate |
| TBDMSCl | *tert*-butyldimethylsilyl chloride |
| TDAE | tetrakis(dimethylamino)ethylene |
| THF | tetrahydrofuran |
| TLC | thin layer chromatography |
| TMAF | tetramethylammonium fluoride |
| TMS | trimethylsilyl |
| Ts | *p*-toluenesulfonyl, tosyl |
| UV-Vis | ultraviolet-visible spectrophotometry |

# Contents

# 1 Introduction

## 1.1. General introduction

Organofluorine chemistry has received an increasing attention in recent years. The incorporation of fluorine into organic molecules often imparts unique properties which are desirable for a wide range of applications. Being the most electronegative element in the periodic table with a relatively small size, fluorine is capable to form one of the strongest bonds known in chemistry with carbon.

Long after the first synthesis of hydrofluoric acid by Marggraf in 1764 and the isolation of elemental $F_2$ by Moissan in 1886,[1,2] the field of fluorine chemistry started to expand as safe and selective fluorinating and fluoroalkylating reagents were increasingly introduced to the chemical community. This introductory chapter will focus on one specific branch of the organofluorine chemistry, namely the introduction of the trifluoromethyl group on nitrogen centers. The introduction will eventually lead to the core of this dissertation which is to provide a way to novel fluorinated building blocks to give access to rare N-perfluoroalkyl derivatives.

## 1.2. N-Trifluoromethylation and perfluoroalkylation

There is a long history of incorporation of the trifluoromethyl group into various organic compounds. Over the decades, numerous research groups have contributed to the development of new synthetic methodologies, efficient fluorinating and fluoroalkylating reagents, and well-designed catalysts for the installation of the $CF_3$ moiety.[3–8] There is a wealth of methods for the introduction of the $CF_3$ group at carbon atoms. In contrast, the synthetic accessibility to heteroatom-bound $CF_3$ derivatives (including $OCF_3$,[6,9] $SCF_3$,[5,6,10] and $NCF_3$ derivatives[6,11]) is significantly lower. Since this thesis is mainly concerned with the synthesis of N-trifluoromethyl and perfluoroalkyl compounds, the purpose of this chapter is to provide an overview of the existing synthetic methods for their preparation.

In general, these methods fall into two main categories based on the type of bond formation: direct and indirect methods (Scheme 1). Direct N-trifluoromethylation reactions can be achieved in a nucleophilic, radical or electrophilic fashion by using different $CF_3$ transfer reagents. In contrast, indirect methods would essentially mean functional group interconversion by fluorinating an already installed carbon center.

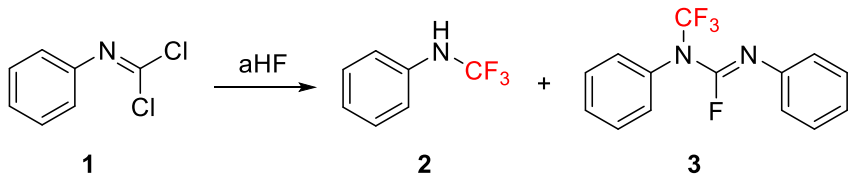

**Scheme 1** Direct and indirect strategies for N-trifluoromethylation.

## 1.2.1. Indirect methods – functional group interconversion

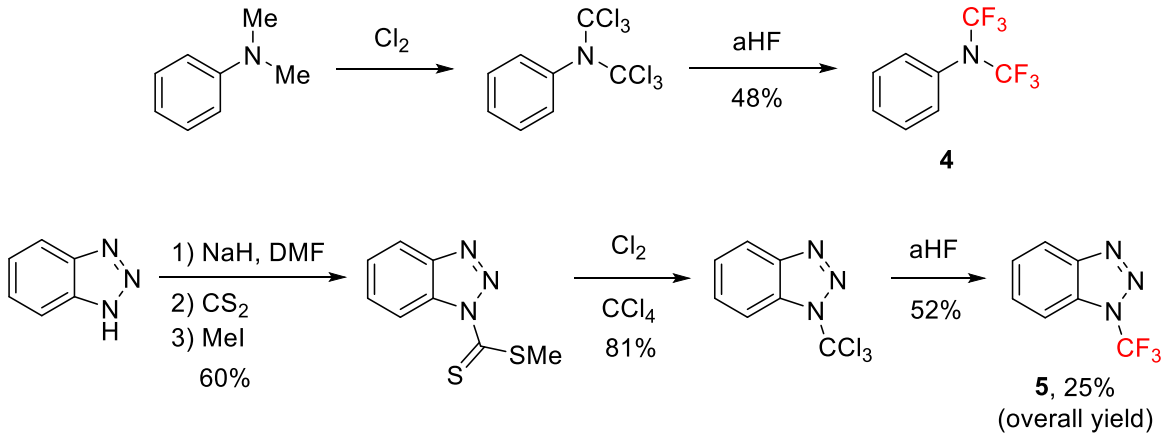
The introduction of the trifluoromethyl group *via* functional group interconversion inherently requires pre-functionalization of the compound. The three main synthetic pathways include the halogen exchange reaction of trihalomethyl or dihalomethylene substrates, the fluorination of N-carbonyl or N-thiocarbonyl amines, and fluorination of compounds *via* the isocyanide difluoride intermediate.

### a. Halogen-exchange reaction

One of the earliest approaches for the synthesis of trifluoromethylamines was reported by Petrov in 1959.[12] Using anhydrous hydrofluoric acid as a reactive fluorine source, phenyl isocyanide dichloride (**1**) can undergo a Cl-F exchange to give *N*-trifluoromethylaniline (**2**) (Scheme 2). The yield was disappointingly low due to the competing polymerization reaction. Later, the same synthetic strategy was applied to convert various isocyanide dichlorides and N-trichloromethyl compounds to the fluorinated counterparts (see selected examples in Scheme 2).[13–16]

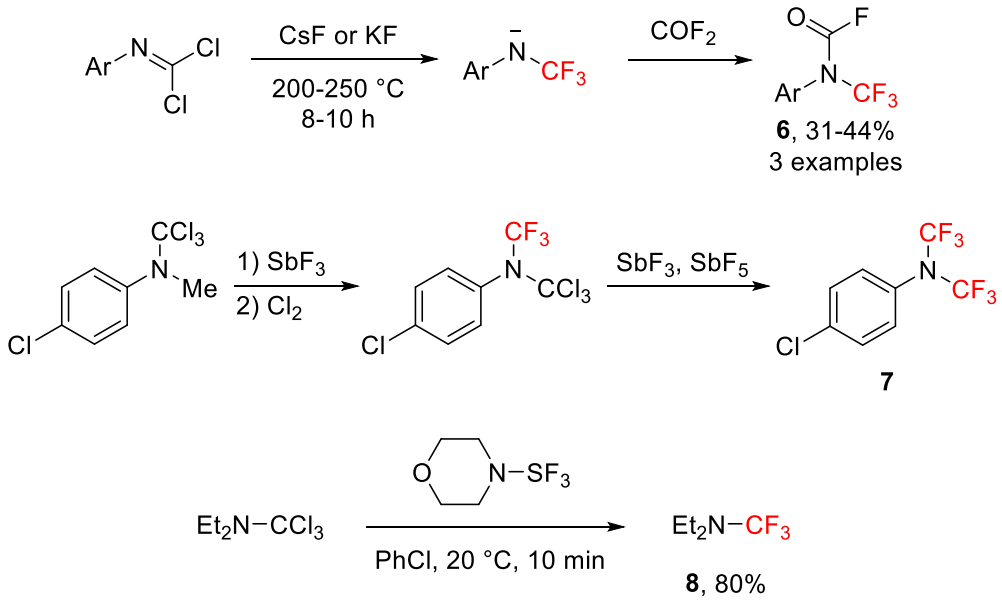



**1** **2** **3**




**Scheme 2** Selected examples of the halogen-exchange reaction using anhydrous HF.[12,14,16]

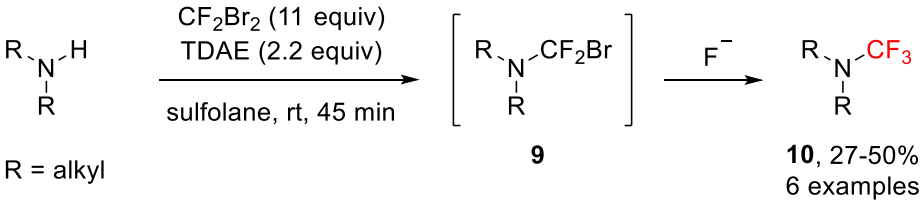
The halogen-exchange (halex) reaction could be accomplished with other fluorinating reagents as it was shown by the research groups of Sheppard, Yagupolskii and Markovski.[17–20] Inorganic fluoride salts, antimony trifluoride and dialkylaminosulfur trifluorides can be equally used to substitute chlorine atoms by fluorine in various chlorinated compounds (Scheme 3).




**Scheme 3** Various fluorinating reagents employed in the halex reaction.[17–19]

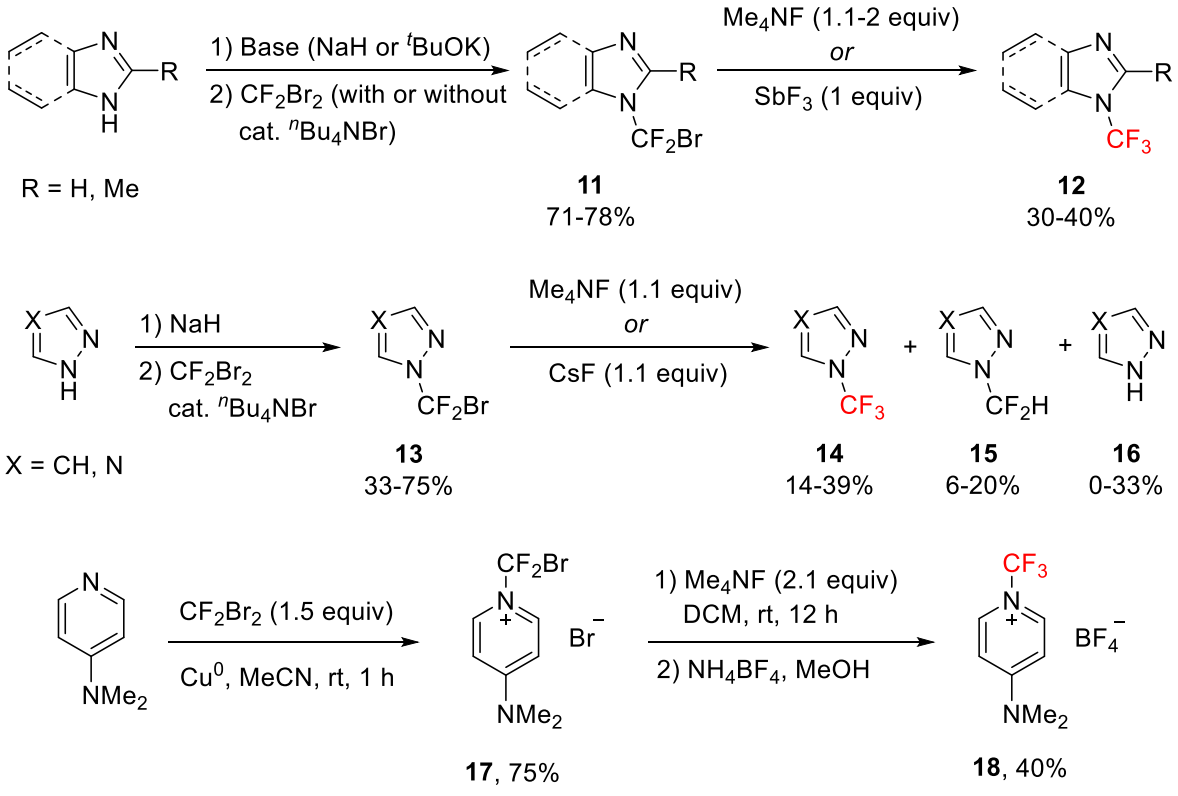
A very common synthetic route is the fluorination of a pre-installed $CF_2Br$ moiety. Pawelke found that secondary amines can be converted into the corresponding N-trifluoromethylated amines using the mixture of $CF_2Br_2$ and tetrakis(dimethylamino)ethylene

(TDAE).[21] The bromodifluoromethylamine (**9**) was generated *in situ* and readily reacted with fluoride to furnish the product (**10**) in modest yield as shown in Scheme 4.




**Scheme 4** Trifluoromethylation of dialkyl amines *via* the $CF_2Br$ intermediate.[21]

Later, the concept of bromodifluoromethylating the N-H bond and fluorinating the resulting N-$CF_2Br$ derivative was applied for the synthesis of N-heterocycles bearing the $CF_3$ functionality. Imidazoles,[16,22,23] pyrazoles,[23] 1,2,4-triazoles[23] and even pyridine[24] were successfully N-trifluoromethylated in this manner by the groups of Yagupolskii and Kolomeitsev (Scheme 5). Interestingly, they also observed the formation of the N-$CF_2H$ and the N-H derivatives (**15** and **16**) in some cases.

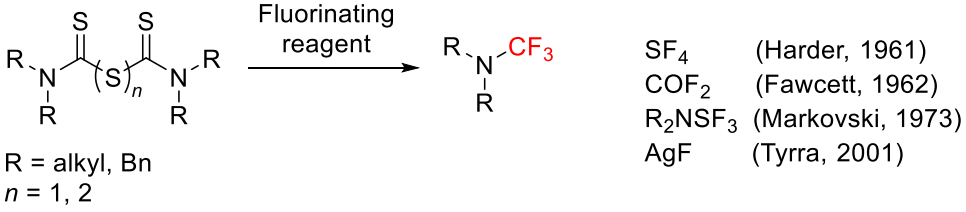



**Scheme 5** Bromodifluoromethylation and subsequent fluorination of N-heterocycles.[16,22–24]

## b. Oxidative desulfurization-fluorination of N-thiocarbonyl amines

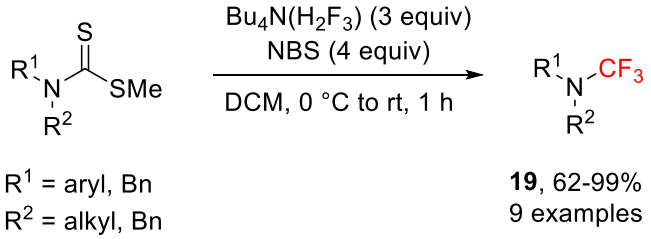
Another approach is the nucleophilic fluorination of N-thiocarbonyl amines. First, the amine has to be functionalized to dithiocarbamoyl (di)sulfides, alkyl dithiocarbamates, thiocarbonyl fluorides or thiocarbonyl amides. Using a suitable fluorinating reagent, the sulfur-containing group is readily transformed into the trifluoromethyl group.

Fluorination of dithiocarbamoyl (di)sulfides dates back to the 1960s when Harder used $SF_4$ to form N-$CF_3$ derivatives (Scheme 6).[25] Sulfur tetrafluoride has been used as a powerful fluorinating reagent, however, it has the drawback of being a highly toxic gas. Thiuramide (di)sulfides can also be fluorinated by carbonyl fluoride,[26] dialkylaminosulfur trifluorides[27] or silver fluoride[28] as depicted in Scheme 6. The latter two reagents are non-toxic, more convenient to handle and allow mild reaction conditions for the preparation of N-trifluoromethylamines.



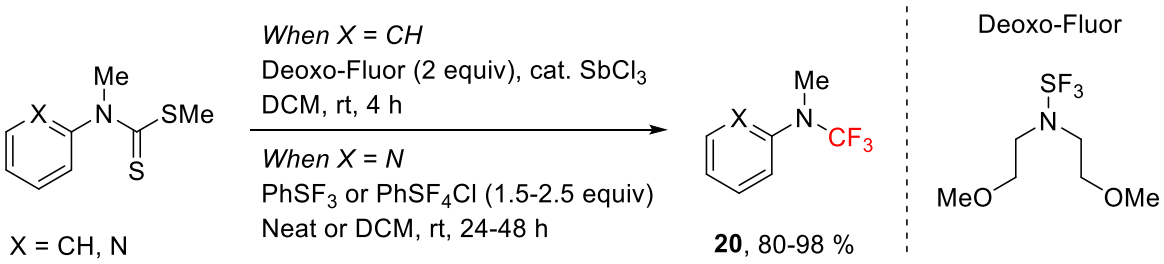

**Scheme 6** Fluorination of dithiocarbamoyl (di)sulfides.[25–28]

Dithiocarbamates can also serve as substrate precursors for the synthesis of N-trifluoromethylated compounds. This transformation was first reported by Hiyama who used tetrabutylammonium dihydrogen trifluoride, as a mild fluoride source, in combination with oxidizing reagents such as NBS, NIS or DBH (1,3-dibromo-5,5-dimethylhydantoin).[29] Under mild reaction conditions, N-trifluoromethylated products (**19**) were obtained in good to excellent yields as shown in Scheme 7. The process is often referred to as oxidative desulfurization-fluorination which is an efficient way to access trifluoromethylamines. In the same fashion, other thiocarbonyl-functionalized amines were also fluorodesulfurized.[30–33]



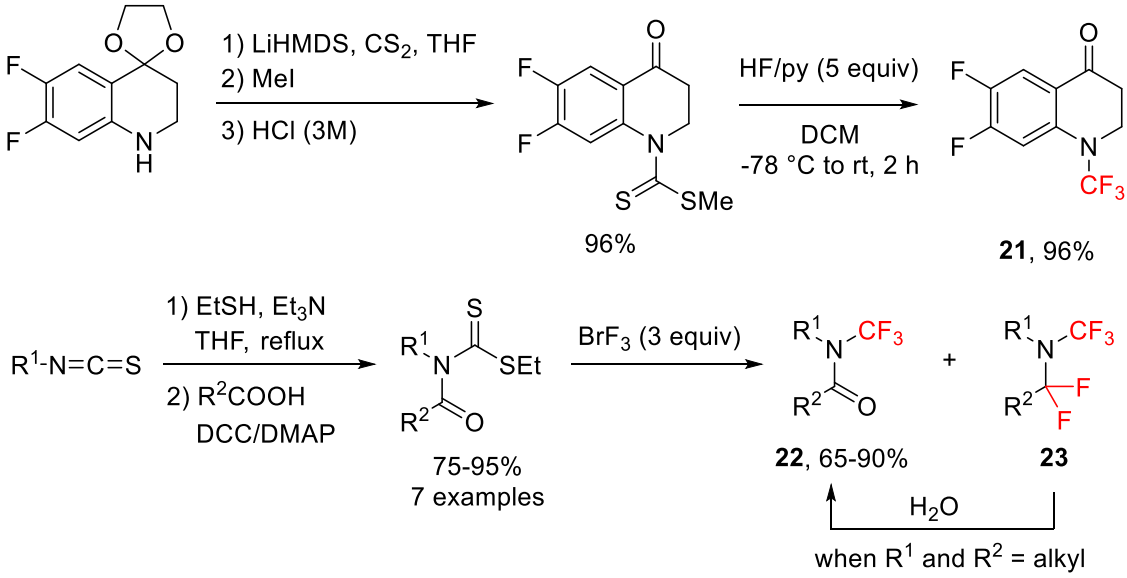

**Scheme 7** Oxidative fluorodesulfurization of dithiocarbamates.[29]

Alternatively, a good number of other fluorinating reagents have been successfully employed in the fluorodesulfurization reaction of dithiocarbonyl compounds as shown in Scheme 8. The Evans group showed that Deoxo-Fluor, a dialkylaminosulfur trifluoride with enhanced thermal stability, is a suitable reagent in this transformation.[34] $PhSF_3$ and $PhSF_4Cl$ were also competent in transforming the thiocarbonyl group to the trifluoromethyl group in hetaryl amines.[35]



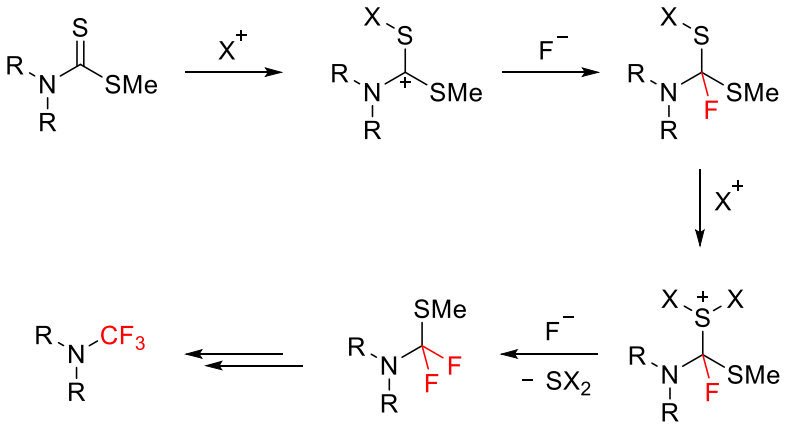

**Scheme 8** Fluorodesulfurization of aryl and hetaryl dithiocarbamates.[34,35]

Furthermore, $BrF_3$ and its complex with pyridine,[36,37] and HF-amine complexes[29,38] (e.g. HF/pyridine also known as Olah's reagent) were also exploited as valuable fluorination reagents in the preparation of trifluoromethylamines (Scheme 9).




**Scheme 9** Installation of the dithiocarbonyl group followed by fluorination.[36,38]

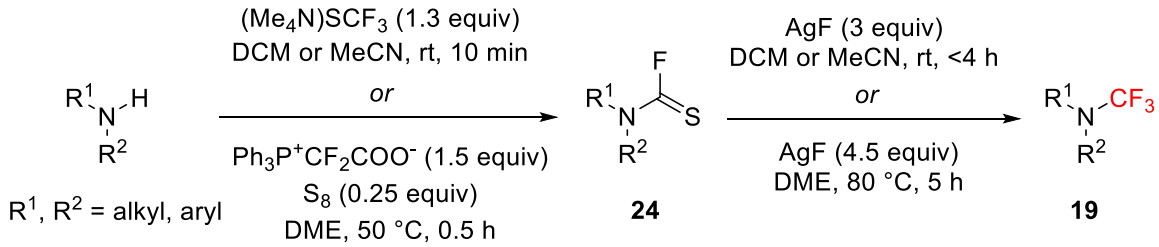
The proposed mechanism for the fluorodesulfurization is depicted in Scheme 10 . The first step is the electrophilic addition of the halonium ion to the thiocarbonyl compound. Next, the nucleophilic attack of the fluoride ion occurs to generate a monofluorinated intermediate. The corresponding sulfur center is converted into a good leaving group by the halonium ion, followed by the attack of another fluoride ion to form a difluorinated intermediate. By repeating these two steps, the reaction is finally completed, furnishing the trifluoromethylamine.




**Scheme 10** Proposed mechanism for the fluorodesulfurization of N-thiocarbonyl amines.

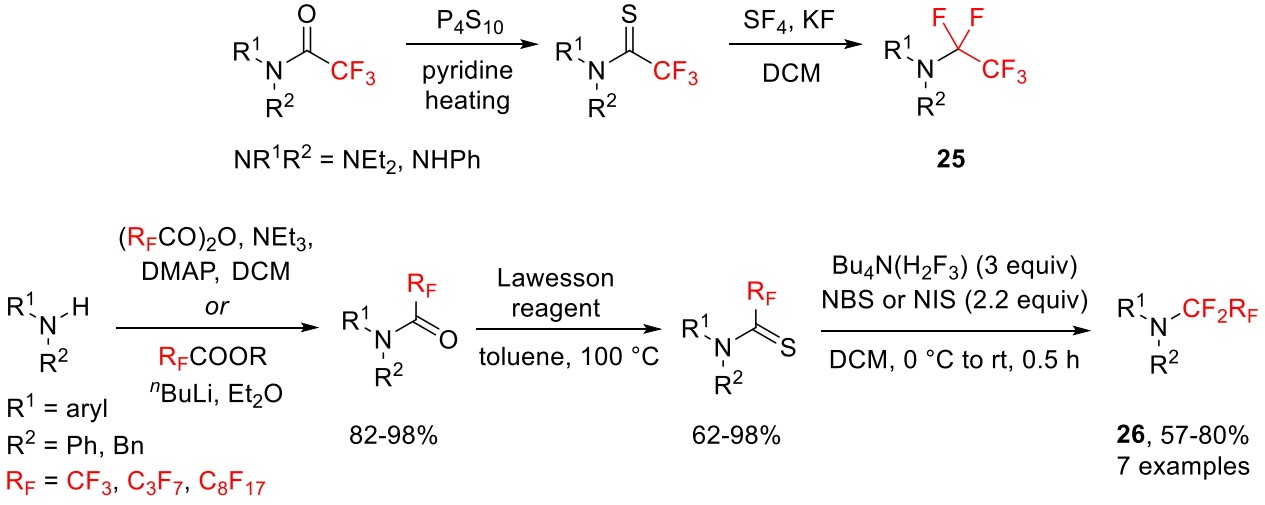
Many of these approaches suffer from harsh reaction conditions, the use of hazardous and often difficult-to-handle fluorinating reagents, and the inherent need of pre-functionalization. The use of many above-mentioned fluorinating reagents results in a rather limited functional group tolerance which necessitates the early-stage introduction of the trifluoromethyl group at the nitrogen atom.

One of the most recent approaches in the functional group interconversion realm is the fluorination of thiocarbonyl fluoride. Starting from secondary amines, the thiocarbonyl fluoride **24** is generated *in situ* and subsequently fluorinated to the corresponding trifluoromethylamines **19** in one pot (Scheme 11). Schoenebeck and co-workers reported the use of bench-stable $(Me_4N)SCF_3$ salt to install the thiocarbonyl functional group and silver fluoride in the next step to complete the synthesis.[39] Using the same strategy, Xiao *et al.* could show that the thiocarbonyl fluoride intermediate **24** can be also made from the reaction of secondary amines with a difluorocarbene precursor in the presence of elemental sulfur.[40] These methods are fast and mild, operationally simple and functional group tolerant, providing an elegant means to late-stage trifluoromethylation of secondary amines.




**Scheme 11** Recent approaches to trifluoromethylamines *via* the thiocarbonyl fluoride intermediate.[39,40]

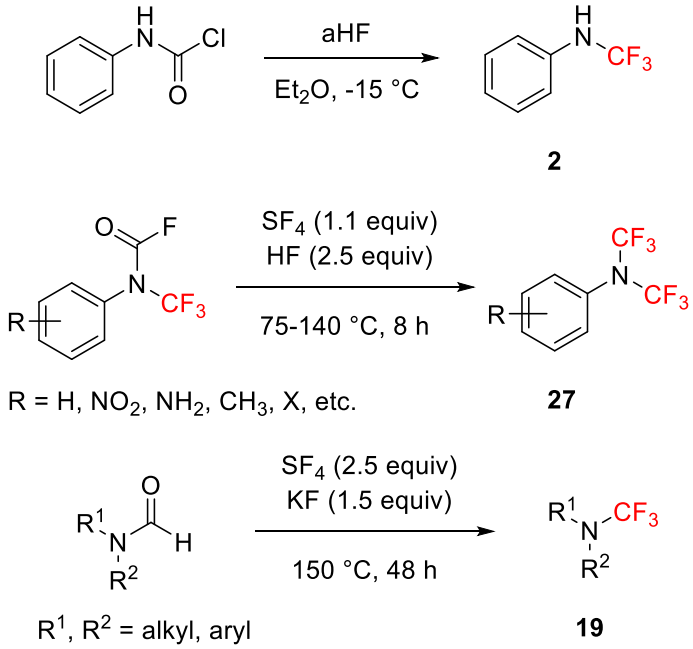
The oxidative desulfurization-fluorination of perfluoroalkyl thioamides was accomplished by Yagupolskii and Hiyama, by using $SF_4$ in the presence of KF or $Bu_4N(H_2F_3)$ with an oxidant (Scheme 12).[41,42] This method enables the preparation of longer carbon chain perfluoroalkylamines (**25** and **26**).




**Scheme 12** Preparation of perfluoroalkylamines from the corresponding thioamides.[41,42]

## c. Deoxyfluorination of acyl halides and formamides

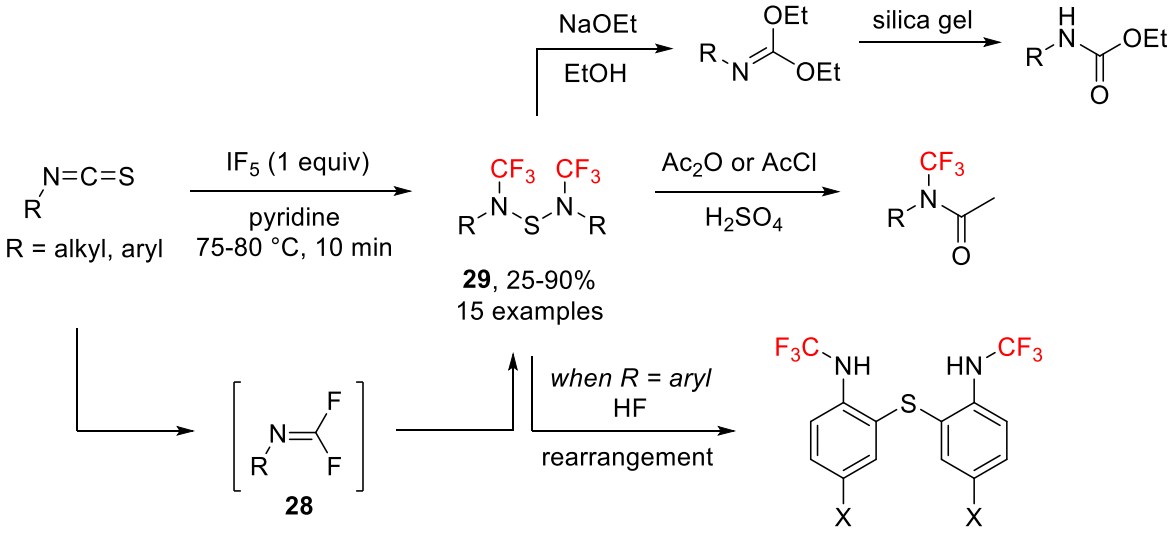
Carbonyl functional groups can also be converted to the $CF_3$ group as it was shown by Petrov, Fawcett and Dmowski.[12,43,44] Fluorination of acyl halides and formamides was achieved by treatment of the carbonyl derivative with hydrogen fluoride or sulfur tetrafluoride in the presence of HF or KF (Scheme 13).




**Scheme 13** Deoxyfluorination of acyl halides and formamides.[12,43,44]

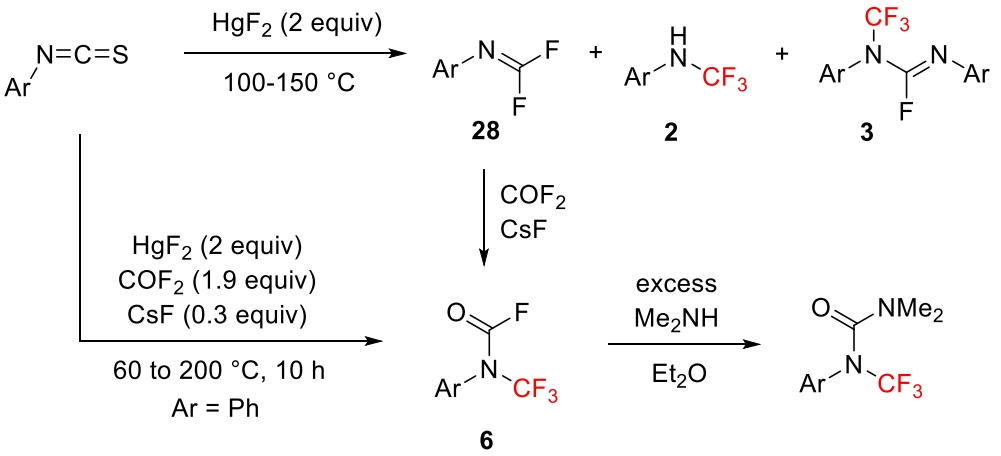
## d. Fluorination *via* the isocyanide difluoride intermediate

As early as 1959, Stevens published the fluorination of alkyl and aryl isothiocyanates with iodine pentafluoride (Scheme 14).[45,46] The reaction is postulated to occur *via* the isocyanide difluoride intermediate **28** which was converted to the thiobis-*N*-(trifluoromethyl)amine **29** by $IF_5$. The thiobisamine **29** was further derivatized with acidic and basic reagents.[46]



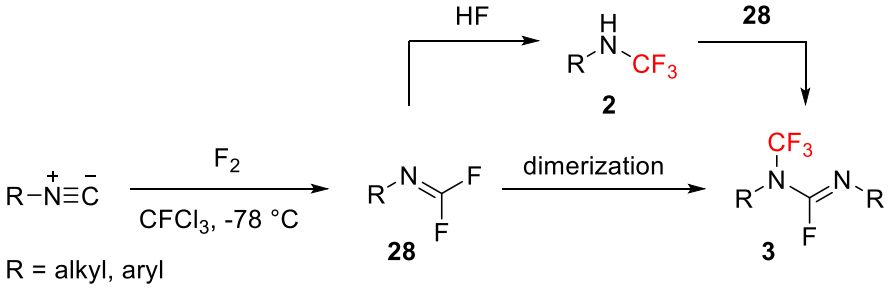

**Scheme 14** Fluorination of isothiocyanates using $IF_5$.[45,46]

Isothiocyanates can also be fluorinated by mercury(II) fluoride as shown by Sheppard (Scheme 15).[17] Unfortunately, the transformation provides a mixture of fluorinated products (**2**, **3** and **28**). The isocyanide difluoride (**28**) can react with $COF_2$ in the presence of CsF to give the *N*-(fluoroformyl)-*N*-(trifluoromethyl)aniline (**6**). As an alternative, the aniline product **6** can be directly prepared from isothiocyanates.[26,43]



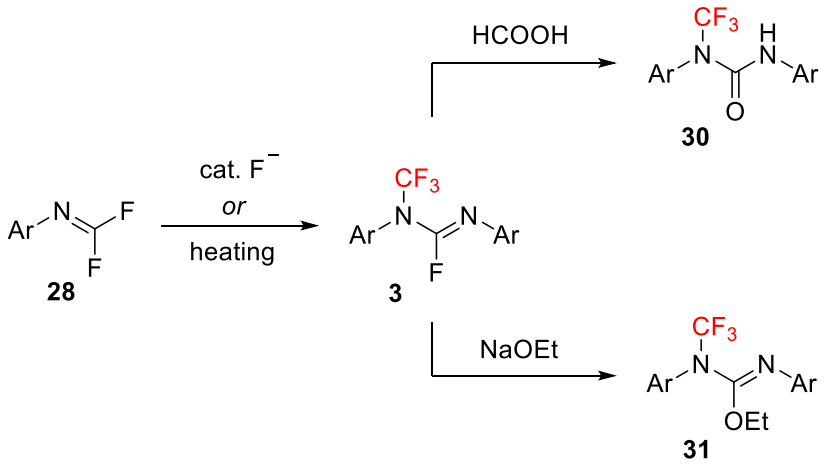

**Scheme 15** Fluorination of isothiocyanates with $HgF_2$.[17,26,43]

Ruppert prepared a few isocyanide difluorides (**28**) by fluorinating alkyl and aryl isocyanides with elemental fluorine (Scheme 16).[47] The product **28** could either dimerize to afford **3** or react with HF to provide the trifluoromethylamine **2**.




**Scheme 16** Preparation of trifluoromethylamines in two steps, starting from isocyanides.[47]

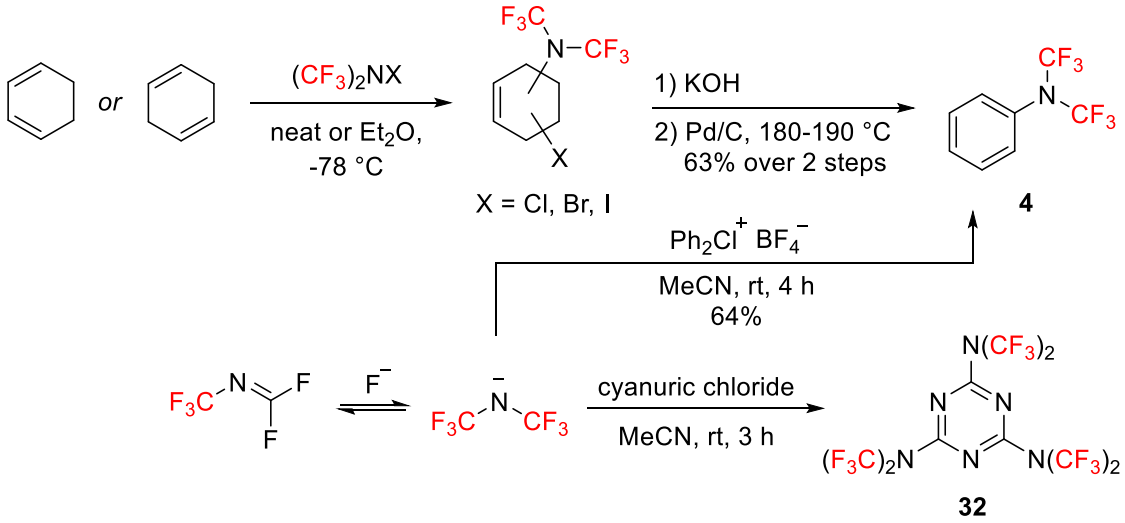
Isocyanide difluorides (**28**) can also dimerize under fluoride catalysis or heating to produce compound **3** (Scheme 17). The dimer can be converted to the urea or the isourea derivatives (**30** and **31**).[15]

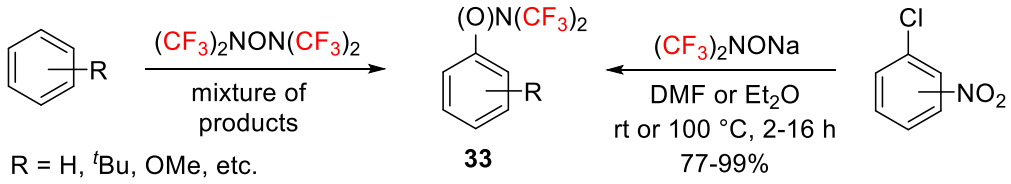



**Scheme 17** Dimerization of isocyanide difluorides and further derivatization thereof.[15]

## e. Preparation of bis(trifluoromethyl)amine derivatives

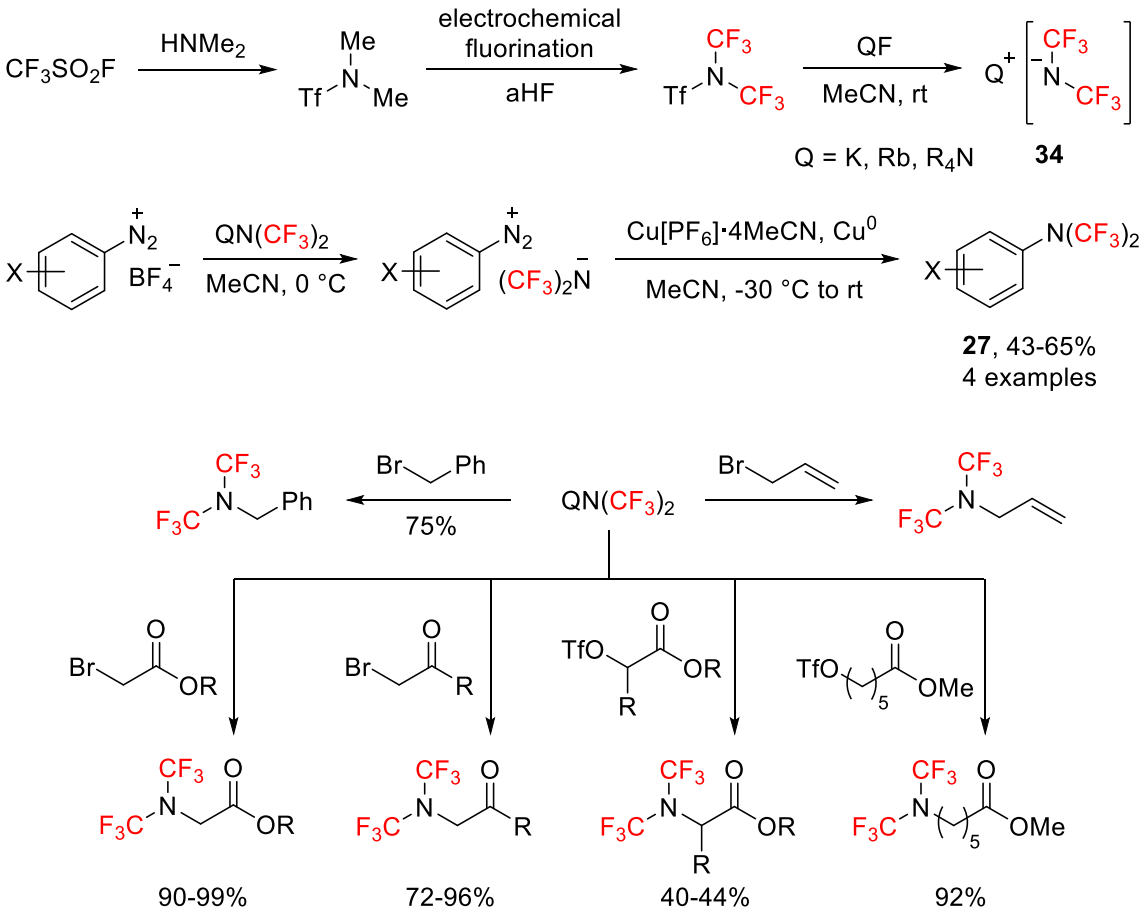
There have been a few examples for the preparation of bis(trifluoromethyl)amine compounds by functional group interconversion (see Scheme 2, 3 and 13). Nevertheless, these substrates are rather prepared from precursors already containing the $N(CF_3)_2$ moiety. In the 1980s, many approaches have been developed but most of them have serious drawbacks such as limited functional group tolerance, lack of selectivity and the starting material being commercially unavailable. Scheme 18 represents some synthetic pathways of that time.[48–52]






**Scheme 18** Synthetic pathways to bis(trifluoromethyl)anilines.[48–52]

Recently, several reports were published on the incorporation of the $N(CF_3)_2$ functionality to aromatic as well as aliphatic compounds as depicted in Scheme 19. The key reagent is the $MN(CF_3)_2$ salt (**34**) which was prepared in three steps starting from trifluoromethanesulfonyl fluoride.[53–55] After anion exchange, the dediazotization took place to afford bis(trifluoromethyl)anilines **27**.[56] The aliphatic derivatives were obtained by a simple nucleophilic substitution reaction at primary and secondary carbon centers.[53–55,57] All the products were subjected to further derivatization to show the versatility of these fluorinated building blocks.




**Scheme 19** Convenient synthesis of aromatic and aliphatic compounds bearing the $N(CF_3)_2$ moiety.[53–57]

### f. Synthesis of N-perfluoroalkylated substrates

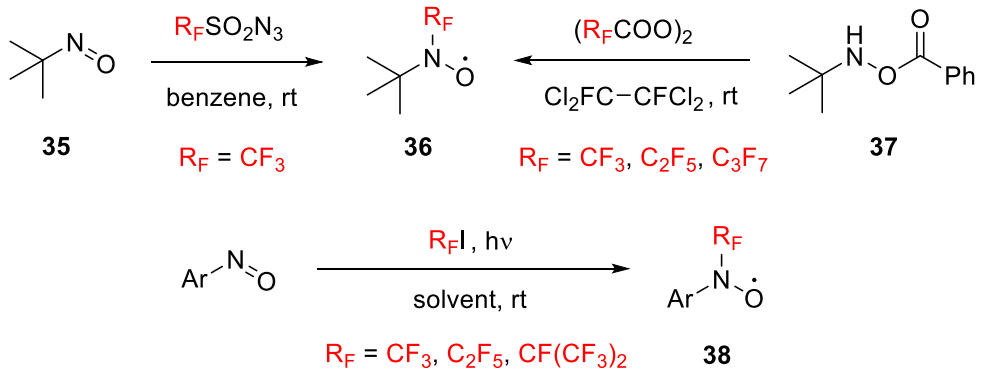
The preparation of N-perfluoroalkylated compounds is a challenging task. It can be accomplished by functional group interconversion (see Scheme 12), nucleophilic fluorination or electrochemical fluorination of various substrates. Only a few examples of nucleophilic fluorination are described to obtain N-perfluoroalkyl compounds.[58–61] The substrate scope is very limited and there is a lack of general methods. In contrast, there is a wealth of publications concerning electrochemical fluorination; however, this approach provides a mixture of heavily polyfluorinated compounds due to the uncontrolled reaction.[62–64]

## 1.2.2. Direct methods

For many decades, indirect methods were the only way how to obtain trifluoromethylamines. Direct N-trifluoromethylation methods were simply not available due to the synthetic challenges deriving from nitrogen being a hard nucleophile. Besides, primary and secondary trifluoromethylamines are challenging substrates to isolate and store owing to their facile decomposition after fluoride elimination.

### a. Radical N-trifluoromethylation

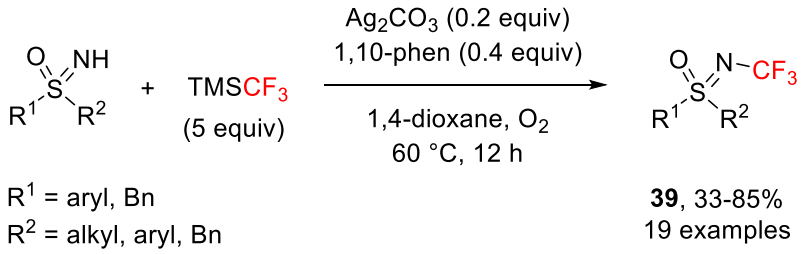
Kamigata *et al.* was the first who reported radical N-trifluoromethylation of a nitroso compound. The resulting *t*-butyl trifluoromethyl nitroxide **36** was detected by electron spin resonance (ESR) spectroscopy.[65] Other perfluoroalkyl nitroxides (**36** and **38**) were prepared from the reaction of *t*-butylhydroxylamine **37** with perfluoroacyl peroxides, or aryl nitroso compounds with perfluoroalkyl iodides (Scheme 20).[66–69]




**Scheme 20** Synthesis of perfluoroalkyl nitroxides *via* radical N-trifluoromethylation.[65–69]

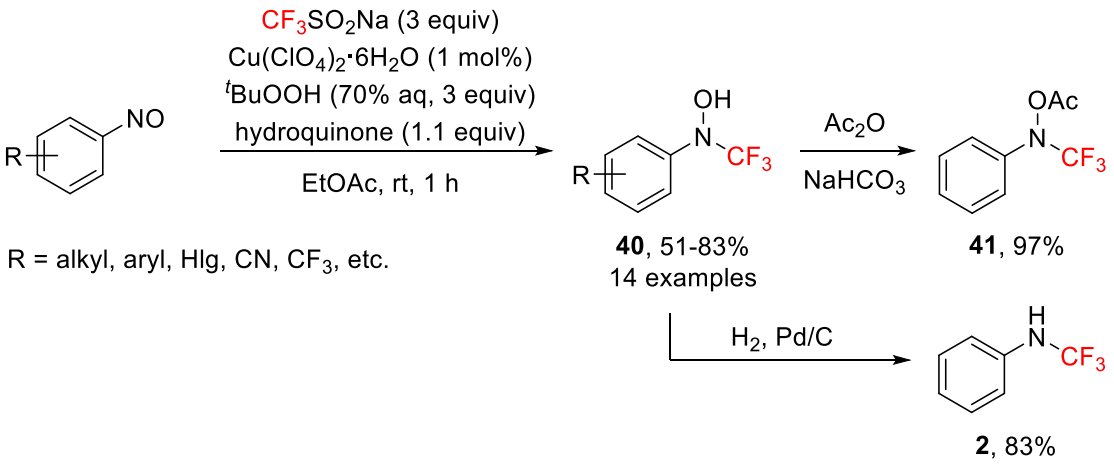
Building on this concept, mechanistic studies were carried out to prove the intermediacy of $CF_3$ radical in certain transformations. The spin trapping of the $CF_3$ radical was achieved by using 2-methyl-2-nitrosopropane (**35**) as a spin trap which enabled the detection of the nitroxide spin adduct (**36**) by ESR.[70–73]

Apart from these ESR studies, only a few radical N-trifluoromethylation reactions have been described. Having an electron-rich nucleophilic site, sulfoximines were subjected to N-trifluoromethylation using $TMSCF_3$ in the presence of Ag(I) and 1,10-phenanthroline (Scheme 21).[74]



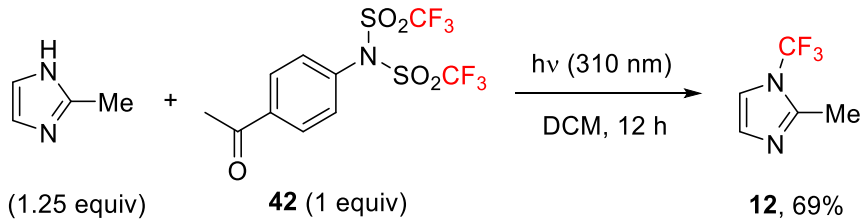

**Scheme 21** Radical N-trifluoromethylation of sulfoximines with $TMSCF_3$.[74]

Selander and co-workers described the N-trifluoromethylation of various nitrosoarenes using the Langlois reagent ($CF_3SO_2Na$) as a source of the $CF_3$ radical (Scheme 22).[75] In the presence of a Cu(II) catalyst and an oxidant, the $CF_3$ radical is generated and added to nitroso compounds to give access to trifluoromethylated hydroxylamines **40**. They showed that the hydroxylamine can be further converted to the aniline and the O-acylated derivatives (**2** and **41**).




**Scheme 22** Radical N-trifluoromethylation of nitrosoarenes using the Langlois reagent.[75]

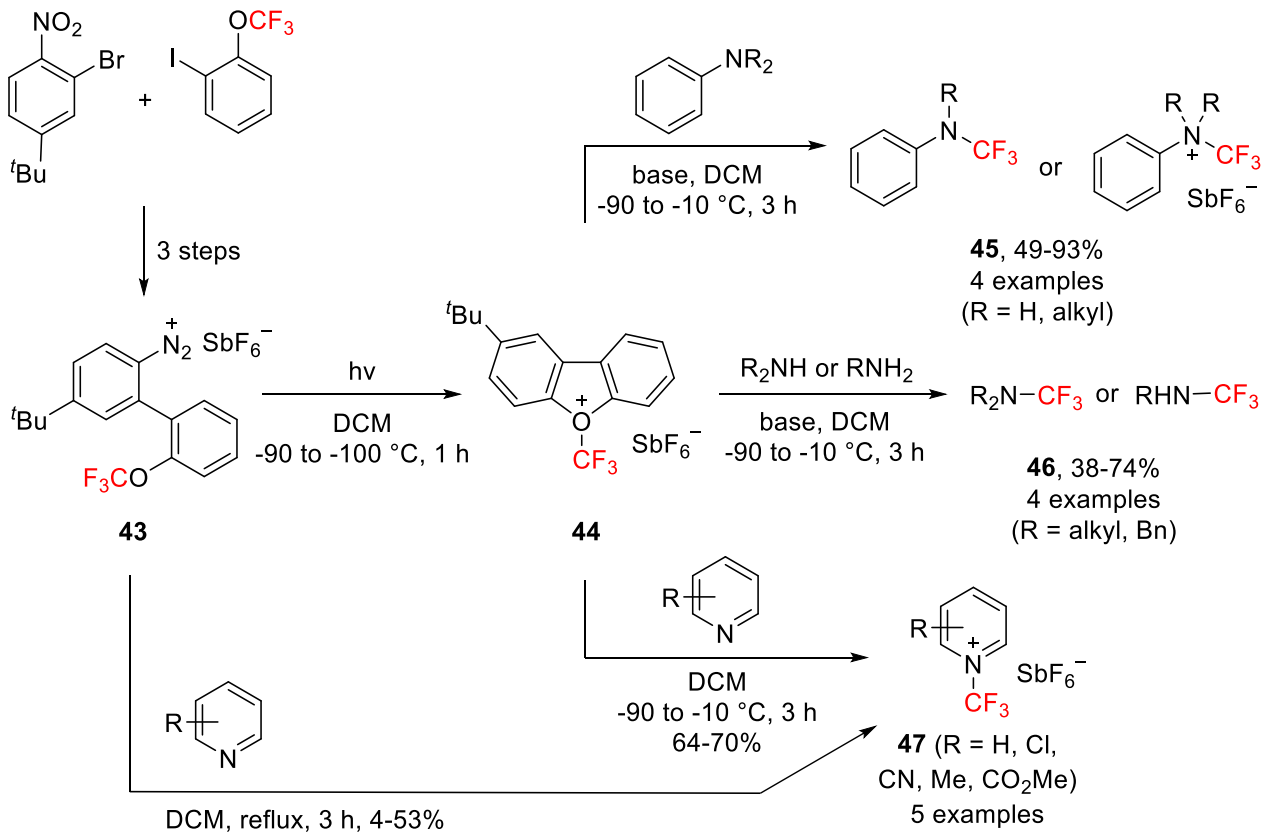
Fagnoni *et al.* reported the photochemically induced radical addition of *N*-aryltrifluoromethanesulfonimide (**42**) to aromatics and heteroaromatics to provide trifluoromethylated products.[76] The radical trifluoromethylation occurred on carbon centers with the only exception of substituted imidazole (Scheme 23).




**Scheme 23** Photochemical trifluoromethylation of imidazole.[76]

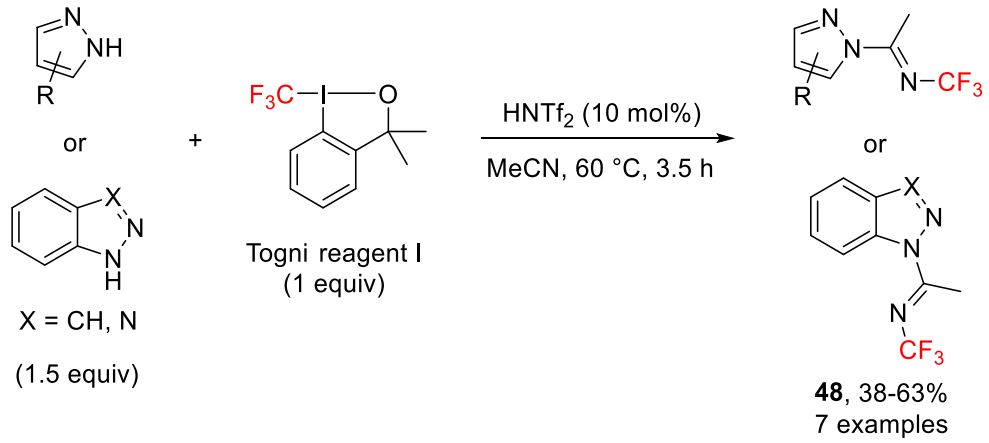
## b. Electrophilic N-trifluoromethylation

Umemoto and co-workers reported the first electrophilic trifluoromethylation of nitrogen nucleophiles. The authors showed that various amines, anilines and pyridines can undergo trifluoromethylation with a highly reactive *O*-(trifluoromethyl)dibenzofuranium salt **44** in the presence or absence of a base to afford the corresponding N-trifluoromethylated products **45**-**47** (Scheme 24).[77] Being thermally unstable, the $CF_3$ oxonium reagent **44** needs to be synthesized prior to the trifluoromethylation reaction. Alternatively, the electrophilic $CF_3^+$ species can be generated *in situ* by the thermal decomposition of the diazonium salt precursor **43** which readily reacts with pyridines, though giving lower yields. Their achievement is impressive and valuable; however, the thermal instability and the arduous synthesis of the reagent are clearly drawbacks and limit practical feasibility of the method.



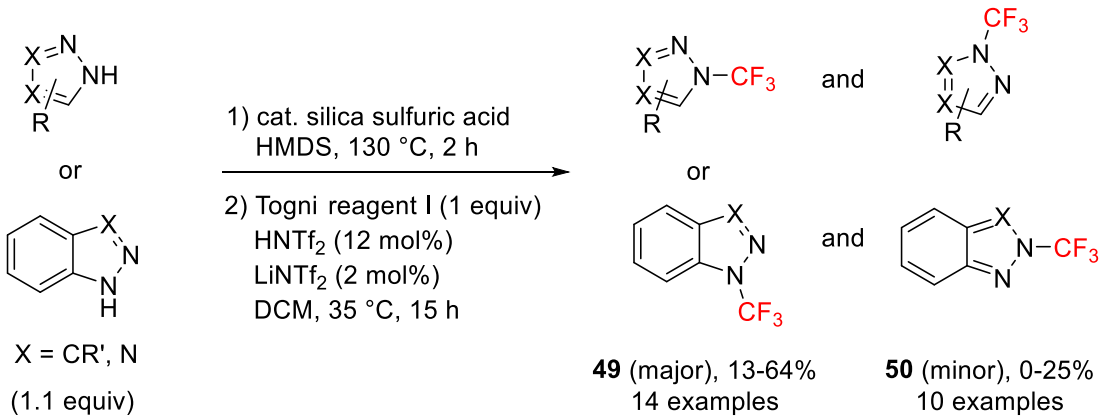

**Scheme 24** Electrophilic trifluoromethylation of various nitrogen nucleophiles using $CF_3$ oxonium salts.[77]

Later, the Togni research group developed new electrophilic reagents (Togni reagents I and II) capable of transferring the $CF_3$ group.[78] These stable hypervalent iodine compounds have been shown to react with a broad range of carbon- and heteroatom-centered nucleophiles.[79] The group discovered that azoles can undergo a Ritter-type reaction with Togni reagent I in the presence of acetonitrile and acid catalyst to afford N-trifluoromethylated imines **48** (Scheme 25).[80]



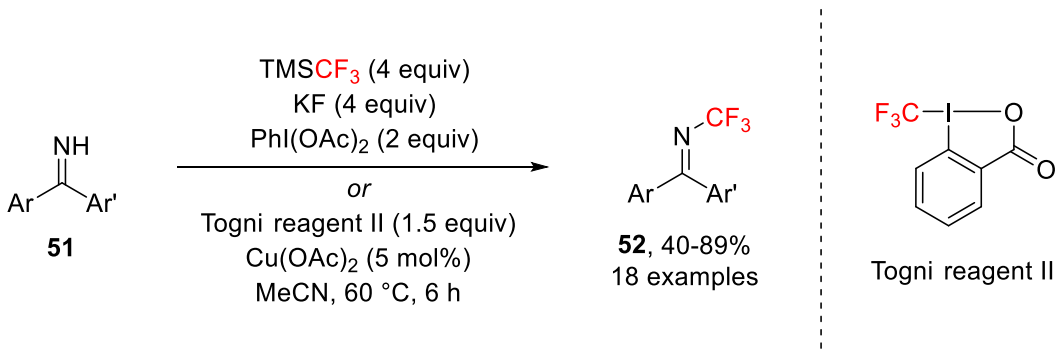

**Scheme 25** Ritter-type reaction of azoles with Togni reagent I.[80]

Interestingly, they observed the formation of a side-product deriving from the direct N-trifluoromethylation of the corresponding benzotriazole.[80] This observation suggested that under the right reaction conditions, the N-trifluoromethylation could be the dominating pathway, leading to N-$CF_3$ heterocycles. The key was that the substrate needs to be silylated *in situ* by HMDS in the presence of catalytic silica sulfuric acid (SSA) in the first step. Without isolation, the silylated intermediate is readily trifluoromethylated with the Togni reagent I, using catalytic amounts of $HNTf_2$ and $LiNTf_2$ (Scheme 26).[81] The transformation provides access to rare N-trifluoromethylated azoles; however, it often gives isomeric product mixtures (**49** and **50**).




**Scheme 26** Direct N-trifluoromethylation of various azoles using Togni reagent I.[81]

Wang *et al.* showed that diaryl ketimines (**51**) can be conveniently trifluoromethylated by using the $TMSCF_3$/KF/$PhI(OAc)_2$ system as shown in Scheme 27.[82] They proposed the formation of $[ArICF_3]^+$ species which serves as an electrophilic source of the $CF_3$ group. Additionally, it was found that the combination of Togni reagent II with Cu(II) catalyst constitutes another system capable of transferring the electrophilic $CF_3$ moiety to ketimines (Scheme 27).

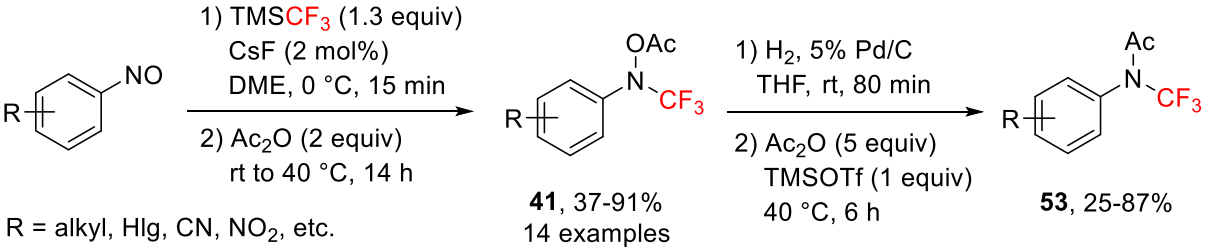



**Scheme 27** Synthesis of N-trifluoromethylated ketimines using Togni reagent II.[82]

## c. Nucleophilic N-trifluoromethylation

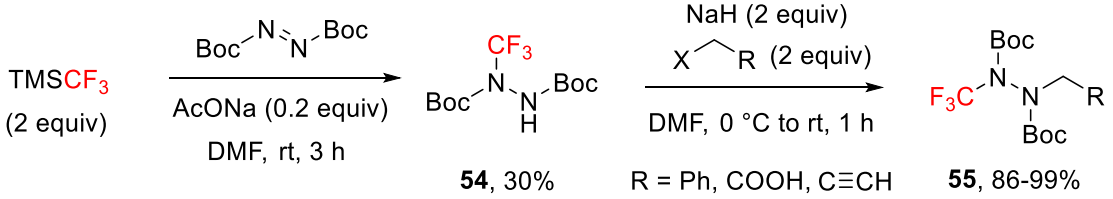
Nucleophilic trifluoromethylation is a challenging task owing to the fact that the "naked" trifluoromethyl anion is prone to fluoride elimination to generate difluorocarbene.[83,84] The decomposition pathway could be circumvented when the trifluoromethyl anion is stabilized through bonding to late-transition metals (Cu, Zn, Cd, etc.) or main group elements (Si, Sn, Bi).[83] Among all these pronucleophiles, $TMSCF_3$ (also known as the Ruppert-Prakash reagent) is the most widely used reagent in nucleophilic trifluoromethylation of many carbon electrophiles and of a few heteroatom-based electrophiles.[4] Here, only the relevant reactions with N electrophiles will be discussed.

A Japanese group has described a fluoride initiated nucleophilic trifluoromethylation of aromatic nitroso compounds using $TMSCF_3$ as depicted in Scheme 28.[85] The *N*-(trifluoromethyl)hydroxylamines **41** can be derivatized by reduction of the hydroxylamines to the *N*-(trifluoromethyl)anilines, followed by acetylation with acetic anhydride to afford *N*-(trifluoromethyl)acetamides **53**.




**Scheme 28** Fluoride initiated nucleophilic trifluoromethylation of nitroso compounds with $TMSCF_3$.[85]

Another way for the synthesis of N-$CF_3$ compounds in a nucleophilic fashion was reported by the group of Crousse. They disclosed the addition of $TMSCF_3$ on azodicarboxylates using a carboxylate as initiator of the Ruppert-Prakash reagent (Scheme 29).[86]



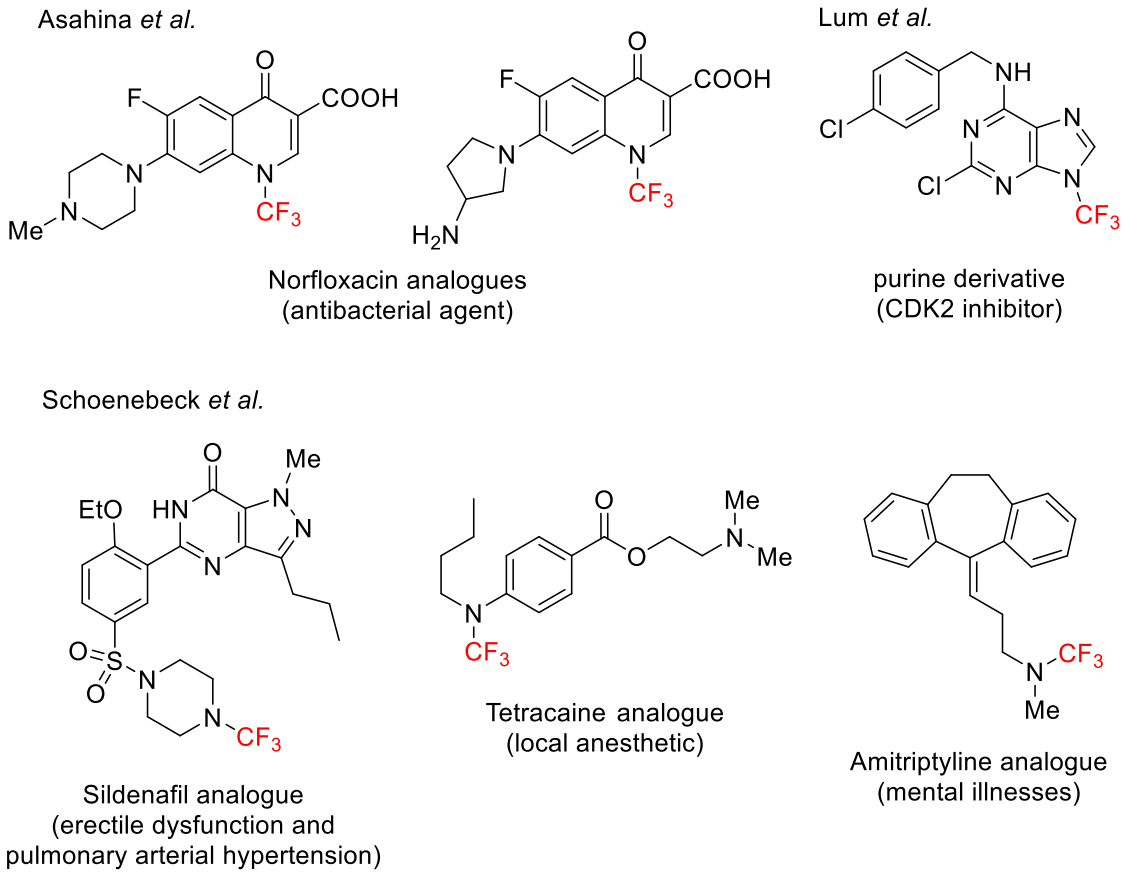

**Scheme 29** Nucleophilic trifluoromethylation of azodicarboxylates.[86]

## 1.3. Applications

Fluorinated molecules have found a broad range of applications including pharmaceutical, agrochemical and material sciences. Many reviews on the synthesis and application of $CF_3$-containing compounds have been published which emphasizes the importance of the field.[9,10,87–90]

The difficulty of trifluoromethylating heteroatoms, especially nitrogen centers, hindered the use of N-trifluoromethyl compounds; however, it is expected that the increasing synthetic accessibility will broaden their use. The promising features make them attractive target compounds with the potential for diverse applications. Without going into detail, the few applications known in the literature are listed below.

The groups of Asahina, Lum and Schoenebeck reported the preparation of N-trifluoromethyl derivatives of potential or marketed pharmaceuticals (Figure 1).[38,39,91]



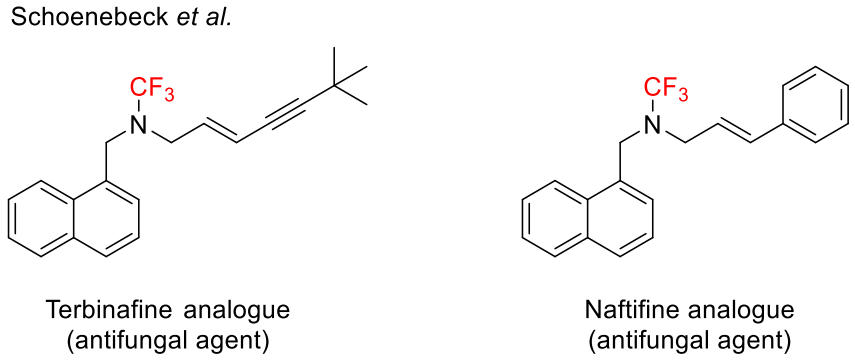



**Figure 1** N-Trifluoromethyl derivatives of biologically active compounds.[38,39,91]

Hiyama and co-workers reported the synthesis of novel liquid crystals bearing the trifluoromethylamino moiety.[30,32] The liquid crystals exhibited promising phase transition temperatures and electro-optical properties. On the other hand, the unique physical properties of $NCF_3$ compounds have been exploited in ionic liquids by Yagupolskii (Figure 2).[23]

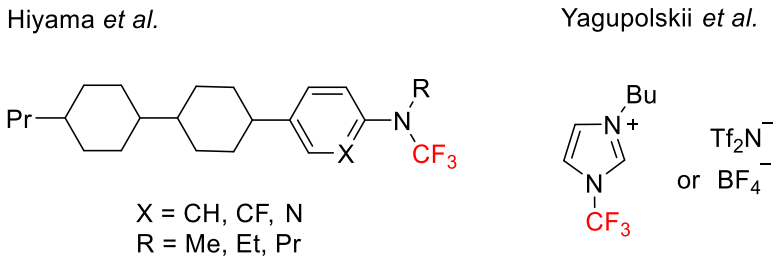



**Figure 2** Potential application as liquid crystals and ionic liquids.[23,30,32]

The Togni research group published the preparation of several ruthenium N-heterocyclic carbene (NHC) complexes containing N-trifluoromethyl NHC ligands (Figure 3).[92–94] The Ru-NHC complexes displayed high selectivity in the alternating copolymerization of cyclooctene and norbornene as well as in the ethenolysis of ethyl oleate or cyclic dienes.

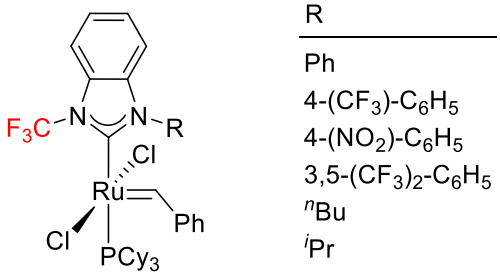



**Figure 3** Ru-NHC catalysts containing N-trifluoromethyl benzimidazole ligands.[92–94]

# 2 Aims of the work

The primary goal of the project was to develop reagents which could serve as building blocks in the preparation of rare N-perfluoroalkyl derivatives and to exploit the synthetic potential of these precursors in various transformations. To fulfil this goal, the following synthetic challenges will be addressed:

- Synthesizing novel azidoperfluoroalkanes as unique fluorinated building blocks
- Exploring the reactivity of azidoperfluoroalkanes in the copper(I)-catalyzed azide-alkyne cycloaddition to access 1,4-disubstituted 1,2,3-triazoles
- Investigating the organocatalytic azide-ketone cycloaddition with the perfluorinated azides for the construction of highly functionalized 1,2,3-triazoles
- Examining the protonation of azidotrifluoromethane in superacidic media

# 3 Azidoperfluoroalkanes

*This chapter encloses contributions from Dr. Svatava Voltrová who joined the project on azidoperfluoroalkanes.*

## 3.1. Introduction to perfluorinated azides

Being highly energetic, organic azides are considered as valuable, highly reactive intermediates with an immense synthetic utility.[95–97] By virtue of their dipolar structure, azides can react as nucleophiles or electrophiles and can also serve as precursors for nitrenes. Furthermore, they are regarded as important players at the chemistry-biology interface. Since the discovery of the copper(I)-catalyzed azide-alkyne cycloaddition,[98,99] organic azides have been enjoying a renaissance. The popular concept of click chemistry has led to many applications in the field of material science, bioconjugation and pharmaceuticals.[100–103] The only limitation in applications lies in the potential hazardous properties of these energy-rich compounds.[97]

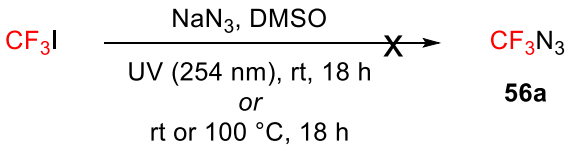
Polyfluorinated azides constitute an interesting class of organic azides, having been known and studied for a long time by many research groups.[104–108] On the other hand, it is quite surprising that fully fluorinated azides are virtually unknown. Azidotrifluoromethane (**56a**) is the only known azidoperfluoroalkane which was first synthesized by Makarov and two decades later by Christe.[109–111] Azide **56a** was prepared in two steps starting from trifluoronitrosomethane as shown in Scheme 30. Nonetheless, its synthetic use quickly came to an end due to the toxic and hazardous gases required for the synthesis.


**Scheme 30** Synthesis of azidotrifluoromethane.[109–111]

Inspired by the reports from Makarov and Christe, we were intrigued to see whether it was possible to synthesize azidotrifluoromethane (**56a**) and previously unknown longer carbon chain azidoperfluoroalkanes in a convenient and safe manner.

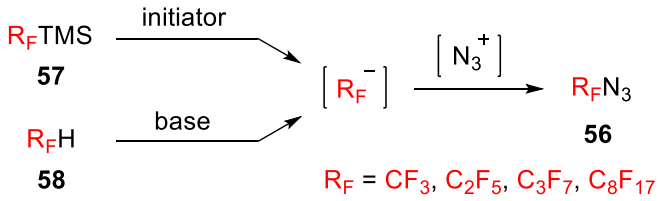
## 3.2. Preparation of azidoperfluoroalkanes

An initial attempt toward the synthesis of azidotrifluoromethane (**56a**) was carried out using trifluoroiodomethane and sodium azide. Disappointingly, this synthetic strategy turned out to be unsuccessful under UV irradiation or thermal conditions (Scheme 31).




**Scheme 31** Attempted synthesis of azidotrifluoromethane from trifluoroiodomethane.

We speculated that a more promising way to prepare azide **56a** would be by reacting a nucleophilic trifluoromethyl source with an electrophilic azide. One of the most widely used and studied nucleophilic $CF_3$-transfer reagent is the $TMSCF_3$, also called the Ruppert-Prakash reagent.[4,112] Being stable and easy-to-handle, this organosilane reagent seemed to be a suitable starting material. We also found that tosyl azide ($TsN_3$) and nonaflyl azide ($NfN_3$) can serve as formally electrophilic reaction partners in this transformation. These stable electrophilic azides can be prepared by formal Umpolung (polarity reversal) of the initially nucleophilic sodium azide. Provided that this synthetic strategy is viable, longer carbon chain azidoperfluoroalkanes could be prepared in an analogous way, starting from the corresponding trimethyl(perfluoroalkyl)silanes (**57**). Besides, we envisioned that 1*H*-perfluoroalkanes (**58**) could also act as perfluoroalkyl anion sources under the right conditions. Our synthetic strategy is outlined in Scheme 32.



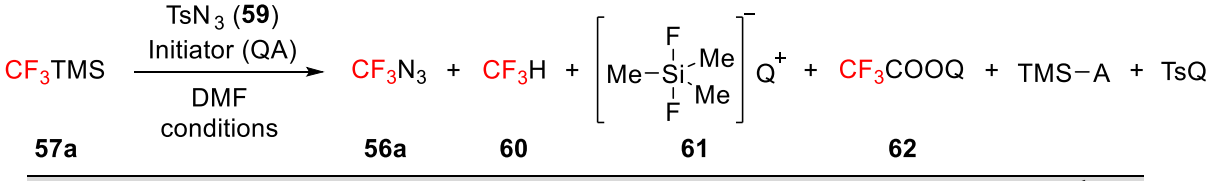

**Scheme 32** Synthetic strategy for the preparation of azidoperfluoroalkanes.

It is known that the nucleophilic $CF_3$ transfer from $TMSCF_3$ to various electrophiles requires an anionic initiator (QA).[4,113–115] When trifluoromethylating aldehydes and ketones with $TMSCF_3$, catalytic amount of initiator is needed for the reaction since the reaction cycle is sustained by the formed trifluoromethylated alkoxide intermediate.[115] When this alkoxide intermediate is not present, such as in our case, equimolar amount of

initiator is required. Hence, a range of fluoride- and oxygen-containing initiators were tested for the synthesis of $CF_3N_3$ as shown in Table 1.

The reaction of $TMSCF_3$ with tosyl azide in DMF using potassium carbonate as initiator provided low yields of the desired azide **56a** at or above room temperature (entries 1-3). Changing to cesium carbonate gave diminished yield of the azide (**56a**) and led to the formation of the trifluoroacetate side product **62** (entry 4). When $TMSCF_3$ was activated by other oxygen-containing or THF-soluble fluoride initiators, it did not lead to any improvement of product formation (entries 5-9). The use of cesium fluoride resulted in higher conversion of the reactants to the azide **56a** (entries 10 and 11). Furthermore, a significant improvement was achieved when cesium fluoride was used as initiator and the reaction was carried out at low temperatures (entries 12 and 13). When the reaction was carried out in other solvents (e.g., toluene, THF, monoglyme, DMSO), inferior results were obtained (not reported in Table 1).

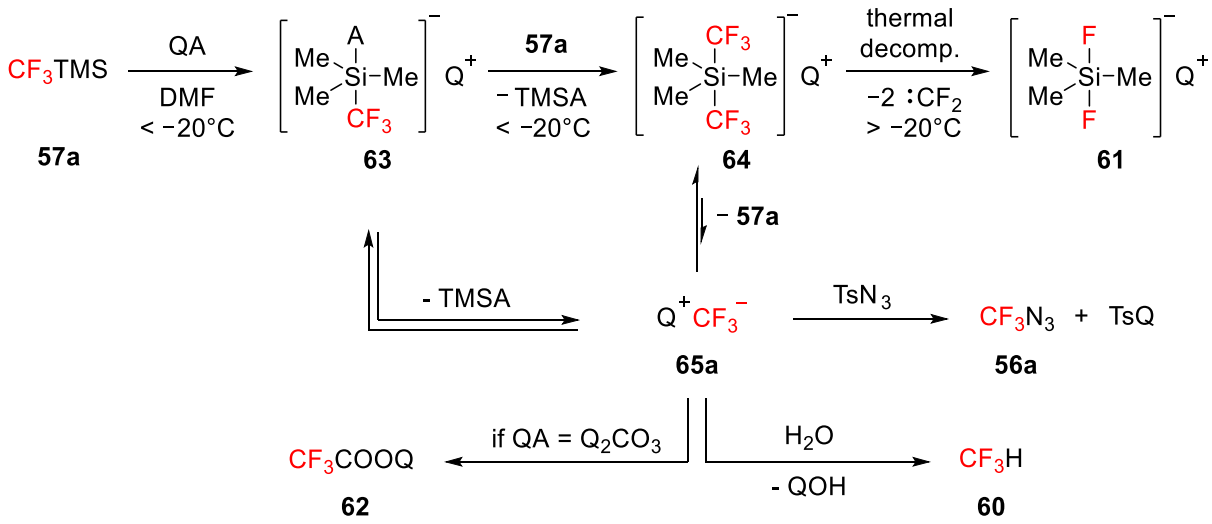
**Table 1** Optimization of the synthesis of azidotrifluoromethane.[a]




| Entry | Initiator (QA) | **57a**/**59**/QA (mmol) | Temperature (°C) | Time (h) | Yield (%)[b] **56a**, **60**, **61**, **62** |
|---|---|---|---|---|---|
| 1 | $K_2CO_3$ | 3:1:3 | rt | 18 | 31, 2, 36, 3 |
| 2 | $K_2CO_3$ | 1:3:1 | rt | 18 | 26, 2, 8, 2 |
| 3 | $K_2CO_3$ | 1:3:1 | 60 | 1 | 25, 3, 8, 3 |
| 4 | $Cs_2CO_3$ | 1:3:1 | rt | 1 | 20, 8, 8, 30 |
| 5 | $K_3PO_4$ | 1:1:1.2 | rt | 18 | 17, 22, 17, - |
| 6 | $Me_3NO$ | 1:1:1.2 | rt | 18 | 6, 16, 0, - |
| 7 | $^nBu_4N(OAc)$ | 1:1:1.2 | rt | 18 | 39, 10, 41, - |
| 8[c] | TBAT | 1:1:1 | -78 to rt | 2 | 25, 3, 20, - |
| 9[c] | TBAF | 1:1:1 | -78 to rt | 1 | 10, 34, 3 |
| 10 | CsF | 1:1:1 | rt | 1 | 27, 5, 38, - |
| 11 | CsF | 2:1:1 | rt | 1 | 52, 2, 29, - |
| 12 | CsF | 1:1:1 | -60 to rt | 18 | 65, 13, 0, - |
| 13 | CsF | 1.2:1:1.2 | -60 to -30 | 4 | **79**, 9, 0, - |

[a] The reaction was set up according to the general procedure described in the experimental section. [b] $^{19}F$ NMR yields using $PhCF_3$ as an internal standard. [c] THF was used instead of DMF.

In the course of the reaction, several fluorinated by-products (**60**, **61** and **62**) were observed by $^{19}F$ NMR spectroscopy whose formation can be explained in the following way (Scheme 33). $TMSCF_3$ is activated by the anionic initiator QA (e.g., cesium fluoride) to eventually give the pentacoordinate siliconate anions **63** and **64** which act as reservoirs of the $CF_3$ anion. The siliconates **63** and **64** are in rapid equilibrium with the free $CF_3^-$ (**65a**) which readily reacts with a) tosyl azide to provide the product **56a**, b) residual water to generate fluoroform (**60**), and c) carbonate initiators to give the trifluoroacetate **62**. The two siliconate intermediates **63** and **64** are known to be thermally unstable and decompose to the difluoro siliconate salt **61** and difluorocarbene. These synthetic routes and the involved intermediates have been described by the research groups of Yagupolskii, Röschenthaler, Prakash and Lloyd-Jones.[116–119]

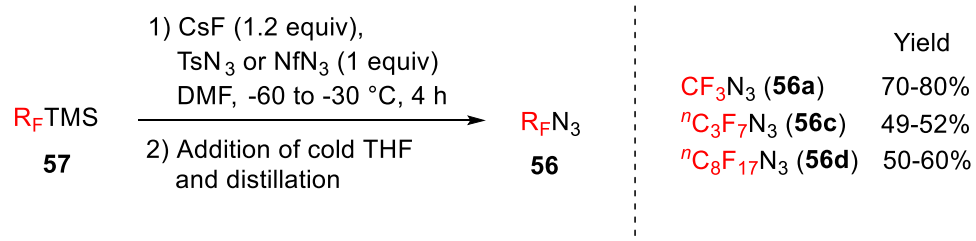



**Scheme 33** Plausible synthetic routes for the formation of $CF_3N_3$ and by-products.[116–119]

The synthesis of azide **56a** can be easily scaled up to 20 mmol scale without the need of changing the conditions. However, we encountered some difficulties during the isolation of the pure $CF_3N_3$ due to its low boiling point (reported b.p. = -28.5 °C).[110] We were able to obtain pure samples from the reaction with $K_2CO_3$ as initiator but the yield was disappointingly low (less than 10%) and the azide was difficult to handle. Eventually, the isolation of **56a** was achieved by the addition of a relatively low boiling point solvent (e.g., THF, DCM, etc.) to the reaction mixture (according to entry 13 in Table 1) and subsequent distillation under ambient pressure to a cooled receiving flask at -78 °C. The resulting solution of **56a** also contained traces of $CF_3H$ and considerable amounts of TMSF which did not interfere with any of the following transformations. At concentrations of 0.3M and lower, the azide solution can be conveniently stored in a closed flask

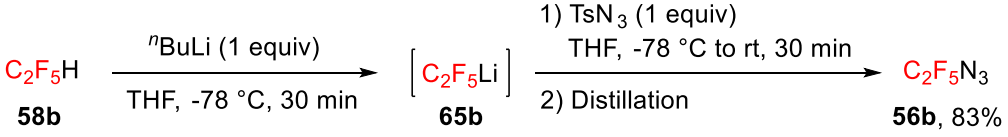
at subambient temperatures (-25 °C) for several weeks without any sign of decomposition.

Having the optimized reaction conditions and a suitable isolation procedure in hand, we have synthesized longer carbon chain homologues of $CF_3N_3$ from the corresponding silanes **57** (Scheme 34). Since silanes **57c** and **57d** showed considerably lower reactivity than that of $TMSCF_3$ (**57a**), a more reactive electrophilic azide had to be employed. The reaction of silanes **57c** and **57d** with nonaflyl azide ($NfN_3$) provided azides **56c** and **56d**, respectively, which were isolated as THF solutions. Interestingly, azide **56d** could be isolated in a pure form owing to its insolubility in THF between -60 and -20 °C.



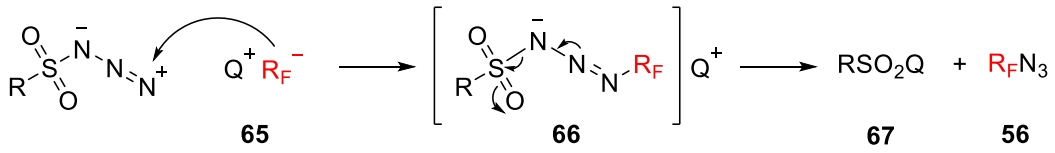

**Scheme 34** Synthesis of azidoperfluoroalkanes **56**.

As outlined in Scheme 32, 1*H*-perfluoroalkanes (**58**) can be suitable starting materials in the construction of azidoperfluoroalkanes (**56**), provided the perfluoroalkyl carbanion is stable under the reaction conditions. Inspired by the reports of low-temperature stable $C_2F_5Li$ salt (**65b**) by Gassman, Roddick and Röschenthaler,[120–124] we decided to investigate the reaction of pentafluoroethane (**58b**) with $^n$BuLi, followed by the addition of tosyl azide (Scheme 35). Since the $C_2F_5Li$ salt (**65b**) is known to be stable below -65 °C,[122,123] the reaction was performed at -78 °C which led to the formation of $C_2F_5N_3$ (**56b**) in 83% yield. Besides, we screened a number of bases (LDA, KO$^t$Bu, $MN(SiMe_3)_2$ where M = Na or K, NaH, $NaNH_2$, etc.) and solvents (toluene, glyme, diglyme, diethyl ether), of which only LDA was able to facilitate the formation of $C_2F_5N_3$ (**56b**), although in much lower yield (49%).




**Scheme 35** Synthesis of azidopentafluoroethane (**56b**).

A plausible mechanism for the formation of azide **56** is shown in Scheme 36. The electrophilic N-3 of tosyl azide is attacked by the *in situ* generated perfluoroalkyl carbanion (**65**) to generate the perfluoroalkyl triazene intermediate (**66**). We presumed that the triazene intermediate (**66**) might be stable at low temperature and upon warming up, decompose to provide the corresponding azide (**56**) and the sulfinate salt (**67**). When synthesizing $C_2F_5N_3$ (**56b**), we observed the formation of a peach-colored precipitate (presumably the triazene salt **66b**) at -78 °C. While warming up the reaction mixture, the precipitate dissolved at -35 °C (presumably the decomposition of **66b** to **56b** and sulfinate salt **67**) and a few minutes later the sulfinate salt (**67**) precipitated at -30 °C.




**Scheme 36** Plausible mechanism for the formation of azides **56**.

The stability of organic azides is a pivotal factor in their synthetic utility. Makarov *et al.* tested the thermal stability of pure $CF_3N_3$ which decomposes explosively upon heating to 330 °C.[110] Since azides **56b-d** are unknown compounds, we have performed thermal stability experiments. The THF solutions of **56b** and **56d** were heated at 150 °C in a pressure-tight NMR tube. The $^{19}$F NMR spectra of both azides showed no sign of decomposition after 80 minutes and therefore we concluded that azides **56** are safe to use under reasonable reaction conditions.

## 3.3. Conclusion and outlook

This chapter described a convenient and scalable preparation of azidoperfluoroalkanes from safe and readily available starting materials. The isolation of the azides was achieved by distillation of the azide with a suitable solvent. Unlike the pure azide, the resulting solution can be conveniently stored and used. With the exception of $CF_3N_3$, these perfluorinated azides are unknown compounds, possessing a great synthetic potential in life and material sciences. The purpose of the following chapters is to give a glimpse into the synthetic utility of these unique fluorinated building blocks.

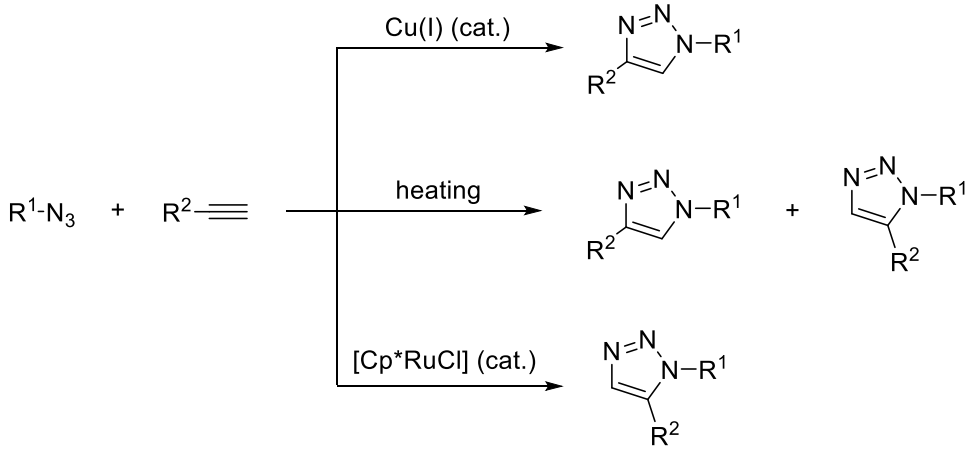
Since then, our group has expanded the arsenal of polyfluorinated azides with tetrafluoroethylene-containing azides ($RCF_2CF_2N_3$) and azidodifluoromethane ($HCF_2N_3$).[125–127] These azides were shown to be competent reaction partners in various cycloadditions.

# 4 Copper-catalyzed azide-alkyne cycloaddition with azidoperfluoroalkanes

*This chapter encloses contributions from Dr. Svatava Voltrová who joined the project on azidoperfluoroalkanes.*

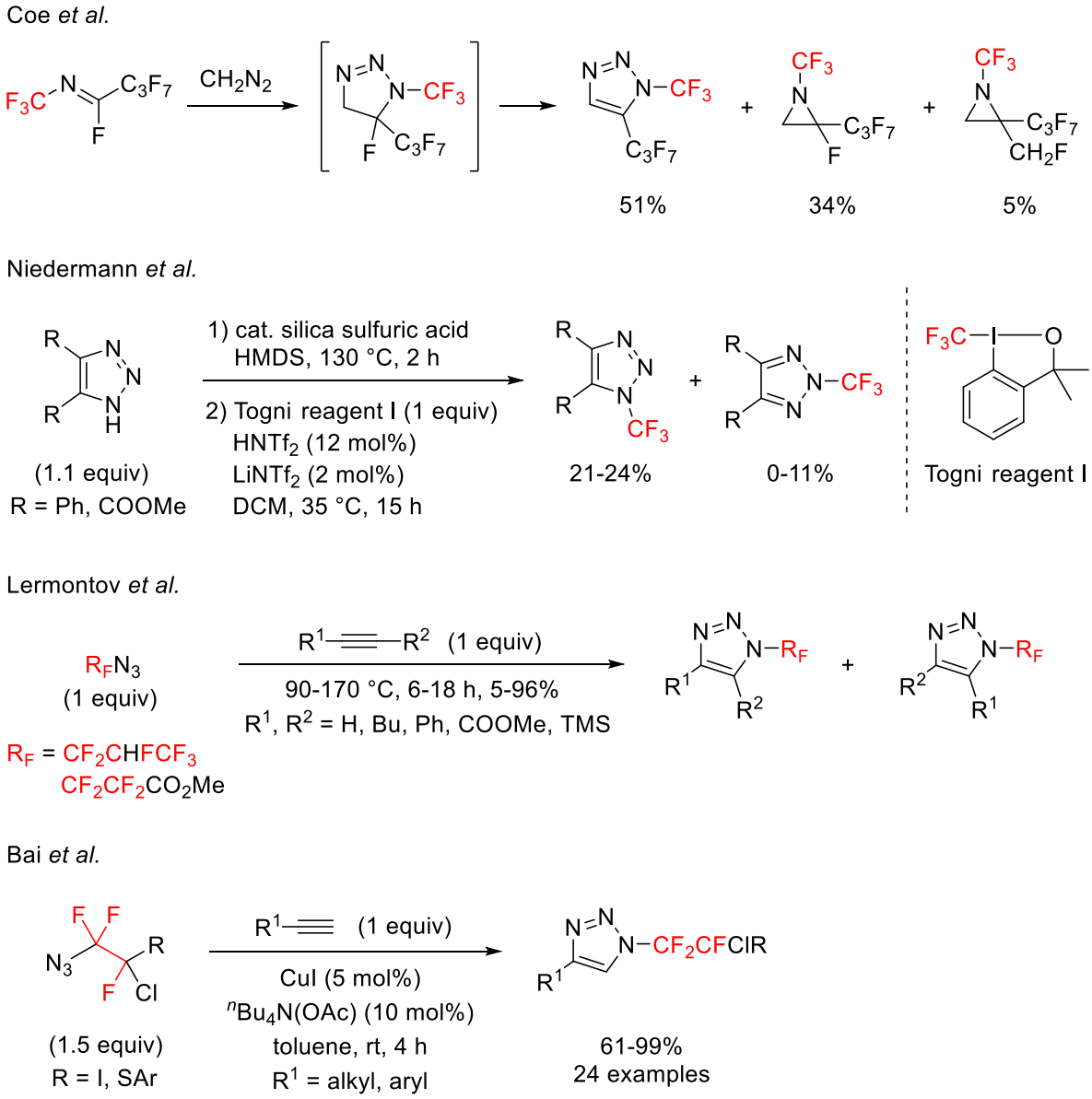
## 4.1. Introduction to the copper-catalyzed azide-alkyne cycloaddition

Huisgen and co-workers thoroughly studied the thermal 1,3-dipolar cycloaddition of alkynes to azides, leading to important 5-membered heterocycles.[128] The transformation has a high activation barrier which accounts for the extremely low reaction rates and therefore requires elevated temperatures and long reaction times. Due to the close HOMO-LUMO energy levels of both reactants, the reaction provides a mixture of regioisomeric 1,2,3-triazoles. For many decades, these limitations withheld the synthetic potential of the Huisgen azide-alkyne cycloaddition. Fortunately, the reaction has been revolutionized by the discovery of the use of a copper(I) catalyst which enabled the exclusive formation of 1,4-disubstituted 1,2,3-triazoles under mild conditions.[98,99] The opposite regioselectivity can be achieved by employing a suitable ruthenium(II) catalyst to furnish 1,5-disubstituted triazoles (Scheme 37).[129] Since the copper- and ruthenium-catalyzed azide-alkyne cycloadditions (CuAAC and RuAAC), many variants have been developed, including the strain-promoted azide-alkyne cycloaddition (SPAAC).[130]




**Scheme 37** Thermal and transition metal-catalyzed azide-alkyne cycloadditions.[98,99,128,129]

Since azidoperfluoroalkanes were unknown before, it is not surprising that no azide-alkyne cycloaddition has been reported with these fluorinated azides. Scheme 38 presents the few known synthetic ways to assemble N-perfluoroalkyl or N-polyfluoroalkyl triazoles.[81,131–134] Unfortunately, these synthetic routes often suffer from the lack of regioselectivity, low yields and harsh reaction conditions.



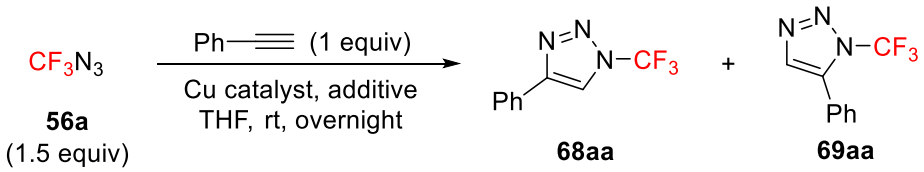

**Scheme 38** Synthetic routes to N-perfluoroalkyl or N-polyfluoroalkyl triazoles.[81,131–134]

We were thus interested in exploring the reactivity of azidoperfluoroalkanes (**56**) in the copper(I)-catalyzed azide-alkyne cycloaddition to furnish previously inaccessible N-perfluoroalkyl 1,2,3-triazoles.

## 4.2. Synthesis of N-perfluoroalkyl triazoles with terminal alkynes

Azidotrifluoromethane (THF solution) and phenylacetylene were chosen as model substrates for catalyst screening experiments. Many known copper catalyst/additive systems were evaluated as summarized in Table 2. To our surprise, the widely used $CuSO_4$/sodium L-ascorbate system provided low conversion of azide **56a** to the desired triazole **68aa** (entry 1). CuBr/$PPh_3$ and $Cu_2O$ gave inferior results and CuI itself could not yield the product (entries 2-4). Triazole **68aa** could be obtained in good to high yields when using CuI with various additives (entries 5-8). Finally, the highest yield of **68aa** was achieved using 10 mol% copper(I) 3-methylsalicylate (CuMeSal) (entry 9). Interestingly, we have occasionally observed traces of the 1,5-disubstituted triazole **69aa**.

**Table 2** Catalyst screening for the CuAAC of $CF_3N_3$ with phenylacetylene.[a]



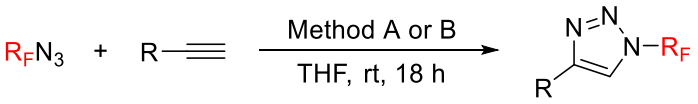

| Entry | Cu catalyst (mol%) | Additive (mol%) | Yield (%)[b] **68aa**:**69aa** |
|---|---|---|---|
| 1[c] | $CuSO_4 \cdot 5H_2O$ (10) | sodium L-ascorbate (10) | 29:0 |
| 2 | CuBr (5) | $PPh_3$ (10) | 17:0 |
| 3 | $Cu_2O$ (5) | - | 12:0 |
| 4 | CuI (5) | - | 1:0 |
| 5 | CuI (5) | TBAA (10) | 59:2 |
| 6 | CuI (5) | $NEt_3$ (10) | 84:<1 |
| 7 | CuI (5) | $NEt_3$, AcOH(10) | 92:1 |
| 8 | CuI (5) | DIPEA (10) | 58:0 |
| 9 | CuMeSal (5) | - | 95:1 |

[a] The reaction was set up according to the procedure described in the experimental section. [b] $^{19}F$ NMR yields using $PhCF_3$ as an internal standard. [c] Using $H_2O$ as co-solvent.

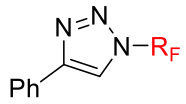
While exploring the scope of the reaction with longer carbon chain azidoperfluoroalkanes, we were quite surprised to find out that the cycloaddition of $C_2F_5N_3$ with phenyla-

cetylene provides the triazole **68ba** in equally high yield, using either $CuSO_4$ in combination with Na L-ascorbate or CuMeSal. Using these two methods, we set out to investigate the scope of this cycloaddition with azidoperfluoroalkanes and a variety of terminal alkynes which is summarized in Table 3.

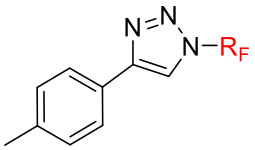
**Table 3** Substrate scope for CuAAC of azidoperfluoroalkanes with terminal alkynes.[a]



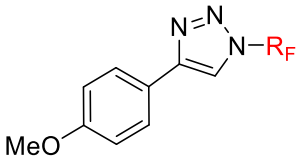

**56a-d** **68**



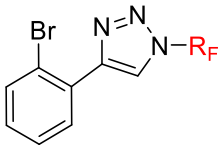

$R_F$ = $CF_3$, **68aa**, 81% (B)
$C_2F_5$, **68ba**, 84% (A)
$C_2F_5$, **68ba**, 84% (B)
$^nC_3F_7$, **68ca**, 41% (B)
$^nC_8F_{17}$, **68da**, 57% (B)



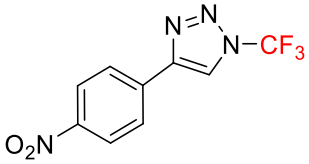

$R_F$ = $CF_3$, **68ab**, 79% (B)
$C_2F_5$, **68bb**, 88% (B)
$^nC_3F_7$, **68cb**, 90% (B)



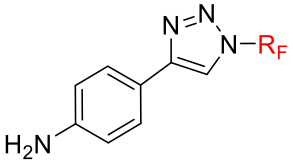

$R_F$ = $CF_3$, **68ac**, 79% (B)
$C_2F_5$, **68bc**, 63% (B)
$^nC_8F_{17}$, **68dc**, 77% (B)



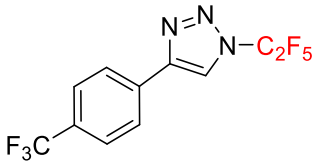

$R_F$ = $CF_3$, **68ad**, 84% (B)
$C_2F_5$, **68bd**, 37% (A)



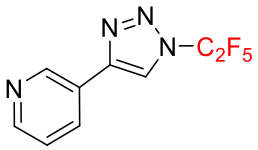

**68ae**, 82% (B)



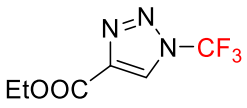

$R_F$ = $CF_3$, **68af**, 76% (B)
$C_2F_5$, **68bf**, 97% (B)



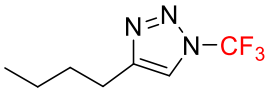

**68bg**, 91% (B)



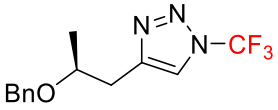

**68bh**, 38% (A)[b]



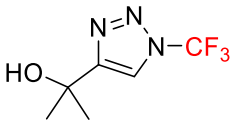

**68ai**, 48% (B)




**68aj**, 24% (B)




**68ak**, 90% (B)



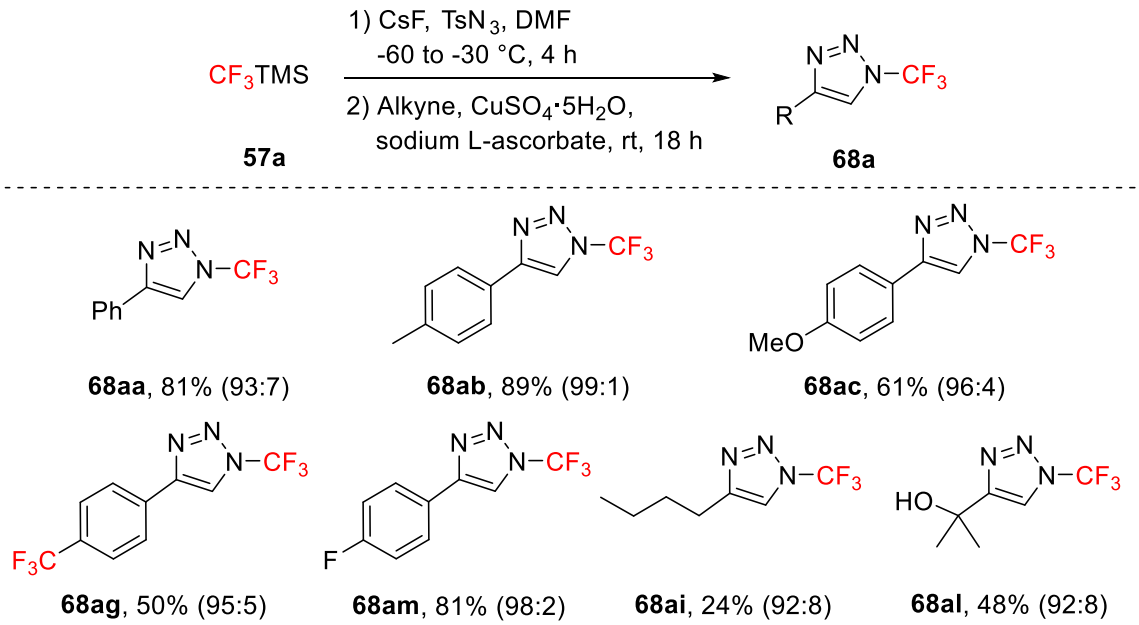

**68al**, 74% (83:17) (B)

[a] Method A: $CuSO_4 \cdot 5H_2O$ (10 mol%), sodium L-ascorbate (10 mol%), $H_2O$ (0.1 mL). Method B: CuMeSal (1–5 mol%). The reaction was set up according to the general procedure described in the experimental section. Yields are given for isolated products, ratio of 1,4- and 1,5-regiosisomers is shown in parentheses. [b] 60 °C.

Aromatic alkynes with diverse electron-withdrawing or -donating groups were suitable reaction partners in this cycloaddition, furnishing the corresponding triazoles (**68aa-68bg**) in good to high yields. Furthermore, heteroaromatic alkynes such as 3-ethynylpyridine can also participate in this transformation to afford triazole **68bh** in moderate yield at higher temperature. Additionally, aliphatic alkynes containing alkoxy, alkoxycarbonyl or hydroxy functionalities can be also successfully engaged in this reaction to give rise to the expected 1,4-disubstituted triazoles (**68ai-68al**). While giving a good $^{19}F$ NMR yield (85%), the isolated yield for compound **68aj** was rather low due to its high volatility. In all cases, the 1,4-regiosisomer was the only product of the cycloaddition. The only exception was the reaction of $CF_3N_3$ and 2-methylbut-3-yn-2-ol in the presence of 5 mol% CuMeSal which gave a mixture of the 1,4- and 1,5-regioisomers (**68al** and **69al**) in 83:17 ratio.

While investigating the optimal reaction conditions, we found out that the synthesis of N-trifluoromethyl triazoles (**68a**) can be performed in one-pot. The azide synthesis/copper(I)-catalyzed cycloaddition sequence represents a useful and convenient alternative to the two-pot process, giving comparable results. This one-pot synthetic method has the advantage of precluding the need of distilling and handling the volatile $CF_3N_3$, however, it provides lower regioselectivity than the two-pot variant. The scope of the one-pot process is presented in Table 4.

**Table 4** A one-pot protocol for the synthesis of N-trifluoromethyl triazoles from **57a**.[a]



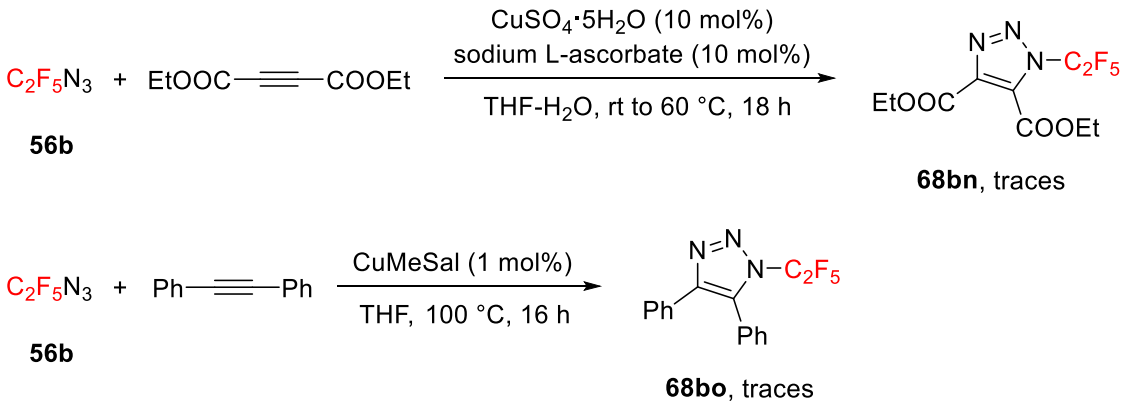

**68aa**, 81% (93:7) **68ab**, 89% (99:1) **68ac**, 61% (96:4)

**68ag**, 50% (95:5) **68am**, 81% (98:2) **68ai**, 24% (92:8) **68al**, 48% (92:8)

[a] The reaction was set up according to the procedure described in the experimental section. Isolated yields, ratio of 1,4- and 1,5-regiosisomers is shown in parentheses.

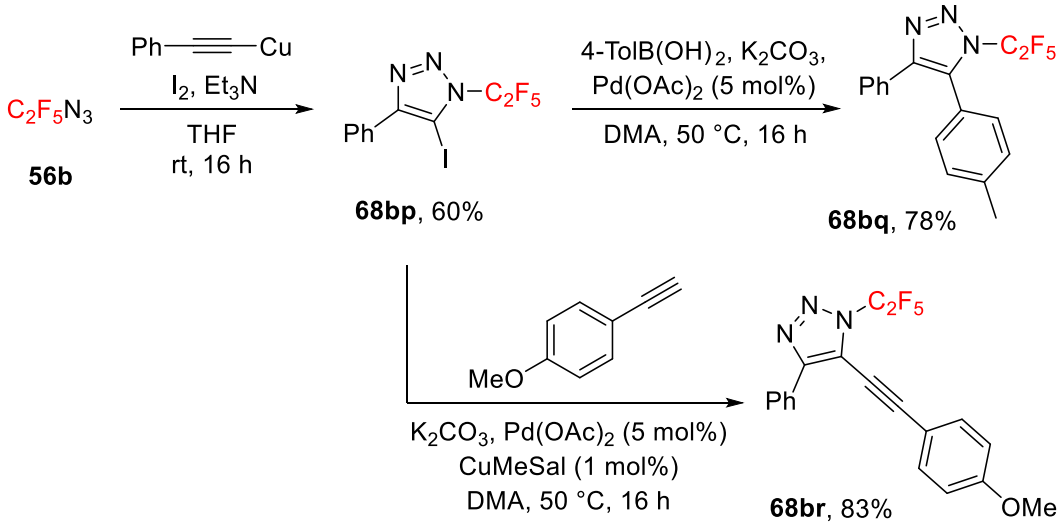
## 4.3. Attempts toward the synthesis of fully substituted N-perfluoroalkyl triazoles

As a next potential goal, we targeted the synthesis of fully substituted triazoles bearing the perfluoroalkyl group on nitrogen. Applying standard CuAAC reaction conditions, the reaction of azide **56b** with internal alkynes failed to produce the triazole products **68bn** and **68bo** even after prolonged heating as shown in Scheme 39. These results were not unexpected since the CuAAC generally lacks the ability to engage internal alkynes.




**Scheme 39** Attempts toward the synthesis of 4,5-disubstituted N-perfluoroalkyl triazoles.

While searching for other synthetic pathways, we found a practical synthesis of fully substituted triazoles in two steps *via* 5-iodotriazoles by Fokin and co-workers.[135] Based on this report, we were curious to see whether azidoperfluoroalkanes are also applicable to a similar reaction sequence. The formation of 5-iodotriazole **68bp** was carried out by reacting azide **56b** with copper(I) phenylacetylide in the presence of iodine (Scheme 40). When purifying **68bp** by column chromatography, we observed the partial deiodination of the iodotriazole accounting for lower yield of **68bp**. Next, the iodotriazole (**68bp**) was subjected to transition metal-catalyzed cross coupling reactions with an arylboronic acid or an arylacetylene to give access to product **68bq** and **68br**, respectively, in high yield (Scheme 40).




**Scheme 40** Synthesis of 4,5-disubstituted N-perfluoroalkyl triazoles *via* 5-iodotriazole.

## 4.4. Properties of N-perfluoroalkyl triazoles and azidoperfluoroalkanes in the CuAAC

The prepared N-perfluoroalkyl triazoles are crystalline solids or oils and can be easily purified either by crystallization or by column chromatography. The structures of compounds **68bc** and **68ae** have been confirmed by X-ray crystallography (Figure 4).

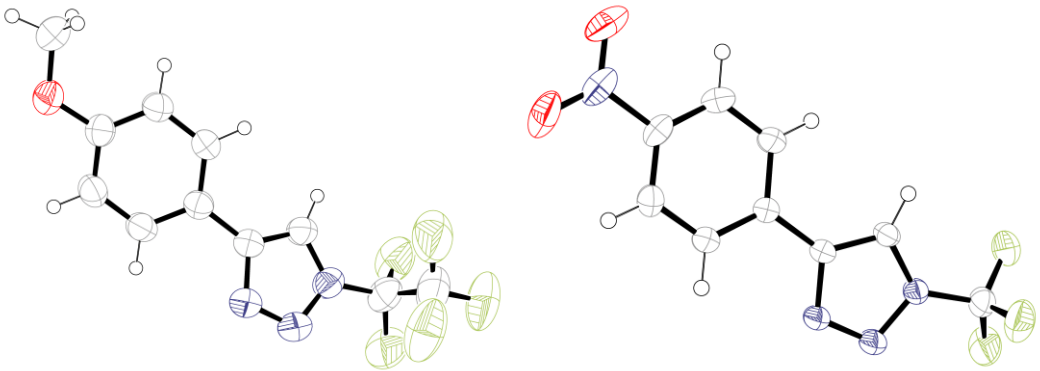


**Figure 4** ORTEP[136] view of **68bc** and **68ae**, displacement ellipsoids shown with 50% probability.

The triazoles proved to be stable under neutral, acidic or basic conditions. When the DMSO-$d_6$ solution of **68aa** was treated with excess $D_2O$, HCl or NaOH in $D_2O$ at ambient temperature, no decomposition or hydrolysis of **68aa** was observed in the NMR spectra.

Interestingly, the aromatic hydrogen of **68aa** underwent proton-deuterium exchange when being treated with NaOH in $D_2O$.

We were also interested in comparing the reactivity of azidoalkanes and corresponding azidoperfluoroalkanes in the CuAAC. The competition experiment of equimolar amounts of $C_2H_5N_3$, $C_2F_5N_3$ and 4-ethynyltoluene revealed that azidopentafluoroethane (**56b**) reacted almost twice as fast as the non-fluorinated azidoethane as shown in Figure 5.

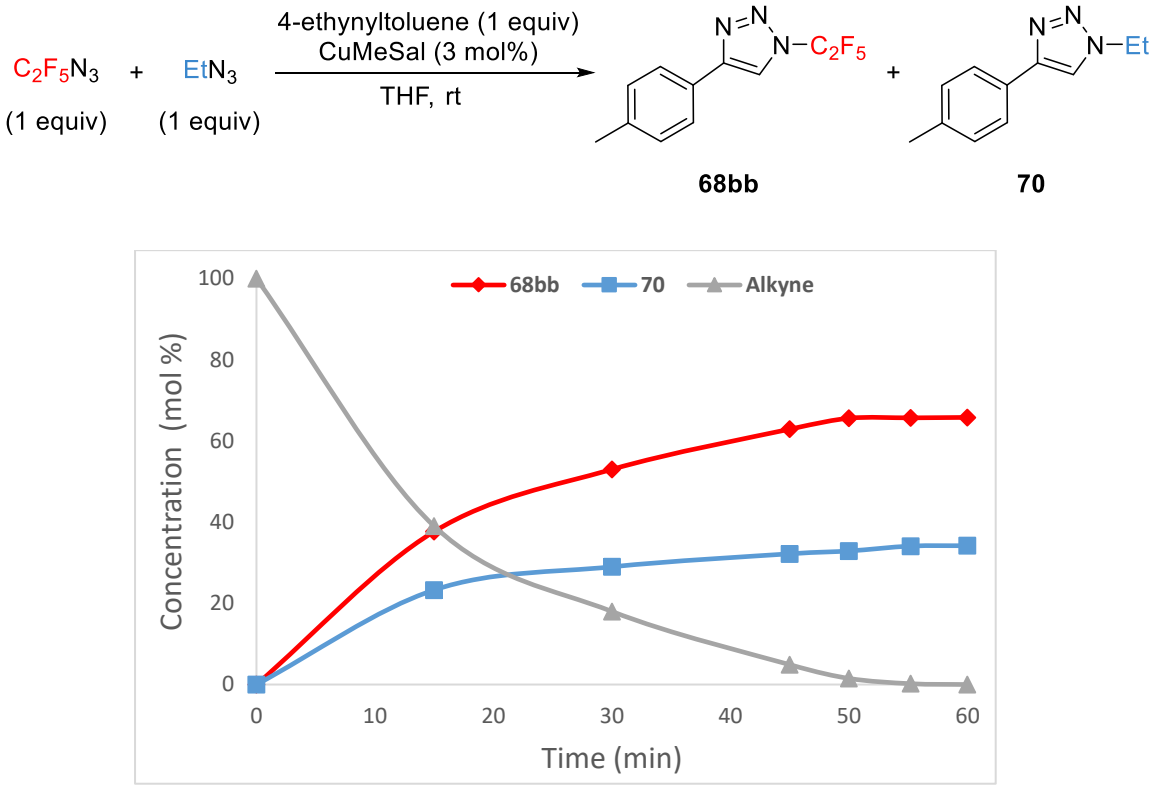



**Figure 5** Competition experiment of $C_2F_5N_3$ and $C_2H_5N_3$ in the CuAAC.

## 4.5. Conclusion and outlook

This chapter describes the first application of novel azidoperfluoroalkanes in the well-known copper(I)-catalyzed azide-alkyne cycloaddition. The azides showed excellent reactivity with a variety of terminal alkynes, forming novel N-perfluoroalkyl 1,2,3-triazoles in good to high yields. Additionally, the synthesis of perfluorinated triazoles can be achieved in one-pot which obviates the distillation step and the handling of volatile azides. Although internal alkynes cannot be engaged in the CuAAC, an alternative synthetic

approach is presented to give access to fully substituted N-perfluoroalkyl triazoles *via* 5-iodotriazoles. The triazoles prepared in this work are hydrolytically stable in acidic and basic media. Interestingly, a competition experiment revealed that azidopentafluoroethane reacted faster in the CuAAC in comparison with azidoethane.

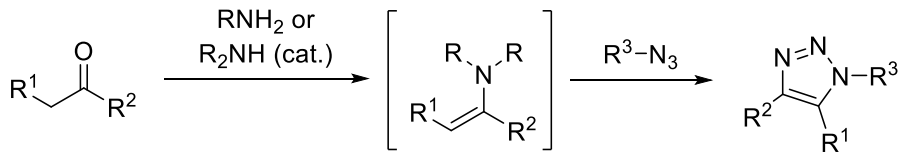
These N-perfluoroalkyl triazoles are excellent substrates in the rhodium-catalyzed transannulation as it was shown by our group.[137] The microwave-assisted synthesis of diverse 5-membered heterocycles bearing the perfluoroalkyl moiety can be achieved in a straightforward manner, using only 1 mol% Rh(II) catalyst.

# 5 Organocatalytic azide-ketone cycloaddition with azidoperfluoroalkanes

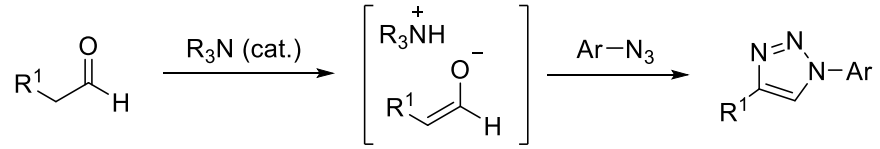
## 5.1. Introduction to the organocatalytic azide-ketone cycloaddition

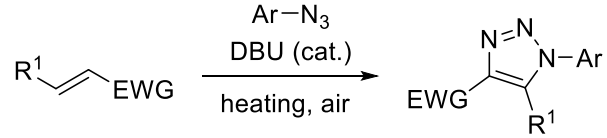
Not long after the discovery of the copper(I)-catalyzed azide-alkyne cycloaddition, metal-free 1,3-dipolar cycloaddition reactions have emerged for the synthesis of 1,2,3-triazoles. The first example was the strain-promoted azide-alkyne cycloaddition (SPAAC) between organic azides and strained cyclooctynes by Bertozzi and co-workers.[130] Besides strained cyclooctynes, diverse dipolarophiles (e.g., enamines, enolates, activated alkenes, etc.) can be used efficiently in the 1,3-dipolar cycloaddition under organocatalysis.[138–144] Scheme 41 represents an overview of the most relevant synthetic routes and reagents used in the organocatalytic [3+2] cycloaddition.

A) Organocatalytic enamine-mediated azide-ketone cycloaddition
*Ramachary, Bressy, Wang*

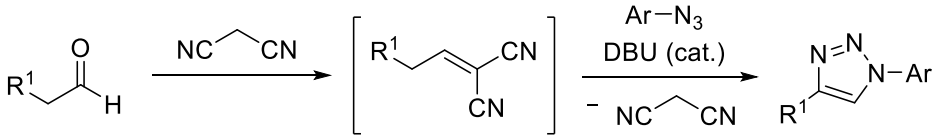


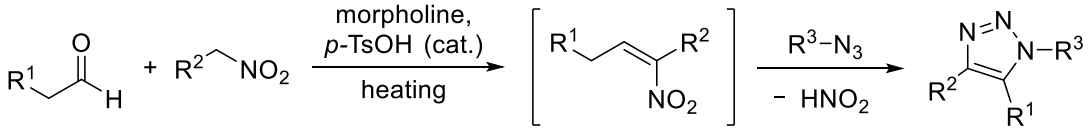

B) Organocatalytic enolate-mediated azide-ketone cycloaddition
*Ramachary, Wang*




C) Inverse electron-demand 1,3-dipolar cycloaddition
*Paixao, Dehaen*






**Scheme 41** Selected examples of organocatalytic azide-carbonyl cycloadditions.[138–144]

## 5.2. Preparation of N-perfluoroalkyl triazoles from activated ketones

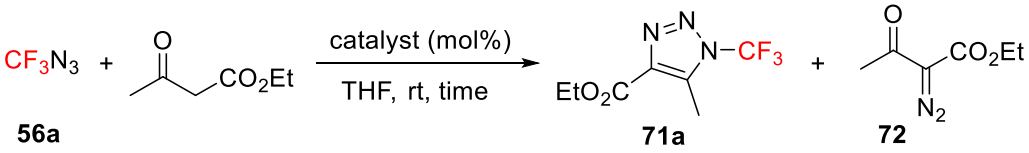
As it was shown, organic azides are able to undergo cycloaddition with activated ketones to yield highly functionalized triazoles in the presence of an organocatalyst. We thus envisioned that azidoperfluoroalkanes would be interesting reaction partners in this azide-ketone [3+2] cycloaddition to afford fully substituted triazole frameworks bearing the N-perfluoroalkyl moiety.

Azidotrifluoromethane (**56a**) and ethyl acetoacetate were selected as model substrates for this cycloaddition. The results for the optimization of reaction conditions are shown in Table 5.

Not surprisingly, the cycloaddition does not occur in the absence of catalyst (entry 1). When using L-proline as catalyst, the corresponding triazole was formed as the only regioisomer, although in low yield (entry 2). The cycloaddition might proceed through different pathways, depending on the catalyst and the reaction partners. One way could be through an enamine intermediate, we thus decided to screen other secondary amines, such as morpholine, diethylamine and piperidine, which resulted in a significant increase in the yield (entries 3–5). The other pathway could be *via* an enolate intermediate of the starting ketone with bases which are unable to form the enamine. Changing the catalyst to tertiary amines ($Et_3N$ or DBU) led to the formation of **71a** in good yields (entries 6–7). At this point, DBU seemed to be an ideal catalyst for the azide-ketone cycloaddition, giving the triazole in 89% yield within a few minutes. However, it was disappointing to see that substantial amount of by-product **72** (11%) was also formed, deriving from the concurrent Regitz diazo transfer reaction.[145] Since the desired triazole proved to be difficult to separate from the diazo ketone **72** by column chromatography, we continued to

pursue a catalyst which would minimize the formation of the diazo side product and increase the yield of triazole **71a**. Interestingly, KO$^t$Bu was also successfully employed but gave diminished yield of **71a** (entry 8). Returning to secondary amines, we were delighted to see that the reaction catalyzed by pyrrolidine afforded the triazole in the highest yield with a negligible amount of by-product **72** (2-3%, entry 9). At last, adjusting the amount of base to 10 mol% furnished **71a** in 78% isolated yield (entries 10–11).

**Table 5** Optimization of the reaction conditions for the azide-ketone cycloaddition.[a]




**56a** **71a** **72**

| Entry | Catalyst (mol%) | Time | Yield of **71a** (%)[b] |
|---|---|---|---|
| 1[c] | pyrrolidine (20) | 18 h | 87 |
| 2[c] | none | 18 h | 0 |
| 3 | pyrrolidine (20) | 18 h | 93 |
| 4 | pyrrolidine (20) | 1 h | 84 |
| 5 | L-proline (20) | 24 h | 21 |
| 6 | morpholine (20) | 24 h | 74 |
| 7 | piperidine (20) | 30 min | 81 |
| 8 | $Et_2NH$ (20) | 3 h | 73 |
| 9 | $Et_3N$ (20) | 24 h | 78 |
| 10 | DBU (20) | 10 min | 89 |
| 11 | KO$^t$Bu (20) | 30 min | 62 |
| 12 | pyrrolidine (10) | 18 h | **95** (**78**) |
| 13 | pyrrolidine (5) | 18 h | 84 |

[a] The reaction was set up according to the general procedure described in the experimental section. [b] $^{19}F$ NMR yields using $PhCF_3$ as an internal standard, isolated yield is in parentheses. [c] Using DMF/THF (1:3) solvent mixture.

Having the optimized reaction conditions in hand, we set out to explore the scope of the azide-ketone cycloaddition (Table 6). A variety of β-ketoesters and 1,3-diketones were first targeted as substrates. The model ethyl ester and bulkier esters proved to be excellent reaction partners, giving the corresponding fully substituted triazoles (**71a-d**) in good yields. Furthermore, 3-oxohexanoate could be also successfully engaged in this transfor-

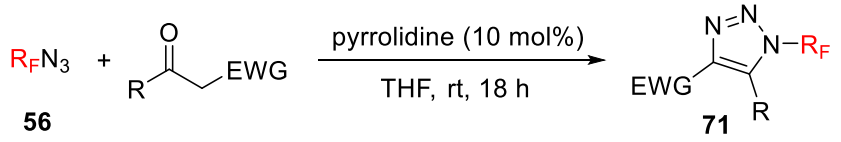
mation, although increased amount of catalyst was needed. Similarly, diketones were successfully employed as substrates to yield the fully substituted triazoles (**71f-h**). In the case of unsymmetrical diketones, we also observed the formation of the other isomer, although in much lower yield. This can be reasoned by the formation of two enamine intermediates which are not equally favored, presumably due to steric reasons. The isolated yields for some of the products are rather low, mainly due to the low volatility of the target compounds.

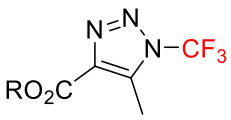
Next, we extended the scope to benzoyl acetates which were also amenable to the optimized reaction conditions. Substrates bearing electron-donating groups on the aromatic ring performed well (**71i-l**), whereas electron-withdrawing groups caused a decrease in the yield (**71m-n**). Varying the azide reaction partner, we could show that longer carbon chain azido(per)fluoroalkanes are equally capable of participating in this azide-ketone cycloaddition (**71o-r**), though higher catalyst loading was necessary.

In order to target a broader scope, we were interested to see whether it was possible to use ketones bearing other electron-withdrawing moieties. Unsurprisingly, challenging substrates required a higher catalyst loading (50 mol%) to provide the triazoles **71s-w** in moderate to good yields. Ketones possessing the phenylsulfonyl and the phosphonate group readily formed the corresponding enamines and were smoothly converted into the desired products (**71s-u**). In contrast, ketones with strong electron-withdrawing groups such as the cyano and the nitro group gave lower yields (**71v-w**), presumably due to the hindrance in the formation of the enamine intermediate.

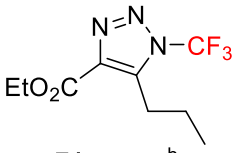
It is important to note that in most of these reactions the diazo derivative of the starting ketone is detected as the side product, yielding from the Regitz diazo transfer reaction.[145] With most of the ketones, the diazo transfer remained a negligible reaction. Nevertheless, when using benzoyl acetonitrile as a substrate, lower formation of the triazole **2v** was observed, accompanied by an increased yield of the diazo compound (21%).

**Table 6** Substrate scope for the enamine-catalyzed azide-ketone cycloaddition with activated ketones.[a]

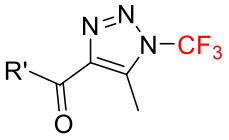


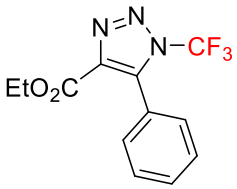
R = Et, **71a**, 78%
$^{i}$Bu, **71b**, 66%
$^{t}$Bu, **71c**, 79%
Bn, **71d**, 81%



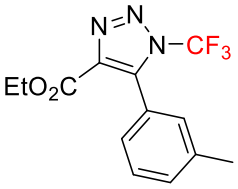
**71e**, 65%[b]



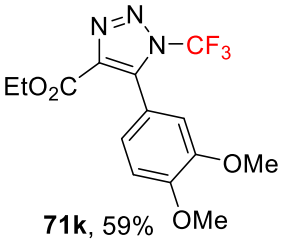
R' = Me, **71f**, (80%) 49%
Bu, **71g**, 74%
Ph, **71h**, 60%



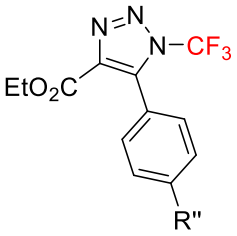
**71i**, 70%



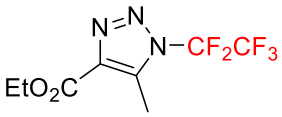
**71j**, 52%



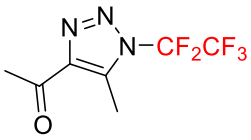
**71k**, 59%



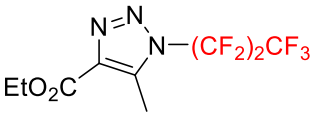
R'' = Me, **71l**, 73%
Cl, **71m**, 45%
$NO_2$, **71n**, 38%[b]



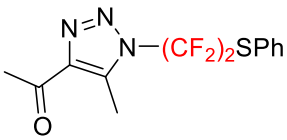
**71o**, 78%[b]



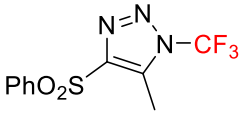
**71p**, 68%[b]



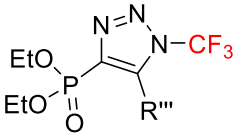
**71q**, 43%[b]



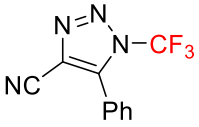
**71r**, 98%[b]



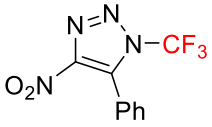
**71s**, 84%[c]



R''' = Me, **71t**, 88%[c]
Ph, **71u**, 55%[c]



**71v**, 35%[c]



**71w**, 40%[c]

[a] The reaction was set up according to the general procedure described in the experimental section. Isolated yields, $^{19}$F NMR yields in parentheses. [b] 20 mol% catalyst. [c] 50 mol% catalyst.

Crystals suitable for X-ray analysis could be obtained for product **71i**, showing that the phenyl ring is approximately perpendicular to the triazole ring. On the other hand, the ethoxycarbonyl group is in the plane of the triazole ring (Figure 6).

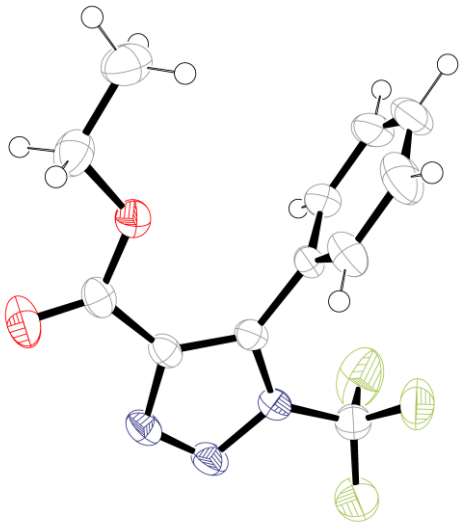
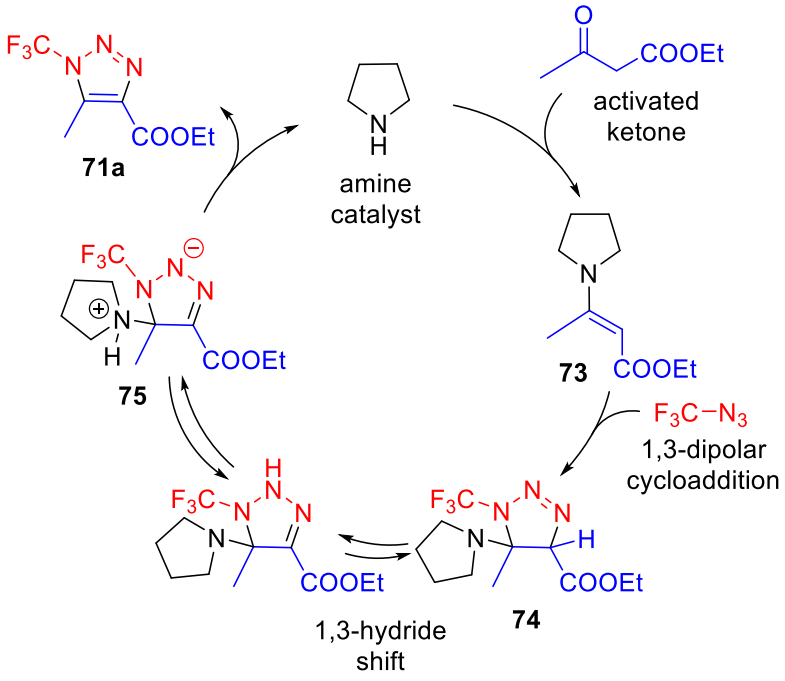


**Figure 6** ORTEP[136] representation of the X-ray structure of **71i**, displacement ellipsoids shown with 50% probability.

## 5.3. Mechanistic considerations

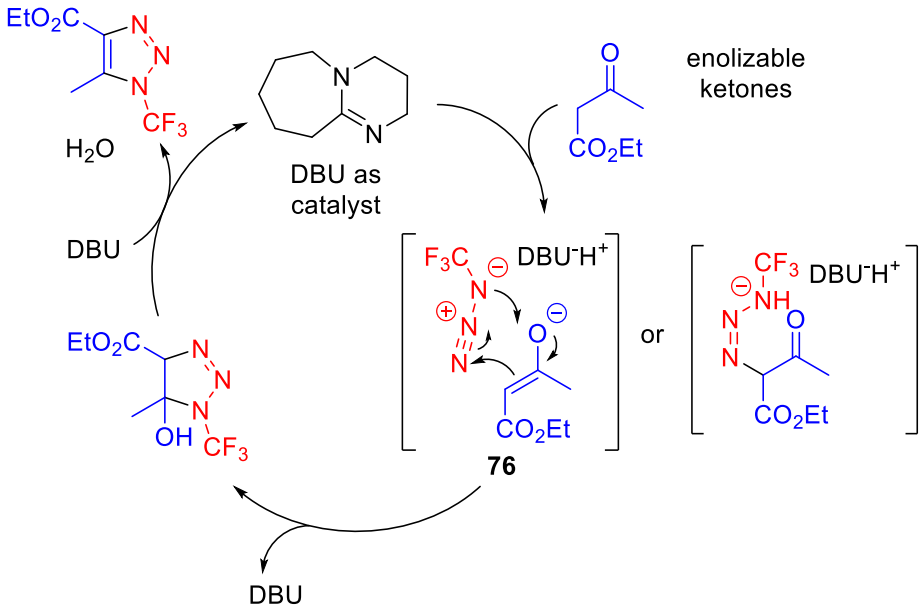
Mechanistic proposals have been extensively published concerning this organocatalytic azide-carbonyl [3+2] cycloaddition.[139,146] Depending on the reaction conditions, two pathways can be envisioned for this transformation which are depicted in Scheme 42 and Scheme 43.

One pathway involves the catalytic formation of an enamine (**73**) which then undergoes cycloaddition with the azidotrifluoromethane to give rise to the triazoline intermediate **74**. After the 1,3-hydride shift, triazoline **74** rearranges to the zwitterion form **75** which rapidly eliminates pyrrolidine, to start a new catalytic cycle, and consequently produces the desired triazole (Scheme 42).




**Scheme 42** Proposed mechanism for the enamine-mediated azide-ketone cycloaddition.

The other pathway starts with the formation of the enolate **76** by the reaction of DBU with the enolizable ketone. The enolate readily reacts with the azide either in a concerted [3+2] cycloaddition or in a stepwise addition/cyclization pathway. The final step of the catalytic cycle is a base-induced water elimination to obtain the fully substituted triazole (Scheme 43).




**Scheme 43** Proposed mechanism for the enolate-mediated azide-ketone cycloaddition.

To gain some mechanistic insight, the reaction of the model substrates was monitored by $^1$H NMR spectroscopy as represented in Figure 7.

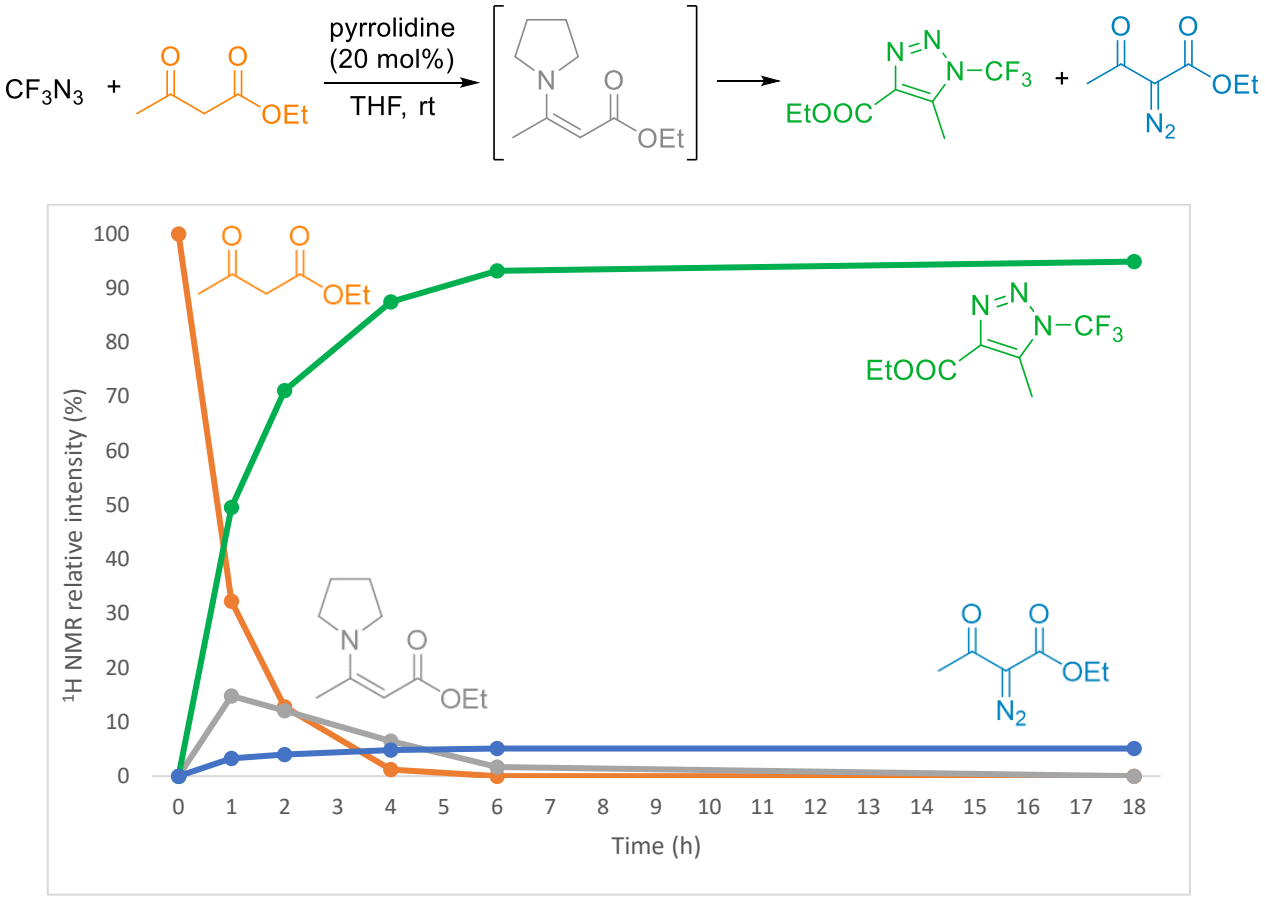
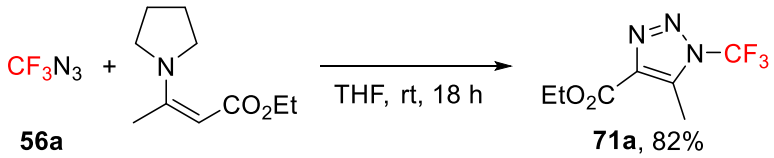



**Figure 7** $^1$H NMR reaction profile of the [3+2] cycloaddition of azidotrifluoromethane and ethyl acetoacetate, using 20 mol% pyrrolidine as catalyst.

We clearly observed the formation of the enamine intermediate which was gradually consumed and transformed into the triazole product. Besides, the diazo compound was also formed in a small amount (5%), deriving from the diazo transfer reaction.

To prove the involvement of the enamine, we ran a control experiment with ethyl acetoacetate and catalytic amount of pyrrolidine, in the absence of the azide (**56a**) reaction partner. The $^1$H NMR spectrum clearly showed the formation of the enamine. Furthermore, another control experiment was designed to corroborate the enamine-mediated mechanism. When mixing the azide **56a** with the previously prepared pyrrolidinyl enamine, a quantitative formation of the triazole product was observed (Scheme 44). These results were able to confirm the intermediacy of the enamine.



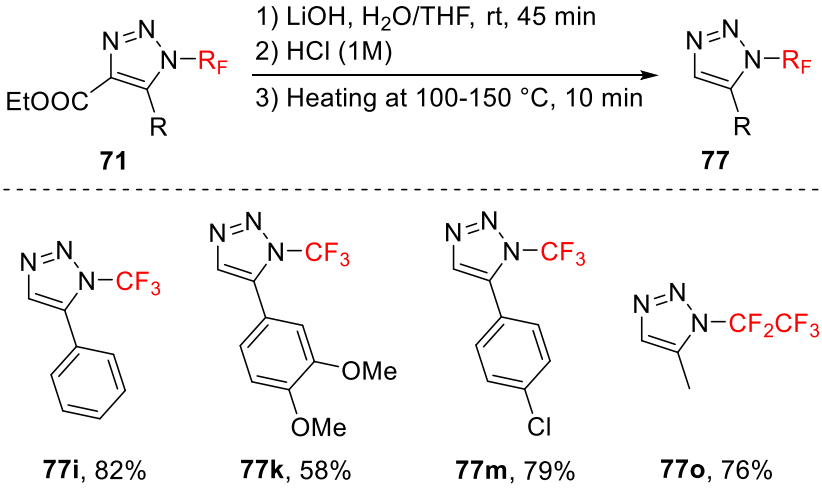

**Scheme 44** The reaction of $CF_3N_3$ with pyrrolidinyl enamine.

## 5.4. Hydrolysis and decarboxylation of N-perfluoroalkyl triazoles

As discussed in Chapter 4, the discovery of the copper-catalyzed azide-alkyne cycloaddition opened a new possibility of regioselective synthesis of 1,4-disubstituted 1,2,3-triazoles.[98,99] The advances in this area prompted organic chemists to explore the synthesis of the 1,5-disubstituted isomer which was first achieved with ruthenium(II) complex catalysis.[129,147] Some alternative approaches have been reported,[148–151] however, new methods of synthesizing the 1,5-disubstituted triazoles are still in demand.

We were thus curious to see if our highly functionalized triazoles with an ester functionality at position 4 could be precursors to 1,5-disubstituted triazoles. The ester hydrolysis of triazole **71** was carried out using lithium hydroxide, followed by addition of diluted HCl solution to furnish the acid. After a simple workup, the acid was subjected to decarboxylation to provide the 1,5-disubstituted triazole (**77**). Table 7 shows a narrow reaction scope for this hydrolysis/decarboxylation reaction.

**Table 7** Ester hydrolysis and decarboxylation of highly functionalized triazoles.[a]

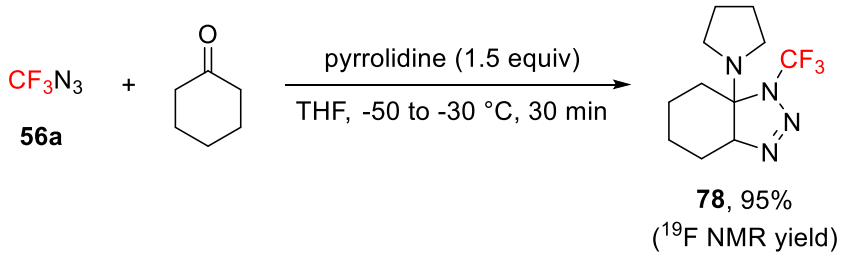



[a] The reaction was set up according to the general procedure described in the experimental section. Yields are given for isolated products.

## 5.5. Cycloaddition with cyclic ketones

As a next potential goal, we targeted the cycloaddition of cyclohexanone derivatives and azidotrifluoromethane, yielding tetrahydro-1*H*-benzotriazoles. When reacting $CF_3N_3$ with cyclohexanone in the presence of 10 mol% pyrrolidine, we were surprised to see that the expected tetrahydro-benzotriazole was not formed. Being curious to find out why the reaction failed, we started to investigate this cycloaddition under various reaction conditions.

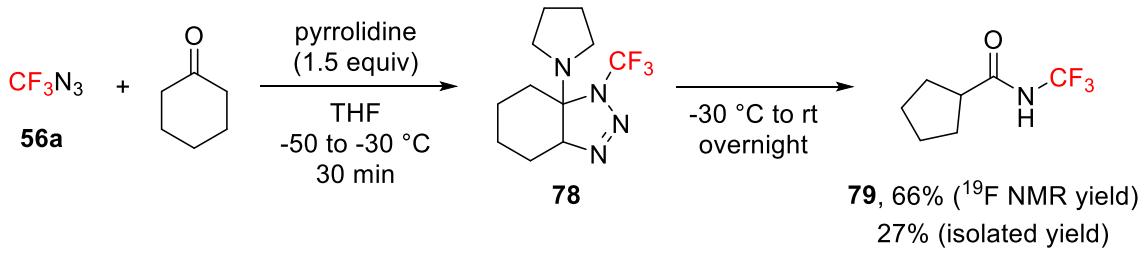
When increasing the amount of pyrrolidine, we observed the appearance of a new species at -57.16 ppm in the $^{19}F$ NMR spectrum. Applying 1.5 equivalents of pyrrolidine, this new species formed almost quantitatively at low temperature within 30 min. However, this compound proved to be highly unstable at room temperature, both in solution and in pure form, and prone to decomposition on silica or alumina. The attempted purification of the compound by column chromatography led to the target triazole in very low yield (<10%), along with other non-identified by-products. After considerable effort, we were able to isolate the compound which was identified as the triazoline **78** (Scheme 45).




**Scheme 45** Reaction of $CF_3N_3$ with cyclohexanone.

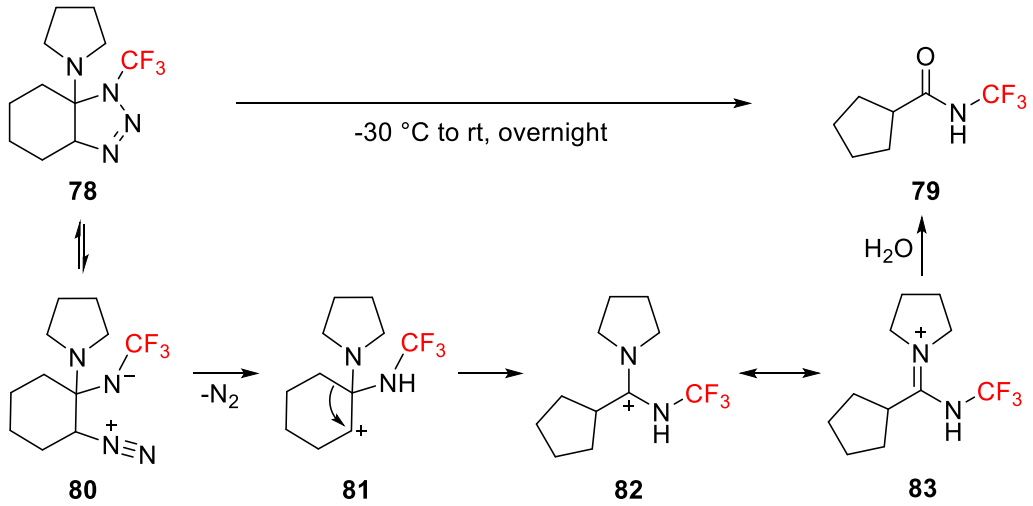
The formation of triazoline **78** is not unexpected since it is the first intermediate formed in the enamine-mediated azide-ketone cycloadditions (see Scheme 42). Although, it is worthy to mention that we have never observed the triazoline intermediate in the cycloaddition with activated ketones. Depending on the substituents, triazolines can be isolated but they are known to easily undergo various transformations upon heating or when being reacted with acids or bases.[152]

When the reaction mixture was stirred overnight reaching slowly to room temperature, we observed a new broad signal at -57.48 ppm by $^{19}$F NMR spectroscopy. After purification by column chromatography, a white crystalline solid was obtained, albeit in low isolated yield, which we identified as being the ring-contracted amide **79** (Scheme 46).




**Scheme 46** Spontaneous transformation of triazoline **78** to amide **79**.

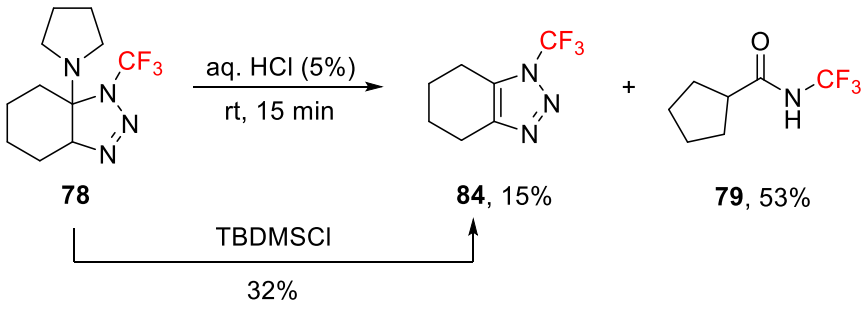
The amide formation is rather surprising since, to the best of our knowledge, there are no reports on the transformation of triazolines to amides as we observed. Scheme 47 outlines a plausible mechanism for this unusual transformation. Triazoline **78** might be in equilibrium with the diazo compound **80** which can release dinitrogen to form a secondary carbocation **81**. Carbocation **81** would quickly rearrange to the more stable tertiary carbocation **82** *via* a 1,2-alkyl shift. Carbocation **82** is hydrolyzed by water present in the mixture, deriving from the enamine formation, to afford the amide **79**.




**Scheme 47** Mechanistic proposal for the formation of amide **79**.

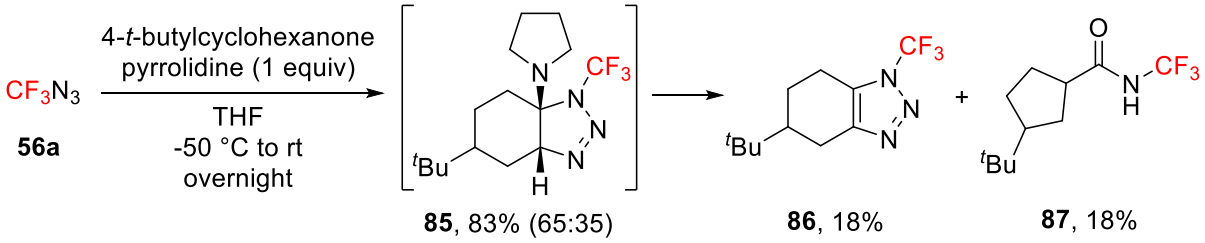
In the hope to obtain the triazole, we investigated various conditions reported in the literature.[153] When the triazoline **78** was subjected to heating at 100 °C, KOH in refluxing MeOH, acetic anhydride in pyridine or MCPBA, we did not observe any product formation. Interestingly, upon quenching the reaction with aqueous HCl (5%), the triazoline

was converted to the mixture of amide **79** and triazole **84** in 53% and 15% yield,[1] respectively (Scheme 48). Another unexpected observation was that the addition of a silylating reagent, TBDMSCl, to the triazoline resulted in the formation of the triazole **84** in 32% isolated yield and other by-products (Scheme 48).




**Scheme 48** Formation of triazole **84** and amide **79** from triazoline **78**.

Next, a few other cyclohexanone derivatives were studied in this cycloaddition reaction. Unfortunately, cyclohexanones with substituents in position 2 (e.g., Me and COOMe) failed to react under the presented conditions. Interestingly, the reaction of racemic 4-*tert*-butylcyclohexanone with $CF_3N_3$ resulted in the quick formation of two products which we believed to be the diastereomers of **85** (Scheme 49). As the reaction mixture was stirred overnight while allowed to warm to room temperature, we observed the formation of triazole **86** and amide **87**, both in 18% $^{19}F$ NMR yield.




**Scheme 49** Cycloaddition of azidotrifluoromethane and 4-*t*-butylcyclohexanone.

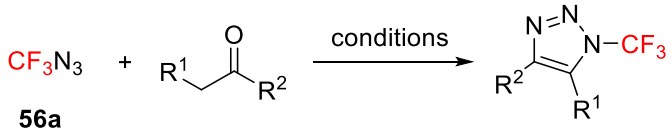
## 5.6. Limitations of the azide-carbonyl cycloaddition

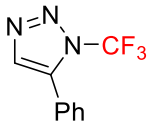
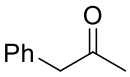
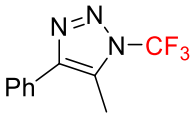
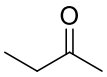
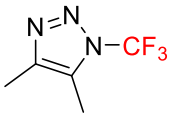
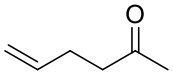
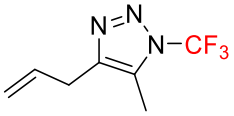
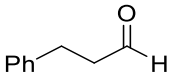
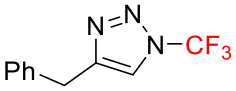
Other carbonyl compounds were also evaluated as summarized in Table 8. No traces of the desired products could be observed in most cases (entries 1, 3 and 4). The only

[1] Yields are of the crude mixture, after workup, without purification.

exception was 1-phenylpropan-2-one which afforded the expected product in 16% isolated yield (entry 2). Disappointingly, 3-phenylpropanal did not react with azidotrifluoromethane under the conditions reported by Ramachary and co-workers (entry 5).[141]

**Table 8** The limitations of the azide-carbonyl cycloaddition.[a]




| Entry | Substrate | Conditions | Product | Yield (%) |
|---|---|---|---|---|
| 1 |  | pyrrolidine, DBU or LDA (0.1-1 equiv), -40 °C to rt, 18 h |  | 0 |
| 2 |  | pyrrolidine (0.2-1 equiv), rt, 18 h |  | 16[b] |
| 3 |  | pyrrolidine (0.2-1 equiv), rt, 18 h |  | 0 |
| 4 |  | pyrrolidine (0.1 equiv), rt, 18 h |  | 0 |
| 5 |  | DBU (0.1 equiv), rt, 18 h |  | 3[c] |

[a] The reaction was set up according to the procedure described in the experimental section. [b] Isolated yield, compound **88**. [c] $^{19}$F NMR yield using $PhCF_3$ as an internal standard.

## 5.7. Conclusion

In this chapter, the application of azidoperfluoroalkanes in the organocatalytic azide-ketone cycloaddition is reported. Activated ketones can be easily transformed into highly functionalized triazoles, using catalytic amount of pyrrolidine. It was shown that the ester functionality on the triazole ring can be removed which allowed the synthesis of 1,5-disubstituted triazoles. Mechanistic studies indicated the intermediacy of the enamine in the cycloaddition. Some cyclohexanone derivatives reacted with the fluorinated azides to

provide the corresponding triazolines. The triazolines are not stable and readily decompose to triazole and amide products under the given conditions. The limitations of the azide-ketone cycloaddition were also demonstrated.

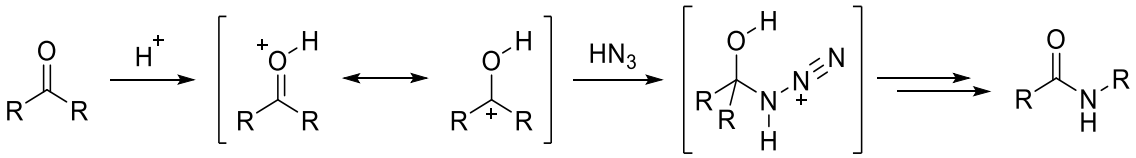
# 6 Protonation of azides in superacids

*This chapter is a result of a collaboration with the group of Dr. Surya Prakash. It encloses contributions from Archith Nirmalchandar with whom the NMR spectroscopic measurements were done, Dr. Golam Rasul who performed the calculations, and Amanda F. Baxter who assisted with the $^{14}N$ NMR measurements.*

## 6.1. Introduction

Reactive intermediates have been a subject of considerable interest, mainly to gain an understanding of organic reaction mechanisms.[154,155] Experimental observation of these fleeting, high-energy species is rather difficult in the condensed phase, however, it is central to provide insight into organic transformations of industrial importance.[156–158] Thanks to the thorough research on carbocations by George Olah and other chemists, there has been a great advancement in general methods to prepare these long-lived electrophilic intermediates.[157,159] The breakthrough came when using superacids, whose acidity are greater than that of 100% sulfuric acid, which enabled to protonate fundamental classes of organic compounds, including alkanes, alkenes, arenes, halocarbons and others.[160,161] Their unique ability to generate stable ionic salts lies not only in their increased acidity but also in the low nucleophilicity of the involved counteranions formed in non-primary superacid systems.[157,158]

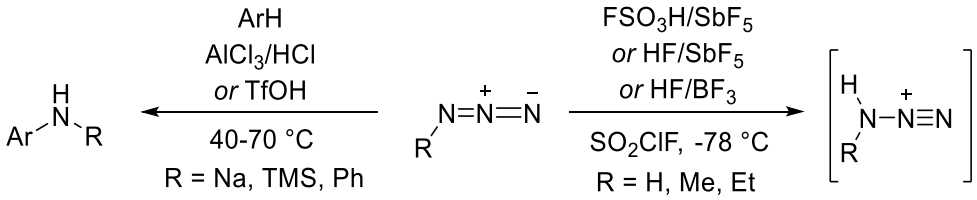
Protonation of organic azides results in the formation of aminodiazonium ions which might dissociate to nitrenium ions with concomitant loss of nitrogen.[162] Aminodiazonium ions have been proposed as intermediates in the Schmidt reaction (Scheme 50).[163,164]




**Scheme 50** The Schmidt reaction of ketones *via* the aminodiazonium intermediate.

However, only a few reports are known to date which describe the preparation and structural characterization of these highly reactive electrophilic species in the condensed phase as summarized in Scheme 51. Schmidt was the first who suggested the existence

of the aminodiazonium ion in 1966, although the IR spectra of the prepared $[SbCl_6]^-$ salt of protonated methyl azide and hydrazoic acid are rather inconclusive.[165] Long after Schmidt's postulate, Olah and co-workers accomplished the first unequivocal formation and spectroscopic characterization of some onium ions.[166] Protonation of small molecule azides ($HN_3$, $MeN_3$, $EtN_3$) was achieved in binary superacid systems ($FSO_3H/SbF_5$, $HF/SbF_5$ or $HF/BF_3$) and the resulting cations were studied by NMR spectroscopy. A more feasible synthetic route was also found to obtain $[H_2N_3]^+$ *in situ* when $NaN_3$ or $TMSN_3$ was reacted with $AlCl_3$/HCl or triflic acid.[166,167] This convenient preparation of the aminodiazonium salt allowed its use as an efficient electrophilic reagent in the amination of aromatic compounds. Phenyl azide was also proved to be a suitable synthon for electrophilic amination of aromatics under superacidic conditions, however, the $[PhNHN_2]^+$ ion could not be characterized due to decomposition.[168] At that time, Christe *et al.* isolated room-temperature stable salts of $[H_2N_3]^+$ from the HF solution of $HN_3$ with different Lewis acids and determined the structure of the $[SbF_6]^-$ salt by X-ray crystallography.[169]




**Scheme 51** Protonation of azides in superacids and their use in amination of arenes.[166–169]

Thus, we were intrigued to see whether azidotrifluoromethane could be protonated in superacidic media and the protonated species could be characterized by spectroscopic methods and potentially used as an aminating reagent in the electrophilic amination of aromatics.

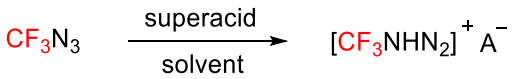
## 6.2. Protonation of azidotrifluoromethane

The protonation of $CF_3N_3$ was initially investigated using a large excess of primary superacids in dichloromethane at ambient and subambient temperatures. Unfortunately, both triflic acid and fluorosulfonic acid failed to protonate the trifluoromethyl azide and the protonated species could not be observed (Table 9, entries 1 and 2). Despite using magic acid (a 1:1 mixture of $FSO_3H/SbF_5$), whose acidity is four magnitudes greater than

that of $CF_3SO_3H$ or $FSO_3H$,[158] azidotrifluoromethane could not be protonated under these reaction conditions (entry 3).

At this point, we had to consider two practical issues. On the one hand, it was suspected that the protonation reaction was hampered by the immiscibility of the DCM solution of the azide and the various superacids. Hence, changing the solvent to $SO_2ClF$, which is known to be a more suitable, low-nucleophilicity solvent for superacid chemistry,[158] could circumvent the issue of miscibility and consequently the formation of a biphasic system. Not only is $SO_2ClF$ able to facilitate the dissolution of both reaction partners but also enables the recording of spectra at low temperatures. On the other hand, aminodiazonium ions are known to be persistent species at low temperatures.[166,169] Therefore, it seemed necessary to perform the protonation reaction at subambient temperature due to the thermal stability of the cation.

**Table 9** Attempted protonation of $CF_3N_3$ under various reaction conditions.[a]




**56a** **89**

| Entry | Solvent | Superacid | Temperature | $[CF_3NHN_2]^+$ observed by NMR |
|---|---|---|---|---|
| 1 | DCM | TfOH | rt or -35 °C | no |
| 2 | DCM | $FSO_3H$ | rt or -78 °C | no |
| 3 | DCM | $FSO_3H/SbF_5$ (1:1) | -78 °C | no |
| 4 | $SO_2ClF$ | $FSO_3H$ | -78 °C | no |
| 5 | $SO_2ClF$ | $FSO_3H/SbF_5$ (1:1) | -78 °C | yes |

[a] The reaction was set up according to the procedure described in the experimental section.

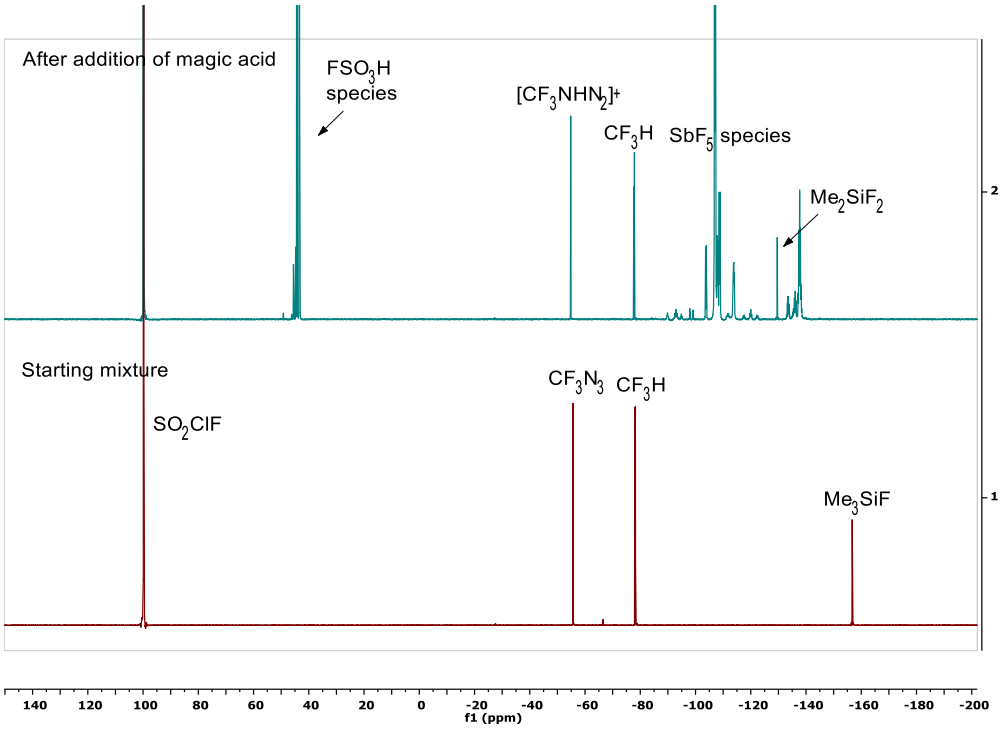
In spite of employing $SO_2ClF$ as a solvent, no evidence could be found for the formation of $[CF_3NHN_2]^+$ when reacting $CF_3N_3$ with fluorosulfonic acid at -78 °C (entry 4). It is known that the counteranions formed in non-primary superacid systems enhance the stability of cationic species due to low nucleophilicity which renders the characterization and isolation of these salts possible.[158] Along with the increased acidity, it can be expected that the anionic species present in magic acid[170–173] would promote the protonation of azidotrifluoromethane. Indeed, upon slow addition of the mixture of $FSO_3H/SbF_5$ (1:1)

to the azide solution in $SO_2ClF$ at -78 °C, a pale yellow solution formed immediately (entry 5). The resulting reaction mixture was studied by low-temperature NMR spectroscopy. It is important to note that the counteranion of the protonated azide has not been identified. Depending on the concentration of $FSO_3H$ and $SbF_5$, magic acid contains a complex mixture of counteranions. Based on the report by Aubke, the main anionic species of magic acid (1:1) is $[FSO_3SbF_5]^-$.[173]

When preparing $CF_3N_3$, fluoroform and fluorotrimethylsilane are also formed in the reaction as described in Chapter 3. While preparing the NMR sample, these two volatile by-products also condensed along with the azide. Upon protonation, TMSF was converted to difluorodimethyl silane whereas $CF_3H$ remained intact. The two compounds are easily recognizable and did not interfere with the measurements of the protonated azide.

## 6.3. Characterization of the $[CF_3NHN_2]^+$ by NMR spectroscopy

The $^{19}F$ NMR spectrum of the protonated species resulting from entry 5 (Table 9) gave rise to a sharp singlet at δ = -54.8 ppm which seemed almost identical to that of the parent azide (δ = -55.6 ppm). However, the coupling constant ($^1J_{C\text{-}F}$ = 284.3 Hz) measured by the $^{13}C$ satellite signals clearly indicated the appearance of a new species (Figure 8).



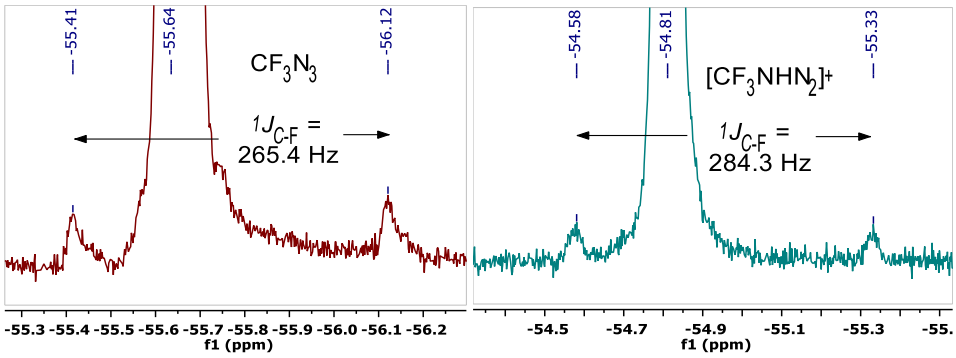



**Figure 8** $^{19}$F NMR spectrum of the $[CF_3NHN_2]^+$ generated from $CF_3N_3$ at -78 °C, using $SO_2ClF$ as reference (99.8 ppm).

The $^{13}$C NMR spectrum showed a quartet at δ = 116.3 ppm with $^1J_{C\text{-}F}$ coupling constant of 282.9 Hz which is in good agreement with the value derived from the $^{19}$F NMR spectrum. Intriguingly, the amino group on N-1 appeared as a broad signal at δ = 10.37 ppm in the $^1$H NMR. The $^{14}$N NMR spectrum displayed a broad resonance at δ = -173.8 ppm for the N-2, which is shifted 24.1 ppm upfield compared to that of the azide precursor (δ = -149.8 ppm). The $^{14}$N chemical shifts for the N-1 and N-3 of $CF_3N_3$ were in accordance with reported values;[174] however, after addition of the magic acid, none of those nitrogen atoms was observed. The recorded chemical shifts are listed in Table 10.

The NMR spectroscopic data for the unprotonated $CF_3N_3$ and protonated $[CF_3NHN_2]^+$ were validated by GIAO-CCSD(T) NMR calculations using tzp level and MP2/cc-pVTZ geometries. The trends in calculated chemical shifts of the neutral and protonated species were in good agreement with the experimentally obtained values (Table 10).

**Table 10** Experimental and calculated chemical shifts of $CF_3N_3$ and $[CF_3NHN_2]^+$.

| | | $CF_3N_3$ | | $[CF_3NHN_2]^+$ | |
|---|---|---|---|---|---|
| | | Experimental[a] | Calculated[b] | Experimental[a] | Calculated[b] |
| δ ($^1$H) | | - | - | 10.37 (s) | not calcd |
| δ ($^{13}$C) | | 121.9 (q)[c] | 125.0 | 116.3 (q)[d] | 122.4 |
| δ ($^{14}$N) | N-1 | -287.1 | -262.0 | n. o. | -246.7 |
| | N-2 | -149.8 | -121.4 | -173.8 | -147.7 |
| | N-3 | -145.5 | -123.5 | n. o. | -61.8 |
| δ ($^{19}$F) | | -55.6 (s) | -47.5 | -54.8 (s) | -41.9 |

[a] NMR chemical shifts (in ppm) were measured at temperatures below -67 °C, using acetone-$d_6$ as external standard; n. o.: not observed. [b] NMR chemical shifts were calculated at the GIAO-CCSD(T)/tzp level using MP2/cc-pVTZ geometries. [c] $^1J_{C\text{-}F}$ = 265.9 Hz. [d] $^1J_{C\text{-}F}$ = 282.9 Hz.

## 6.4. NMR studies on the protonation of $^{15}N$ enriched azidotrifluoromethane in magic acid

For further structural information, $^{15}N$-labeled azidotrifluoromethane, a 1:1 mixture of $CF_3{}^{15}NNN$ and $CF_3NN{}^{15}N$, was prepared in two steps as described in Chapter 3, starting from terminally enriched sodium azide. After protonation of $^{15}N$ enriched $CF_3N_3$ with magic acid ($FSO_3H/SbF_5$, 1:1) at -78 °C, two NH groups were observed in the $^1H$ NMR spectrum (Figure 9). The NH of $[CF_3{}^{15}NHNN]^+$ is split to a doublet by the $^{15}N$ ($^1J_{H\text{-}N}$ = 106.9 Hz), whereas the NH of $[CF_3NHN{}^{15}N]^+$ remains a singlet.

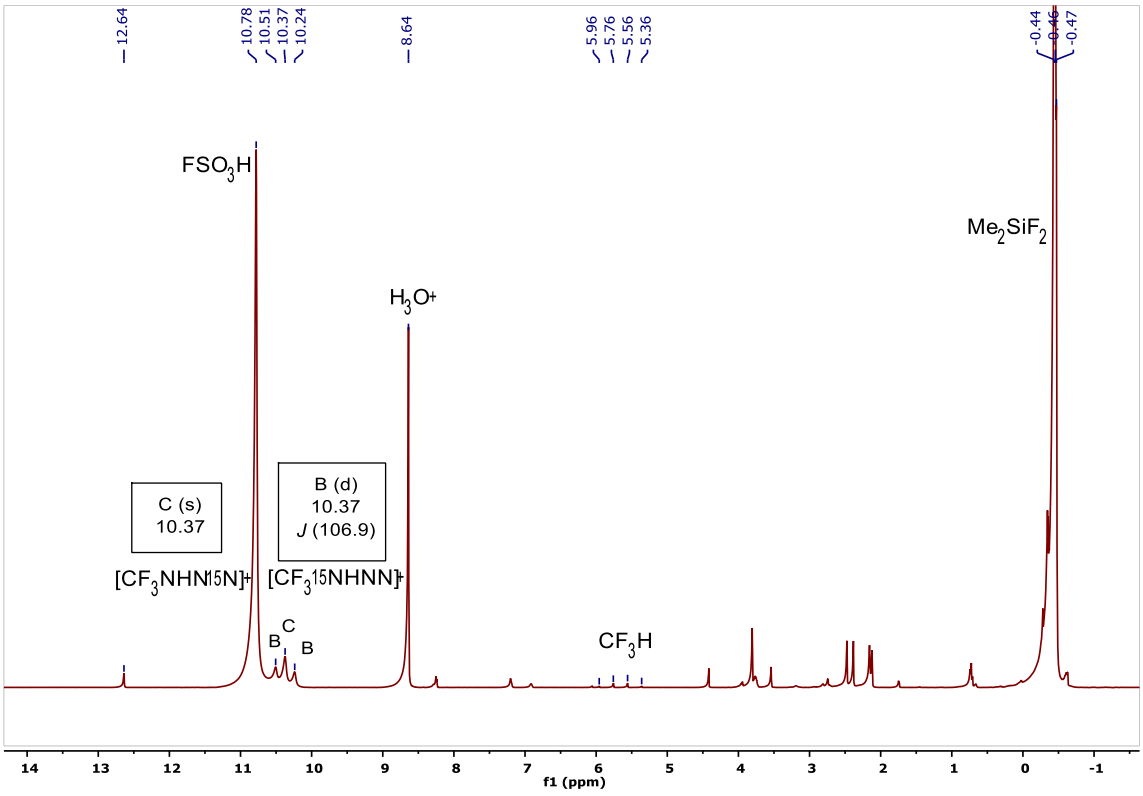



**Figure 9** $^1H$ NMR spectrum of the $SO_2ClF$ solution of $^{15}N$ enriched $CF_3N_3$ after protonation with magic acid ($FSO_3H/SbF_5$, 1:1) at -78 °C, using acetone-$d_6$ as external standard (2.05 ppm).

The two protonated species are also easily distinguishable by their splitting patterns in the $^{13}C$ and $^{19}F$ NMR spectra as $[CF_3{}^{15}NHNN]^+$ exhibits an additional doublet. In the $^{15}N$ NMR spectrum, the $^{15}N$ of $[CF_3{}^{15}NHNN]^+$ shows a characteristic doublet of quartets, whereas the terminal $^{15}N$ remains a singlet, which is an unequivocal proof of the protonation taking place at N-1 (Figure 10). Interestingly, N-1 shows a rather small downfield

shift, while N-3 is considerably deshielded in comparison with the azide precursor. The NMR spectroscopic data of the $^{15}N$-labeled sample are summarized in Table 11.

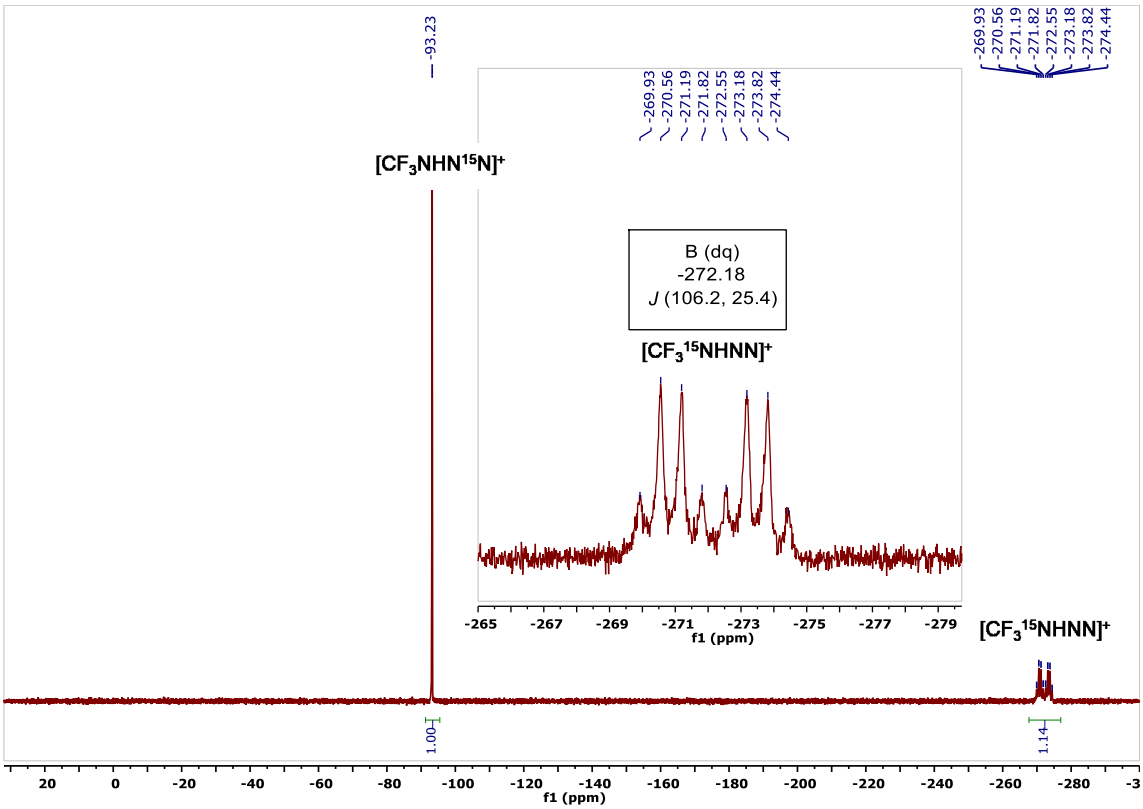



**Figure 10** $^{15}N$ NMR spectrum of $[CF_3{}^{15}NHNN]^+$ and $[CF_3NHN^{15}N]^+$, generated from the $^{15}N$-labeled trifluoromethyl azide at -78 °C, using $CH_3{}^{15}NO_2$ as reference (0 ppm).

**Table 11** NMR spectroscopic data of $^{15}N$-labeled $CF_3N_3$, before and after protonation.[a]

| | $CF_3NN^{15}N$ | $CF_3{}^{15}NNN$ | $[CF_3NHN^{15}N]^+$ | $[CF_3{}^{15}NHNN]^+$ |
|---|---|---|---|---|
| δ ($^1H$) | - | - | 10.37 (s) | 10.37 (d) |
| δ ($^{13}C$) | 121.89 (q) | 121.86 (qd) | 116.39 (q) | 116.39 (qd) |
| δ ($^{15}N$) | -145.39 (s) | -287.11 (q) | -93.23 (s) | -272.18 (dq) |
| δ ($^{19}F$) | -56.05 (s) | -56.07 (d) | -54.82 (s) | -54.84 (d) |

[a] NMR chemical shifts (in ppm) were measured at or below -50 °C, using acetone-$d_6$ as external standard.

## 6.5. Thermal stability of the trifluoromethyl aminodiazonium ion

The $[CF_3NHN_2]^+$ cation was found to be reasonably stable when stored at -78 °C and no sign of decomposition was observed even after three weeks. Variable-temperature $^{19}F$ NMR experiments revealed that the cation also possesses a good thermal stability up to -32 °C (Figure 11). Integration of the area under the cation signal relative to that of the solvent remained essentially constant.

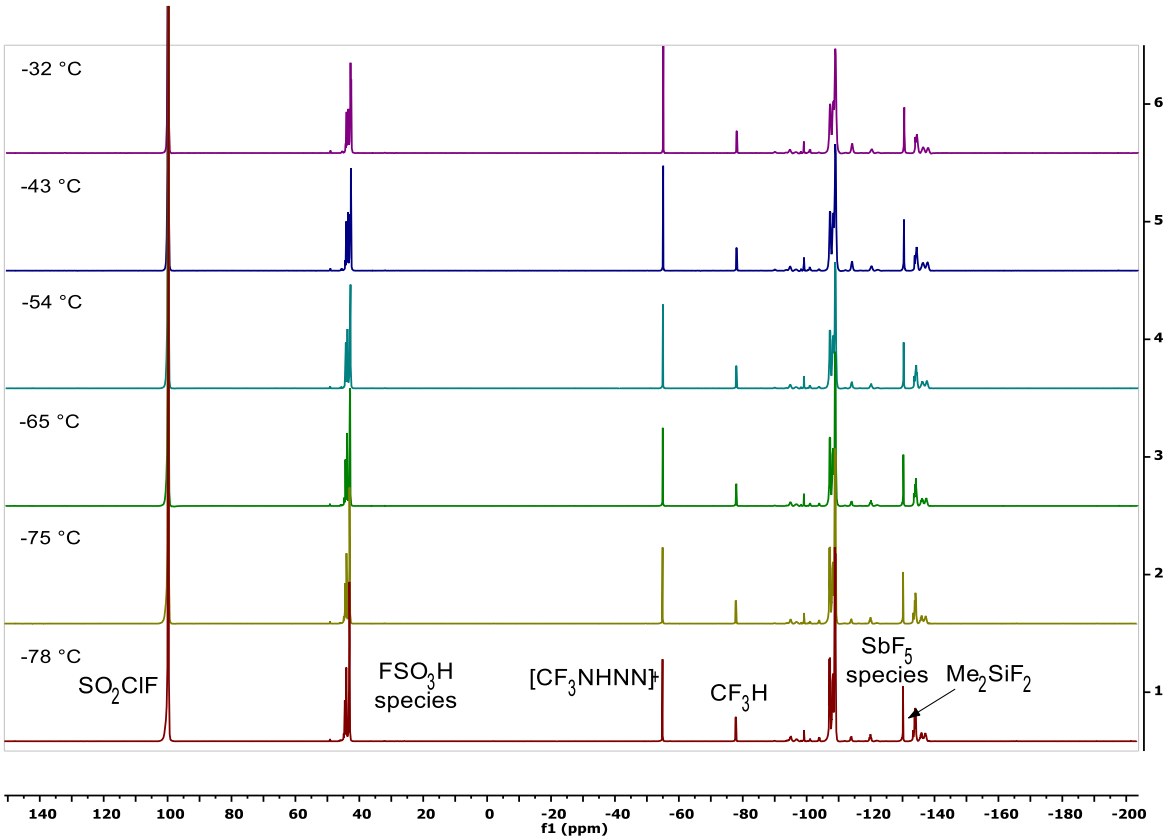
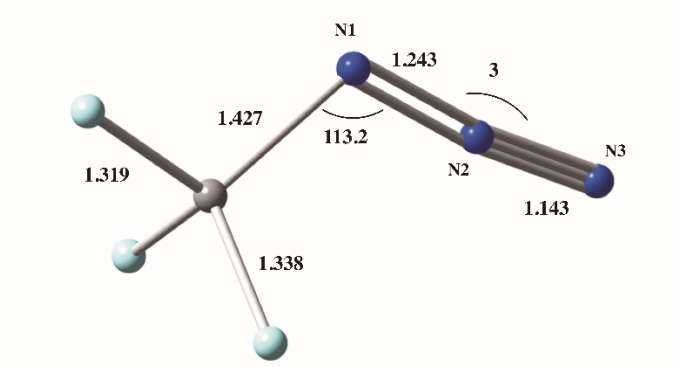



**Figure 11** Variable-temperature $^{19}F$ NMR experiments for the thermal stability of the trifluoromethyl aminodiazonium ion.

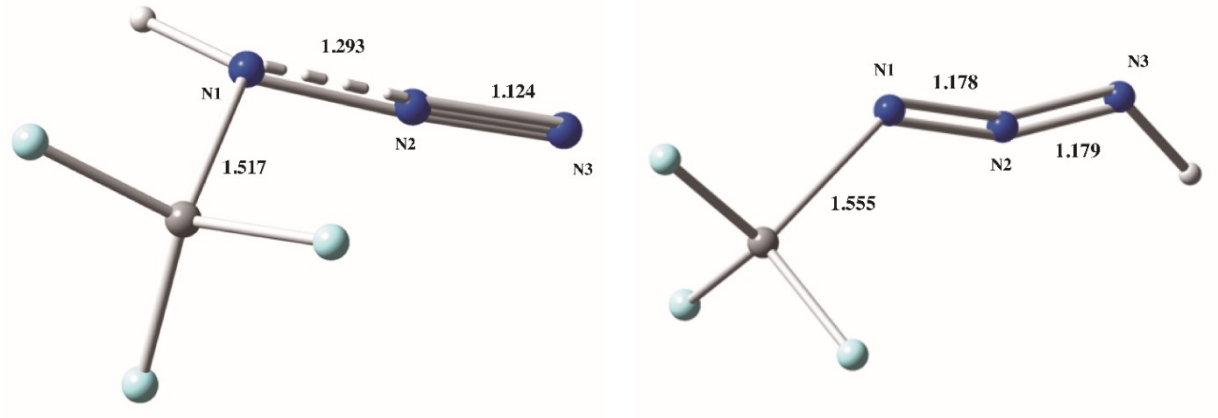
## 6.6. Computational results for the $[CF_3NHN_2]^+$ cation

Having two proton-acceptor sites, organic azides could be protonated potentially on N-1 or N-3, resulting in the formation of aminodiazonium ion (**89**) or iminodiazenium ion (**90**), respectively. Our quantum chemical calculation at the MP2/cc-pVTZ level predicted

that the difference in free energy between the two protonated forms in solution is considerable, favoring the aminodiazonium cation by 21.9 kcal/mol. These findings are in accordance with the observations and calculations regarding the $[H_2N_3]^+$ cation by Olah and co-workers.[166] Calculated critical (N-1)-C bond distances in $CF_3N_3$ and protonated $[CF_3NHN_2]^+$ are 1.427 and 1.517 Å, respectively, indicating bond elongation (0.090 Å, about 6%) upon protonation of trifluoromethyl azide (Figure 12).




**56a** $CF_3N_3$ ($C_s$)




**89** $[CF_3NHN_2]^+$ ($C_1$) **90** $[CF_3N_2NH]^+$ ($C_s$)

**Figure 12** MP2/cc-pVTZ calculated structures of unprotonated and protonated $CF_3N_3$.

## 6.7. Conclusion and outlook

In this chapter, the protonation of azidotrifluoromethane in superacidic media is described. Azidotrifluoromethane was successfully protonated in magic acid at low temperature and the resulting $[CF_3NHN_2]^+$ cation was characterized by low-temperature NMR spectroscopy. A $^{15}N$-labeling experiment was also accomplished which proved that the

protonation occurs at the nitrogen adjacent to the $CF_3$ group. The experimental results are supported by computational studies which show a free energy difference of 21.9 kcal/mol between the two plausible protonated structures, favoring the $[CF_3NHN_2]^+$ cation.

Encouraged by these findings, we are interested in protonating other (per)fluorinated azides. These fluorinated aminodiazonium ions are expected to be excellent aminating reagents in electrophilic aromatic amination which will be the subject of future work.

# 7 General conclusions and outlook

The main purpose of this work was to provide a feasible and convenient means to give access to rare N-perfluoroalkyl derivatives. We have envisioned that azidoperfluoroalkanes would be a great starting point which could be transformed into unknown, yet promising fluorinated building blocks.

First, the preparation of azidotrifluoromethane was investigated based on the reaction of $TMSCF_3$ with an electrophilic azide. The reaction required equimolar amount of cesium fluoride which activated $TMSCF_3$ for the nucleophilic $CF_3$ transfer. The activated siliconate intermediates are in equilibrium with the free $CF_3$ anion which readily reacted with tosyl azide to furnish $CF_3N_3$. Longer carbon chain azidoperfluoroalkanes were prepared in a similar manner, starting from the corresponding silanes. The only exception was azidopentafluoroethane which was synthesized by the reaction of $C_2F_5H$ with $^n$BuLi, followed by the addition of tosyl azide. Since these fluorinated azides are volatile compounds, their isolation was achieved by distillation with a suitable solvent. In this way, the azide solutions can be conveniently stored and used in further transformations. Importantly, azidoperfluoroalkanes were found to be thermally stable when heated in THF solution at 150 °C.

The second part of the thesis focuses on the application of azidoperfluoroalkanes in various transformations. The azides proved to be excellent reaction partners in the copper(I)-catalyzed azide-alkyne cycloaddition with diverse terminal alkynes, affording the N-perfluoroalkyl 1,2,3-triazoles. Furthermore, it was shown that the azide synthesis and the subsequent cycloaddition with alkynes can be performed in one-pot. As expected, internal alkynes did not react with the fluorinated azides to access fully substituted triazoles with the perfluoroalkyl group. Gratifyingly, an alternative route enabled the synthesis of such compounds in two steps through 5-iodotriazoles. A competition experiment between azidoethane and azidopentafluoroethane in the CuAAC showed that the reactivity of the fluorinated azide was greater than that of the non-fluorinated analogue.

Next, we turned our attention to the organocatalytic azide-ketone cycloaddition with azidoperfluoroalkanes to furnish highly functionalized triazoles bearing the perfluoroalkyl group. Activated ketones easily engaged in this cycloaddition, using pyrrolidine as

catalyst. Triazoles with an ester functionality were hydrolyzed and decarboxylated to provide 1,5-disubstituted triazoles. Interestingly, the cycloaddition of $CF_3N_3$ with cyclohexanone led to the formation of a triazoline product, using equimolar amount of pyrrolidine. The triazoline is the first intermediate formed in the enamine-mediated azide-ketone cycloaddition; however, it was never observed in the cycloaddition with activated ketones. Depending on the applied conditions, the triazoline can be converted to a triazole or an amide product. The limitations of this azide-ketone cycloaddition have been also explored.

At last, the protonation of azidotrifluoromethane was examined in superacidic media. Magic acid was powerful enough to protonate $CF_3N_3$ and the protonated species was studied by low-temperature NMR spectroscopy. To complete the characterization of the $[CF_3NHN_2]^+$ cation, $^{15}N$-labeled azide was prepared and protonated. The $^{15}N$-labeling experiment also proved the site of protonation taking place at the nitrogen bearing the $CF_3$ group. The experimental findings were validated by computational studies. The trends observed in the calculated chemicals shifts for the neutral and protonated $CF_3N_3$ were in good agreement with the values obtained experimentally. Future studies should include investigations in using protonated azidoperfluoroalkanes in electrophilic amination of aromatic compounds to access perfluoroalkylated aniline derivatives.

In summary, an efficient synthesis of novel azidoperfluoroalkanes is presented in this work which offers a powerful and elegant way to access simple, yet significant fluorinated building blocks. As it was demonstrated, azidoperfluoroalkanes hold a great potential in various transformations, leading to previously inaccessible N-perfluoroalkyl derivatives. These fluorinated derivatives are otherwise difficult to obtain and of great value, especially for pharmaceutical and agrochemical research.

# 8 Experimental part

## 8.1. General remarks

Reactions with air-sensitive materials were carried out under argon atmosphere using standard Schlenk techniques. All solvents were dried by activated molecular sieves (3 Å) and stored under argon. All commercially available chemicals were used as received unless stated otherwise.

Flash column chromatography was performed using silica gel 60 (0.040–0.063 mm) supplied by Sigma-Aldrich. Dry column vacuum chromatography (DCVC) was done using silica gel 60 (0.015–0.040 mm) supplied by Merck. Automated flash column chromatography was performed on Teledyne ISCO CombiFlash Rf+ Lumen Automated Flash Chromatography System with UV/Vis detection using standard manufacturer's RediSep Rf columns. The TLC analyses were done using TLC silica gel 60 F254 aluminum sheets from Merck, which were visualized under UV (254/366 nm) or using the $KMnO_4$ stain solution.

$^{1}H$, $^{13}C$, $^{14}N$, $^{15}N$, $^{19}F$ and $^{31}P$ NMR spectra were measured at ambient temperature, unless stated otherwise, using 5 mm diameter NMR tubes on the following spectrometers: Bruker Avance III HD (400 MHz), Bruker AMX-500, Varian NMRS-400, Varian NMRS-500 and Varian NMRS-600. $^{13}C$ spectra were proton decoupled. The chemical shift values ($\delta$) are reported in ppm relative to internal $Me_4Si$ (0 ppm for $^{1}H$ and $^{13}C$ NMR) or residual solvents and internal $CFCl_3$ (0 ppm for $^{19}F$ NMR). Coupling constants ($J$) are reported in Hertz. Multiplicity is described by abbreviations (s = singlet, d = doublet, t = triplet, q = quartet, br s = broad singlet, dd = doublet of doublets, etc.). Structural elucidation was aided by additional acquisition of $^{13}C$ APT and/or various 2D spectra ($^{1}H$-$^{1}H$ COSY, $^{1}H$-$^{13}C$ HSQC, $^{1}H$-$^{13}C$ HMBC and $^{13}C$-$^{19}F$ HMBC).

GC-MS spectra were recorded on Agilent 7890A GC (column HP-5MS, 30 m × 0.25 mm × 0.25 µm, 5% phenyl methylpolysiloxane) coupled with 5975C quadrupole mass selective electron impact (EI) detector (70 eV). High resolution MS spectra (HRMS) were recorded on an LTQ Orbitrap XL using electrospray ionization (ESI), on a Waters Micro-

mass AutoSpec Ultima or Agilent 7890A GC coupled with Waters GCT Premier orthogonal acceleration time-of-flight detector using electron impact (EI) ionization, and on a Bruker solariX 94 ESI/MALDI-FT-ICR using dual ESI/MALDI ionization. UPLC-MS analyses were performed on Acquity UPLC Instrument (Waters Corporation), IR spectra ($CHCl_3$ film) were measured on Bruker IFS 55 Equinox or Bruker Alpha-P spectrometer. The melting points are uncorrected.

Computations were performed in Gaussian 09, Revision A.02.[175] Geometries were optimized at the MP2/cc-pVTZ level. NMR chemical shifts were calculated by the GIAO (Gauge Invariant Atomic Orbitals) method using MP2/cc-pVTZ geometries. GIAO-CCSD(T) NMR calculations using tzp basis sets have been performed with the CFOUR program.[176,177] The δ ($^{13}C$) and δ ($^{19}F$) were computed using TMS (calculated absolute shift i.e. σ (C) = 197.4), $CFCl_3$ (calculated absolute shift i.e. σ (F) = 222.9), and $CH_3NO_2$ (calculated absolute shift i.e. σ (N) = -98.7) as references, respectively.

## 8.2. Synthesis of azidoperfluoroalkanes

**Azidotrifluoromethane (56a)**

$CF_3N_3$

CsF (3.65 g, 24 mmol) was dried overnight at 120 °C under high vacuum in a two-neck round-bottom flask. The flask was cooled to rt, backfilled with argon, dry DMF (44 mL) was added and the mixture was cooled to -60 °C while being stirred. A cold solution of $CF_3TMS$ (3.55 mL, 24 mmol) and $TsN_3$ (3.07 mL, 20 mmol) in dry DMF (6 mL) was added dropwise over 20 min, and then the reaction mixture was stirred at -60 °C to -30 °C for 4 h. Cold dry THF (40 mL) was added and the product was distilled (heating up to 120 °C, ambient pressure) together with THF to a cooled (-78 °C) receiving flask containing $PhCF_3$ as an internal standard. The product was obtained as a solution in THF containing TMSF as a side-product and traces of $CF_3H$.

**Yield**: 70–80% (determined by $^{19}F$ NMR)

**$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 122.0 (q, $^1J_{C-F}$ = 267.6 Hz); **$^{19}$F NMR** (376 MHz, $CDCl_3$) δ = -56.3 (s);[111] **HRMS** (EI) *m/z* calcd for $CF_3N_3$ $[M]^+$: 111.0044, found 111.0040.

**Azidopentafluoroethane (56b)**

$CF_3CF_2N_3$

An oven-dried Schlenk flask was evacuated, backfilled with argon and then charged with dry THF (40 mL). $C_2F_5H$ (1.71 g, 14.3 mmol) was bubbled into the THF, followed by cooling the solution to -78 °C and slow addition of $^n$BuLi (1.6 M in hexanes, 8.9 mL, 14.3 mmol, or 2.0 M in cyclohexane, 7.15 mL, 14.3 mmol). Stirring was continued for 30 min at -78 °C while the color changed from transparent to deep yellow. A solution of the $TsN_3$ (2.2 mL, 14.3 mmol) in THF (9.5 mL) was slowly added, resulting in the formation of a peach-colored precipitate. Stirring was continued for another 30 min at -78 °C and then the product was distilled together with THF (up to 33 °C, 120 torr) to a cooled (-78 °C) receiving flask containing $PhCF_3$ as an internal standard.

**Yield**: 83% (determined by $^{19}$F NMR)

**$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 117.0 (qt, $^1J_{C-F}$ = 267.6 Hz, $^2J_{C-F}$ = 41.9 Hz, $CF_3$), 113.2 (tq, $^1J_{C-F}$ = 272.9 Hz, $^2J_{C-F}$ = 41.4 Hz, $CF_2$); **$^{19}$F NMR** (376 MHz, $CDCl_3$) δ = -85.9 (s, 3F), -93.6 (s, 2F); **HRMS** (EI) *m/z* calcd for $C_2F_5N_3$ $[M]^+$: 161.0012, found 161.0010.

**Azidoperfluoropropane (56c)**

$CF_3CF_2CF_2N_3$

CsF (0.25 g, 1.66 mmol) was dried for 48 h at 135 °C under high vacuum in a 10 mL screw-cap glass tube. The tube was cooled to rt, backfilled with argon, dry DMF (1.0 mL) was added and the mixture was cooled to -60 °C while being stirred. A cold solution of $^n$$C_3F_7TMS$ (0.284 mL, 1.4 mmol) and perfluorobutanesulfonyl azide ($NfN_3$) (0.455 g, 1.4 mmol) in dry DMF (0.5 mL) was added dropwise over 10 min, and then the reaction mixture was stirred at -60 °C to -30 °C for 4 h. Cold dry THF (2.0 mL) was added and

the product was distilled (heating up to 90 °C, ambient pressure) together with THF to a cooled (-78 °C) flask containing $PhCF_3$ as an internal standard. The product was obtained as a solution in THF.

**Yield**: 49–52% (determined by $^{19}F$ NMR)

**$^{13}C$ NMR** (101 MHz, $CDCl_3$) δ = 117.1 (qt, $^1J_{C-F}$ = 287.0 Hz, $^2J_{C-F}$ = 33.3 Hz, $CF_3$), 114.6 (tt, $^1J_{C-F}$ = 275.7 Hz, $^2J_{C-F}$ = 30.3 Hz, $CF_2$), 107.5 (tqt, $^1J_{C-F}$ = 267.7 Hz, $^2J_{C-F}$ = 39.4 Hz, $^3J_{C-F}$ = 11.1 Hz, $CF_2$); **$^{19}F$ NMR** (376 MHz, $CDCl_3$) δ = -80.9 (t, $^3J_{F-F}$ = 8.1 Hz, 3F), -89.1 (m, 2F), -128.3 (t, $^3J_{F-F}$ = 3.0 Hz, 2F). **HRMS** (EI) *m/z* calcd for $C_3F_6N_3$ $[M - F]^+$: 191.9994, found 191.9996.

**Azidoperfluorooctane (56d)**

$^nC_8F_{17}N_3$

CsF (0.25 g, 1.66 mmol) was dried for 48 h at 135 °C under high vacuum in a 10 mL screw-cap glass tube. The tube was cooled to rt, backfilled with argon, dry DMF (1.0 mL) was added and the mixture was cooled to -60 °C while being stirred. A cold solution of $^nC_8F_{17}TMS$ (0.474 mL, 1.4 mmol) in dry DMF (0.5 mL) was added dropwise over 10 min and the whole reaction mixture was degassed (one freeze-pump-thaw cycle). Perfluorobutanesulfonyl azide ($NfN_3$) (0.455 g, 1.4 mmol) in dry DMF (0.5 mL) was added dropwise over 10 min, and then the reaction mixture was stirred at -60 °C to -30 °C for 4 h. Cold dry THF (2.0 mL) was added and the product was distilled (heating up to 90 °C, ambient pressure) together with THF to a cooled (-78 °C) flask containing $PhCF_3$ as an internal standard. The product was obtained as a two-phase solution (upper phase THF, lower phase azide solidifying at ca. -60 °C).

**Yield**: 50–60% (determined by $^{19}F$ NMR)

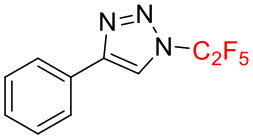
**$^{13}C$ NMR** (101 MHz, $CDCl_3$) δ = 117.1 (qt, $^1J_{C-F}$ = 311.1 Hz, $^2J_{C-F}$ = 32.3 Hz, $CF_3$), 115.9 (tt, $^1J_{C-F}$ = 292.9 Hz, $^2J_{C-F}$ = 33.3 Hz, $CF_2$(1)), 113.5–105.1 (m, $CF_2$(2– 7)); **$^{19}F$ NMR** (376 MHz, $CDCl_3$) δ = -81.3 (tt, $^3J_{F-F}$ = 10.0 Hz, $^4J_{F-F}$ = 2.3 Hz, 3F), -88.6 (m, 2F), -121.6 (m, 2F), -122.4 (m, 2F), -123.2 (m, 2F), -124.4 (m, 2F), -126.3 (m, 2F), -126.6 (m, 2F). **HRMS** (EI) *m/z* calcd for $C_8F_{16}N_3$ $[M - F]^+$: 441.9837, found 441.9836.

## 8.3. Synthesis of N-perfluoroalkyl triazoles in the CuAAC

### 8.3.1. General method A

Alkyne (0.5 mmol) was placed into a 10 mL screw-cap glass tube and a solution of **56** in THF (ca. 0.60 mmol, 3–4 mL) was added. Aqueous solutions of $CuSO_4 \cdot 5H_2O$ (1M, 0.05 mmol, 50 µL) and sodium L-ascorbate (1M, 0.05 mmol, 50 µL) were added, the flask was closed, and the mixture was stirred at rt for 18 h. Aqueous saturated solution of $NH_4Cl$ (10 mL) was added and the mixture was extracted with $CH_2Cl_2$ (3 × 10 mL). The combined organic layers were washed with water (2 × 10 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by column chromatography on silica gel.

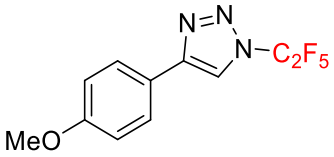
**1-(Pentafluoroethyl)-4-phenyl-1*H*-1,2,3-triazole (68ba)**




**Yield**: 111 mg (84%), white crystalline solid;

**m.p.** 82–83 °C, $R_f$ (cyclohexane:EtOAc 97:3) = 0.28; **IR** ($CHCl_3$ film) ν 1216, 1172, 1120, 1075, 691 $cm^{-1}$; **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 8.13 (s, 1H), 7.90–7.86 (m, 2H), 7.51–7.46 (m, 2H), 7.45–7.40 (m, 1H); **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 148.9, 129.5, 129.2, 128.6, 126.3, 117.9, 117.2 (qt, $^1J_{C\text{-}F}$ = 287.6 Hz, $^2J_{C\text{-}F}$ = 41.3 Hz, $CF_3$), 110.4 (tq, $^1J_{C\text{-}F}$ = 270.9 Hz, $^2J_{C\text{-}F}$ = 43.1 Hz, $CF_2$); **$^{19}$F NMR** (376 MHz, $CDCl_3$) δ = -84.4 (s, 3F), -99.2 (s, 2F); **HRMS** (ESI) *m/z* calcd for $C_{10}H_7N_3F_5$ $[M + H]^+$: 264.0555, found 264.0555.

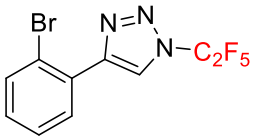
**4-(4-Methoxyphenyl)-1-(pentafluoroethyl)-1*H*-1,2,3-triazole (68bc)**




**Yield**: 92 mg (63%), white crystalline solid;

**m.p.** 100–102 °C, ***R*$_f$** (cyclohexane:EtOAc, 95:5) = 0.26; **IR** ($CHCl_3$ film) ν 1618, 1501, 1434, 1223, 1123, 536 $cm^{-1}$; **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 8.04 (s, 1H), 7.82–7.78 (m, 2H), 7.01–6.97 (m, 2H), 3.86 (s, 3H); **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 160.6, 148.7, 127.7, 121.2, 117.2 (qt, $^1J_{C\text{-}F}$ = 287.5 Hz, $^2J_{C\text{-}F}$ = 41.4 Hz, $CF_3$), 116.9, 114.6, 110.3 (tq, $^1J_{C\text{-}F}$ = 270.6 Hz, $^2J_{C\text{-}F}$ = 43.1 Hz, $CF_2$), 55.5; **$^{19}$F NMR** (376 MHz, $CDCl_3$) δ = -84.4 (s, 3F), -99.2 (s, 2F); **HRMS** (ESI) *m/z* calcd for $C_{11}H_9ON_3F_5$ $[M + H]^+$: 294.0660, found 294.0661.

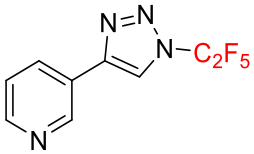
**4-(2-Bromophenyl)-1-(pentafluoroethyl)-1*H*-1,2,3-triazole (68bd)**




**Yield**: 63 mg (37%); yellow oil;

***R*$_f$** (cyclohexane:EtOAc 95:5) = 0.53; IR ($CHCl_3$ film) ν 1430, 1210, 1128, 1077, 972 $cm^{-1}$; **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 8.63 (s, 1H), 8.15 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.70 (dd, *J* = 8.1, 1.2 Hz, 1H), 7.47 (td, *J* = 7.6, 1.3 Hz, 1H), 7.29 (td, 1H); **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 146.4, 133.9, 131.1, 130.6, 129.4, 128.1, 121.6, 121.4, 117.2 (qt, $^1J_{C\text{-}F}$ = 287.5 Hz, $^2J_{C\text{-}F}$ = 41.2 Hz, $CF_3$), 110.3 (tq, $^1J_{C\text{-}F}$ = 271.4 Hz, $^1J_{C\text{-}F}$ = 43.2 Hz, $CF_2$); **$^{19}$F NMR** (376 MHz, $CDCl_3$) δ = -84.4 (s, 3F), -99.2 (s, 2F); **HRMS** (ESI) *m/z* calcd for $C_{10}H_6N_3BrF_5$ $[M + H]^+$: 341.9660, found 341.9661.

**3-(1-(Pentafluoroethyl)-1*H*-1,2,3-triazol-4-yl)pyridine (68bh)**




**Yield**: 50 mg (38%), white crystalline solid;

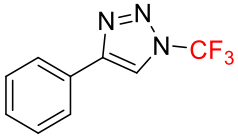
**m.p.** 120–122 °C, ***R*$_f$** (cyclohexane:EtOAc 1:1) = 0.48; **IR** ($CHCl_3$ film) ν 1578, 1439, 1218, 1169, 1121, 1078 $cm^{-1}$; **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 9.09 (d, *J* = 2.5 Hz, 1H), 8.68 (dd, *J* = 4.9, 1.6 Hz, 1H), 8.29 (s, 1H), 8.27 (dt, *J* = 8.0, 2.0 Hz, 1H), 7.45 (dd, *J* = 8.0, 4.9 Hz, 1H); **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 150.5, 147.4, 145.9, 133.7, 124.9,

124.0, 118.5, 117.1 (qt, $^{1}J_{C\text{-}F}$ = 287.5 Hz, $^{2}J_{C\text{-}F}$ = 40.6 Hz, $CF_3$), 110.3 (tq, $^{1}J_{C\text{-}F}$ = 272.2 Hz, $^{2}J_{C\text{-}F}$ = 43.1 Hz, $CF_2$); **$^{19}$F NMR** (376 MHz, $CDCl_3$) δ = -84.3 (s, 3F), -99.1 (s, 2F); **HRMS** (ESI) *m/z* calcd for $C_9H_6N_4F_5$ $[M+H^+]$: 265.0507, found 265.0508.

### 8.3.2. General method B

Copper(I) 3-methylsalicylate (2.1–10.7 mg, 0.01–0.05 mmol) was placed in a 10 mL screw-cap glass tube and a cold solution of **56** in THF (ca. 1.5 mmol, 3–4 mL) was added. Subsequently alkyne (1.0 mmol) in THF (0.5 mL) was added, the flask was closed and stirred at rt for 18 h. THF was removed under reduced pressure, $Et_2O$ (20 mL) was added and the organic phase was washed with aqueous $NaHCO_3$ solution (5%, 2 × 10 mL), water (10 mL), aqueous LiCl solution (1M, 10 mL) and brine (10 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by column chromatography on silica gel.

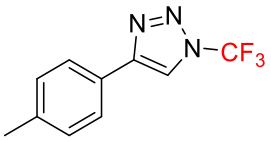
**4-Phenyl-1-(trifluoromethyl)-1*H*-1,2,3-triazole (68aa)**




**Yield**: 86 mg (81%), white crystalline solid;

**m.p.** 91–92 °C, ***R*$_f$** (cyclohexane:EtOAc 97:3) = 0.27; **IR** ($CHCl_3$ film) ν 1430, 1205, 1006, 694 $cm^{-1}$; **$^{1}$H NMR** (400 MHz, $CDCl_3$) δ = 8.14 (s, 1H), 7.89–7.86 (m, 2H), 7.50–7.46 (m, 2H), 7.44–7.40 (m, 1H); **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 148.6, 129.4, 129.2, 128.6, 126.2, 117.7 (q, $^{1}J_{C\text{-}F}$ = 267.7 Hz, $CF_3$), 117.3; **$^{19}$F NMR** (376 MHz, $CDCl_3$) δ = -59.3 (s); **HRMS** (EI) *m/z* calcd for $C_9H_6N_3F_3$ $[M]^+$: 213.0514, found 213.0520.

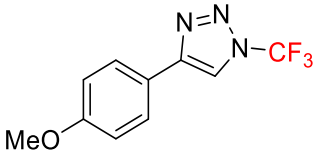
**4-(*p*-Tolyl)-1-(trifluoromethyl)-1*H*-1,2,3-triazole (68ab)**



**Yield**: 90 mg (79%), white crystalline solid;

**m.p.** 99–101 °C, ***R*$_f$** (cyclohexane:EtOAc 97:3) = 0.19; **IR** ($CHCl_3$ film) ν 1444, 1189, 1007, 814 $cm^{-1}$; **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 8.09 (s, 1H), 7.77–7.74 (m, 2H), 7.30–7.27 (m, 2H), 2.41 (s, 3H); **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 148.7, 139.5, 129.8, 126.1, 125.8, 117.7 (q, $^1J_{C\text{-}F}$ = 268.1 Hz, $CF_3$), 116.8, 21.4 (s); **$^{19}$F NMR** (376 MHz, $CDCl_3$) δ = -59.3 (s); **HRMS** (ESI) *m/z* calcd for $C_{10}H_9N_3F_3$ $[M + H]^+$: 228.0743, found 228.0742.

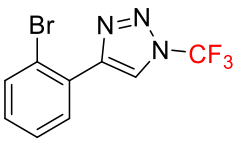
**4-(4-Methoxyphenyl)-1-(trifluoromethyl)-1*H*-1,2,3-triazole (68ac)**



**Yield**: 96 mg (79%), off-white crystalline solid;

**m.p.** 112–115 °C, ***R*$_f$** (cyclohexane:EtOAc 97:3) = 0.12; **IR** ($CHCl_3$ film) ν 1445, 1257, 1215, 1194, 828 $cm^{-1}$; **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 8.04 (s, 1H), 7.82–7.78 (m, 2H), 7.02–6.98 (m, 2H), 3.86 (s, 3H); **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 160.5, 148.5, 127.6, 121.2, 117.8 (q, $^1J_{C\text{-}F}$ = 268.0 Hz, $CF_3$), 116.3, 114.6, 55.5 (s); **$^{19}$F NMR** (376 MHz, $CDCl_3$) δ = -59.4 (s); **HRMS** (ESI) *m/z* calcd for $C_{10}H_9N_3OF_3$ $[M + H]^+$: 244.0692, found 244.0693.

**4-(2-Bromophenyl)-1-(trifluoromethyl)-1*H*-1,2,3-triazole (68ad)**

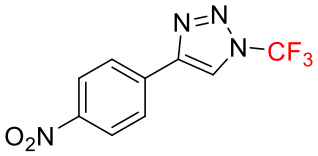


**Yield**: 123 mg (84%), yellow liquid;

***R*$_f$** (cyclohexane:EtOAc 97:3) = 0.27; **IR** ($CHCl_3$ film) ν 1420, 1206, 1191, 760 $cm^{-1}$; **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 8.63 (s, 1H), 8.16–8.14 (ddd, *J* = 7.8, 1.7, 0.4 Hz, 1H),

7.71–7.69 (ddd, *J* = 8.1, 1.3, 0.4 Hz, 1H), 7.49–7.45 (ddd, *J* = 7.9, 7.4, 1.3 Hz, 1H), 7.31–7.27 (ddd, *J* = 8.1, 7.4, 1.8 Hz, 1H); **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 146.1, 133.8, 131.0, 130.5, 129.4, 128.0, 121.4, 120.6, 117.7 (q, $^1J_{C\text{-}F}$ = 268.4 Hz); **$^{19}$F NMR** (376 MHz, $CDCl_3$) δ = -59.2 (s); **HRMS** (ESI) *m/z* calcd for $C_9H_6N_3F_3Br$ $[M + H]^+$: 291.9692, found 291.9692.

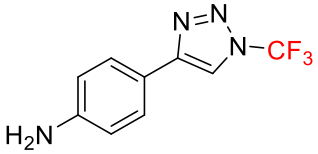
**4-(4-Nitrophenyl)-1-(trifluoromethyl)-1*H*-1,2,3-triazole (68ae)**




**Yield**: 106 mg (82%), yellow solid;

**m.p.** 166–168 °C, ***R*$_f$** (cyclohexane:EtOAc 9:1) = 0.25; **IR** ($CHCl_3$ film) ν 1518, 1350, 1217, 1002 cm$^{-1}$; **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 8.38–8.34 (m, 2H), 8.31 (s, 1H), 8.10–8.06 (m, 2H); **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 148.3, 146.4, 134.8, 127.0, 124.6, 118.9, 117.6 (q, $^1J_{C\text{-}F}$ = 269.1 Hz); **$^{19}$F NMR** (376 MHz, $CDCl_3$) δ = -59.3 (s); **HRMS** (CI) *m/z* calcd for $C_9H_6N_4O_2F_3$ $[M + H]^+$: 259.0437, found 259.0439.

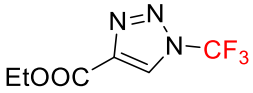
**4-(1-(Trifluoromethyl)-1*H*-1,2,3-triazol-4-yl)aniline (68af)**




**Yield**: 87 mg (76%), dark yellow solid;

**m.p.** 104–106 °C, ***R*$_f$** (cyclohexane:EtOAc:$Et_3N$, 80:19:1) = 0.14; **IR** ($CHCl_3$ film) ν 3398, 3321, 1432, 1195, 819 cm$^{-1}$; **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 7.98 (s, 1H), 7.67–7.64 (m, 2H), 6.77–6.73 (m, 2H), 3.86 (br s, 2H); **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 149.0, 147.7, 127.5, 118.7, 117.7 (q, $^1J_{C\text{-}F}$ = 267.7 Hz), 115.6, 115.2; **$^{19}$F NMR** (376 MHz, $CDCl_3$) δ = -59.4 (s); **HRMS** (ESI) *m/z* calcd for $C_9H_8N_4F_3$ $[M + H]^+$: 229.0696, found 229.0696.

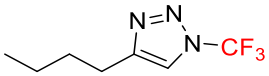
**Ethyl 1-(trifluoromethyl)-1*H*-1,2,3-triazole-4-carboxylate (68ai)**



**Yield**: 50 mg (48%), yellow liquid;

***R*$_f$** (cyclohexane:EtOAc 95:5) = 0.12; **IR** ($CHCl_3$ film) ν 1744, 1444, 1266, 1222 $cm^{-1}$; **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 8.53 (s, 1H), 4.48 (q, *J* = 7.1 Hz, 2H), 1.43 (t, *J* = 7.1 Hz, 3H); **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 159.3, 140.9, 125.8, 117.4 (q, $^1J_{C\text{-}F}$ = 269.8 Hz), 62.2, 14.3; **$^{19}$F NMR** (376 MHz, $CDCl_3$) δ = -59.3 (s); **HRMS** (ESI) *m/z* calcd for $C_6H_7N_3O_2F_3$ $[M + H]^+$: 210.0485, found 210.0485, $C_6H_6N_3O_2F_3Na$ $[M + Na]^+$: 232.0304, found 232.0304.

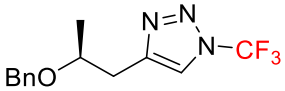
**4-Butyl-1-(trifluoromethyl)-1*H*-1,2,3-triazole (68aj)**



**Yield**: 23 mg (24%), pale yellow liquid;

***R*$_f$** (cyclohexane:EtOAc 97:3) = 0.17; **IR** ($CHCl_3$ film) ν 2938, 1382, 1194, 974 $cm^{-1}$; **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 7.69 (s, 1H), 2.79 (d, *J* = 7.7 Hz, 2H), 1.70 (dt, *J* = 15.4, 7.5 Hz, 2H), 1.41 (dq, *J* = 14.7, 7.4 Hz, 2H), 0.95 (t, *J* = 7.4 Hz, 3H); **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 149.4, 118.5, 117.7 (q, $^1J_{C\text{-}F}$ = 267.3 Hz), 31.1, 25.0, 22.3, 13.8; **$^{19}$F NMR** (376 MHz, $CDCl_3$) δ = -59.4 (s); **HRMS** (EI) *m/z* calcd for $C_7H_{10}N_3F_3$ $[M]^+$: 193.0827, found 193.0828.

**(S)-4-(2-(Benzyloxy)propyl)-1-(trifluoromethyl)-1*H*-1,2,3-triazole (68ak)**

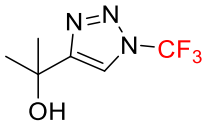


**Yield**: 128 mg (90%), pale yellow liquid;

***R*$_f$** (cyclohexane:EtOAc 95:5) = 0.09; **IR** ($CHCl_3$ film) ν 1440, 1278, 1207, 980 $cm^{-1}$; **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 7.71 (s, 1H), 7.34–7.27 (m, 3H), 7.26–7.22 (m, 2H), 4.61 (d, *J* = 11.6 Hz, 1H), 4.41 (d, *J* = 11.6 Hz, 1H), 3.92–3.85 (m, 1H), 3.02 (dd, *J* = 15.0, 4.7

Hz, 1H), 2.96 (dd, *J* = 15.0, 7.0 Hz, 1H), 1.28 (d, *J* = 6.1 Hz, 3H); **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 145.9, 138.4, 128.5, 127.8, 120.3, 117.7 (q, $^1J_{C\text{-}F}$ = 267.9 Hz), 73.6, 70.8, 32.8, 19.5; **$^{19}$F NMR** (376 MHz, $CDCl_3$) δ = -59.4 (s); **HRMS** (ESI) *m/z* calcd for $C_{13}H_{15}N_3OF_3$ $[M+H^+]$: 286.1162, found 286.1162, $[M+Na^+]$: 308.0981, found 308.0983.

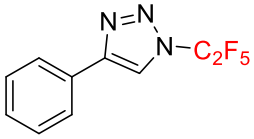
**2-(1-(Trifluoromethyl)-1*H*-1,2,3-triazol-4-yl)propan-2-ol (68al)**



**Yield**: 72 mg (74%), white crystalline solid;

**m.p.** 42–43 °C, ***R*$_f$** (cyclohexane:EtOAc 7:3) = 0.21; **IR** ($CHCl_3$ film) ν 3401, 1435, 1191, 982 $cm^{-1}$; **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 7.90 (s, 1H), 2.39 (s, 1H), 1.69 (s, 6H); **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 156.8, 117.9, 117.7 (q, $^1J_{C\text{-}F}$ = 268.2 Hz), 68.7, 30.4; **$^{19}$F NMR** (376 MHz, $CDCl_3$) δ = -59.3 (s); **HRMS** (EI) *m/z* calcd for $C_6H_8N_3OF_3Na$ $[M + Na]^+$: 218.0512, found 218.0511.

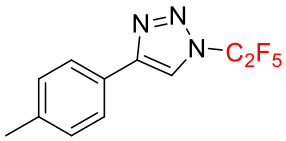
**1-(Pentafluoroethyl)-4-phenyl-1*H*-1,2,3-triazole (68ba)**



**Yield**: 111 mg (84%), white crystalline solid;

m.p., all spectra and analyses are in accordance with the triazole prepared by general method A (see above). **HRMS** ($EI^+$) *m/z* calcd for $C_{10}H_6N_3F_5$ $[M]^+$: 263.0482, found 263.0474.

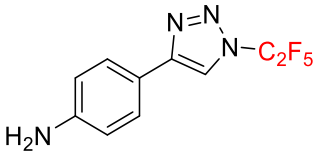
**1-(Pentafluoroethyl)-4-(*p*-tolyl)-1*H*-1,2,3-triazole (68bb)**



**Yield**: 122 mg (88%), white crystalline solid;

**m.p.** 92–94 °C; **IR** ($CHCl_3$ film) ν 1219, 1175, 1122, 1075, 736 $cm^{-1}$; **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 8.09 (s, 1H), 7.77–7.74 (m, 2H), 7.30–7.27 (m, 2H), 2.41 (s, 3H); **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 149.0, 139.6, 129.9, 126.2, 125.8, 117.5, 117.2 (qt, $^1J_{C\text{-}F}$ = 287.9 Hz, $^2J_{C\text{-}F}$ = 41.4 Hz, $CF_3$), 110.3 (tq, $^1J_{C\text{-}F}$ = 270.7 Hz, $^2J_{C\text{-}F}$ = 41.4 Hz, $CF_2$), 21.5; **$^{19}$F NMR** (376 MHz, $CDCl_3$) δ = -84.4 (s, 3F), -99.2 (s, 2F); **HRMS** ($EI^+$) *m/z* calcd for $C_{11}H_8N_3F_5$ $[M]^+$: 277.0638, found 277.0639.

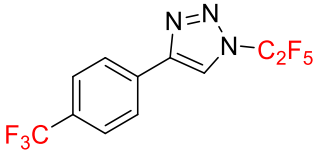
**4-(1-(Pentafluoroethyl)-1*H*-1,2,3-triazol-4-yl)aniline (68bf)**




**Yield**: 135 mg (97%), light yellow solid;

**m.p.** 86–89 °C; **IR** ($CHCl_3$ film) ν 1625, 1353, 1217, 1185, 1123, 1074, 755 $cm^{-1}$; **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 8.00 (s, 1H), 7.70–7.68 (m, 2H), 6.79–6.77 (m, 2H), 3.92 (br s, 2H); **$^{13}$C NMR** (125.7 MHz, $CDCl_3$) δ = 149.2, 147.6, 127.6, 118.7, 117.2 (qt, $^1J_{C\text{-}F}$ = 287.3 Hz, $^2J_{C\text{-}F}$ = 41.5 Hz, $CF_3$), 116.0, 115.4, 110.3 (tq, $^1J_{C\text{-}F}$ = 270.1 Hz, $^2J_{C\text{-}F}$ = 42.8 Hz, $CF_2$); **$^{19}$F NMR** (376 MHz, $CDCl_3$) δ = -84.4 (s, 3F), -99.2 (s, 2F); **HRMS** (ESI) *m/z* calcd for $C_{10}H_8N_4F_5$ $[M + H]^+$: 279.06636, found 279.06641.

**1-(Pentafluoroethyl)-4-(4-(trifluoromethyl)phenyl)-1*H*-1,2,3-triazole (68bg)**

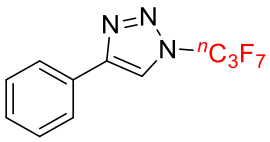



**Yield**: 151 mg (91%), white solid;

**m.p.** 121–124 °C; **IR** ($CHCl_3$ film) ν 1329, 1218, 1130, 1065, 747 $cm^{-1}$; **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 8.24 (s, 1H), 8.02–8.00 (m, 2H), 7.75–7.73 (m, 2H); **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 147.5, 132.0, 131.5 (q, $^2J_{C\text{-}F}$ = 33.3 Hz), 126.6, 126.3 (q, $^3J_{C\text{-}F}$ = 3.0 Hz), 124.0 (q, $^1J_{C\text{-}F}$ = 272.7 Hz, $CF_3$), 118.8, 117.1 (qt, $^1J_{C\text{-}F}$ = 287.9 Hz, $^2J_{C\text{-}F}$ = 41.4 Hz, $CF_3$), 110.3 (tq, $^1J_{C\text{-}F}$ = 271.7 Hz, $^2J_{C\text{-}F}$ = 43.4 Hz, $CF_2$); **$^{19}$F NMR** (376 MHz, $CDCl_3$)

δ = -63.3 (s, 3F), -84.4 (s, 3F), -99.2 (s, 2F); **HRMS** (ESI) *m/z* calcd for $C_{11}H_5N_3F_8$ $[M]^+$: 331.0356, found 331.0350.

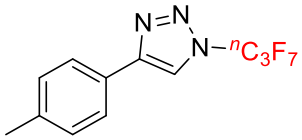
**1-(Perfluoropropyl)-4-phenyl-1*H*-1,2,3-triazole (68ca)**




**Yield**: 64 mg (41%), white crystalline solid;

**m.p.** 72–74 °C; **IR** ($CHCl_3$ film) ν 1423, 1226, 1196, 1137, 1051, 883, 694 $cm^{-1}$; **$^1$H NMR** (500 MHz, $CDCl_3$) δ = 8.12 (s, 1H), 7.89–7.87 (m, 2H), 7.50–7.46 (m, 2H), 7.44–7.40 (m, 1H); **$^{13}$C NMR** (125.7 MHz, $CDCl_3$) δ = 148.9, 129.6, 129.3, 128.6, 126.3, 118.1, 117.4 (qt, $^1J_{C\text{-}F}$ = 295.4 Hz, $^2J_{C\text{-}F}$ = 32.7 Hz, $CF_3$), 112.0 (tt, $^1J_{C\text{-}F}$ = 272.8 Hz, $^2J_{C\text{-}F}$ = 32.7 Hz, $CF_2$), 107.6 (tq, $^1J_{C\text{-}F}$ = 264.0 Hz, $^2J_{C\text{-}F}$ = 40.2 Hz, $CF_2$); **$^{19}$F NMR** (376 MHz, $CDCl_3$) δ = -81.0 (s, 3F), -96.5 (s, 2F), -127.6 (s, 2F); **HRMS** (EI) *m/z* calcd for $C_{11}H_6N_3F_7$ $[M]^+$: 313.0450, found 313.0445.

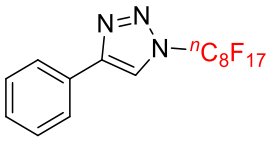
**1-(Perfluoropropyl)-4-(*p*-tolyl)-1*H*-1,2,3-triazole (68cb)**




**Yield**: 67 mg (41%), white crystalline solid;

**m.p.** 86–88 °C; **IR** ($CHCl_3$ film) ν 1236, 1139, 882, 750, 671 $cm^{-1}$; **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 8.08 (s, 1H), 7.78–7.76 (m, 2H), 7.29–7.27 (m, 2H), 2.41 (s, 1H); **$^{13}$C NMR** (101.0 MHz, $CDCl_3$) δ = 148.9, 129.6, 139.6, 129.9, 126.2, 125.8, 117.7, 117.4 (qt, $^1J_{C\text{-}F}$ = 287.9 Hz, $^2J_{C\text{-}F}$ = 28.3 Hz, $CF_3$), 112.0 (tt, $^1J_{C\text{-}F}$ = 273.7 Hz, $^2J_{C\text{-}F}$ = 32.3 Hz, $CF_2$), 107.6 (tq, $^1J_{C\text{-}F}$ = 269.7 Hz, $^2J_{C\text{-}F}$ = 40.4 Hz, $CF_2$), 21.5; **$^{19}$F NMR** (376 MHz, $CDCl_3$) δ = -81.0 (s, 3F), -96.5 (s, 2F), -127.7 (s, 2F); **HRMS** (EI) *m/z* calcd for $C_{12}H_9N_3F_7$ $[M + H]^+$: 328.06792, found 328.06807.

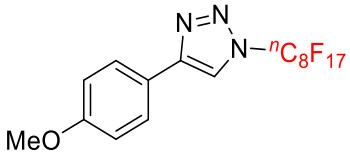
**1-(Perfluorooctyl)-4-phenyl-1*H*-1,2,3-triazole (68da)**



**Yield**: 161 mg (57%), white crystalline solid;

**m.p.** 132–133 °C; **IR** ($CHCl_3$ film) ν 1218, 1151, 749, 671 $cm^{-1}$; **$^1$H NMR** (500 MHz, $CDCl_3$) δ = 8.11 (s, 1H), 7.89–7.87 (m, 2H), 7.50–7.47 (m, 2H), 7.44–7.41 (m, 1H); **$^{13}$C NMR** (125.7 MHz, $CDCl_3$) δ = 148.8, 129.6, 129.3, 128.6, 126.3, 118.1, 117.2, 112.5, 110.9, 110.82, 110.79, 110.3, 109.8, 108.5; **$^{19}$F NMR** (470.4 MHz, $CDCl_3$) δ = -81.2 (t, $^3J_{F-F}$ = 9.9 Hz, $CF_3$), -95.6 (t, $^3J_{F-F}$ = 11.0 Hz, $CF_2$), -121.7–-122.9 (m, 3x $CF_2$), -123.0–-123.3 (m, 2x $CF_2$), -126.6 (bs, $CF_2$); **HRMS** (EI) *m/z* calcd for $C_{16}H_7N_3F_{17}$ $[M]^+$: 564.03630, found 564.03631.

**4-(4-Methoxyphenyl)-1-(perfluorooctyl)-1*H*-1,2,3-triazole (68dc)**



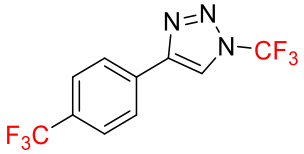
**Yield**: 228 mg (77%), white crystalline solid;

**m.p.** 159–160 °C; **IR** ($CHCl_3$ film) ν 1218, 746, 670 $cm^{-1}$; **$^1$H NMR** (500 MHz, $CDCl_3$) δ = 8.02 (s, 1H), 7.82–7.80 (m, 2H), 7.01–6.99 (m, 2H), 3.87 (s, 3H); **$^{13}$C NMR** (125.7 MHz, $CDCl_3$) δ = 160.6, 148.7, 127.7, 121.2, 117.2, 117.1, 114.5, 112.5, 110.9, 110.82, 110.79, 110.3, 109.8, 108.5, 55.5; **$^{19}$F NMR** (470.4 MHz, $CDCl_3$) δ = -81.2 (t, $^3J_{F-F}$ = 9.9 Hz, $CF_3$), -95.6 (t, $^3J_{F-F}$ = 11.6 Hz, $CF_2$), -122.0–-122.5 (m, 3x $CF_2$), -123.0–-123.3 (m, 2x $CF_2$), -126.6 (bs, $CF_2$); **HRMS** (EI) *m/z* calcd for $C_{17}H_9ON_3F_7$ $[M + H]^+$: 594.04687, found 594.04695.

### 8.3.3. One-pot two-step synthesis of N-trifluoromethyl triazoles from $CF_3TMS$

A 10 mL oven-dried screw-cap glass tube was charged with CsF (182 mg, 1.2 mmol) and dried at 120 °C under high vacuum overnight. The flask was cooled to rt, backfilled with argon, dry DMF (4 mL) was added and cooled to -60 °C. A solution of $CF_3TMS$ (177 µL, 1.2 mmol) and $TsN_3$ (153 µL, 1.0 mmol) in dry DMF (1 mL) was added dropwise, and then the reaction mixture was stirred at -60 °C to -30 °C for 4 h. A solution of alkyne (1.2 mmol) in dry DMF (0.5 mL) and aqueous solutions of $CuSO_4 \cdot 5H_2O$ (1M, 0.12 mmol, 120 µL) and sodium L-ascorbate (1M, 0.12 mmol, 120 µL) were added. The flask was sealed, removed from the cooling bath and stirred at rt for 18 h. The mixture was diluted with water (5 mL), extracted with $Et_2O$ (3 × 5 mL), combined organic phase was washed with water (5 mL), aqueous LiCl (1M, 2 × 5 mL) and water (5 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification by column chromatography on silica gel afforded pure **68**.

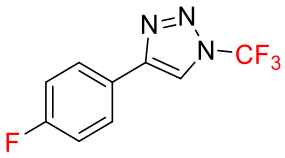
**1-(Trifluoromethyl)-4-(4-(trifluoromethyl)phenyl)-1*H*-1,2,3-triazole (68ag)**




**Yield**: 70 mg (50%), white solid;

**m.p.** 112–115 °C; ***R*$_f$** (cyclohexane:EtOAc 97:3) = 0.18; **IR** ($CHCl_3$ film) ν 1444, 1223, 1204, 1109, 827 $cm^{-1}$; **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 8.23 (s, 1H), 8.00 (d, *J* = 8.0 Hz, 2H), 7.73 (d, *J* = 8.1 Hz, 2H); **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 147.2, 132.1, 131.4 (q, $^2J_{C\text{-}F}$ = 32.8 Hz, *C*-$CF_3$), 126.5, 126.3 (q, $^3J_{C\text{-}F}$ = 3.7 Hz, *C*=C-$CF_3$), 124.0 (q, $^1J_{C\text{-}F}$ = 272.1 Hz, C-*C*$F_3$), 118.2, 117.7 (q, $^1J_{C\text{-}F}$ = 268.7 Hz, N-*C*$F_3$); **$^{19}$F NMR** (376 MHz, $CDCl_3$) δ = -59.3 (s, 3F, N-$CF_3$), -63.3 (s, 3F, Ar$CF_3$); **HRMS** (EI) *m/z* calcd for $C_{10}H_5N_3F_6$ $[M]^+$: 281.0388, found 281.0391.

**4-(4-Fluorophenyl)-1-(trifluoromethyl)-1*H*-1,2,3-triazole (68am)**



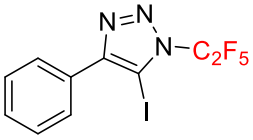
**Yield**: 94 mg (81%), white crystalline solid;

**m.p.** 110–111 °C; ***R*$_f$** (cyclohexane:EtOAc 97:3) = 0.13; **IR** ($CHCl_3$ film) ν 1444, 1207, 1011, 823 $cm^{-1}$; **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 8.14 (s, 1H), 7.88–7.83 (m, 2H), 7.19–7.13 (m, 2H); **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 163.4 (d, $^1J_{C\text{-}F}$ = 249.3 Hz), 147.7, 128.2 (d, $^3J_{C\text{-}F}$ = 8.3 Hz), 124.9 (d, $^4J_{C\text{-}F}$ = 3.4 Hz), 117.7 (q, $^1J_{C\text{-}F}$ = 268.4 Hz), 117.0, 116.3 (d, $^2J_{C\text{-}F}$ = 15.1 Hz); **$^{19}$F NMR** (376 MHz, $CDCl_3$) δ = -59.3 (s, 3F), -111.9 (ddd, $J_{C\text{-}F}$ = 13.6, 8.5, 5.5 Hz, 1F); **HRMS** (EI) *m/z* calcd for $C_9H_5N_3F_4$ $[M]^+$: 231.0420, found 231.0410.

## 8.3.4. Synthesis of N-perfluoroalkyl 1,4,5-trisubstituted 1,2,3-triazoles *via* 5-iodotriazole

### 8.3.4.1. Synthesis of 5-iodo-1-(pentafluoroethyl)-4-phenyl-1*H*-1,2,3-triazole (**68bp**)

To an ice-cooled 10 mL screw-cap glass tube containing copper(I) phenylacetylide (116 mg, 0.704 mmol, 1.1 equiv) and iodine (164 mg, 0.64 mmol, 1 equiv), cold THF solution of azidopentafluoroethane (2.7 mL, 0.64 mmol) and triethylamine (145 mg, 1.43 mmol, 2.24 equiv) were slowly added. After slow warming to ambient temperature, the reaction mixture was stirred under Ar for 16 h. The reaction mixture was then poured into water (10 mL) and extracted with $Et_2O$. The ethereal solution was dried over $MgSO_4$ and chromatographed on silica gel to obtain **68bp**.

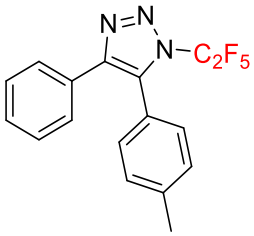


**Yield**: 301 mg (60%), white crystalline solid;

**m.p.** 119–120 °C; **$^{1}$H NMR** (400 MHz, $CDCl_3$) δ = 7.91–7.89 (m, 2H), 7.54–7.46 (m, 3H); **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 152.6, 129.7, 128.9, 128.6, 128.5, 117.2 (qt, $^{1}J_{C\text{-}F}$ = 288.8 Hz, $^{2}J_{C\text{-}F}$ = 38.4.3 Hz, $CF_3$), 112.2 (tq, $^{1}J_{C\text{-}F}$ = 271.7 Hz, $^{2}J_{C\text{-}F}$ = 43.4 Hz, $CF_2$), 71.4; **$^{19}$F NMR** (376 MHz, $CDCl_3$) δ = -81.4 (s, 3F), -93.4 (s, 2F); **HRMS** ($EI^+$) *m/z* calcd for $C_{10}H_6N_3F_5I$ $[M + H]^+$: 389.95211, found 389.95225.

### 8.3.4.2. Synthesis of 1-(pentafluoroethyl)-4-phenyl-5-(*p*-tolyl)-1*H*-1,2,3-triazole (**68bq**)

To a 10 mL screw-cap glass tube containing 5-iodo-1-(pentafluoroethyl)-4-phenyl-1*H*-1,2,3-triazole (**68bp**) (140 mg, 0.36 mmol, 1.0 equiv), *p*-tolylboronic acid (73.4 mg, 0.54 mmol, 1.5 equiv), and potassium carbonate (138.2 mg, 1 mmol, 2.8 equiv), dry DMF (2.0 mL) and palladium(II) acetate (2.5 mg, 0.01 mmol, 2.8%) were added. The reaction mixture was stirred at rt in the closed vial for 16 h (UPLC-MS control), then poured into 5% HCl (10 mL) and extracted with $Et_2O$. The ethereal solution was dried over $MgSO_4$ and chromatographed on silica gel to obtain **68bq**.

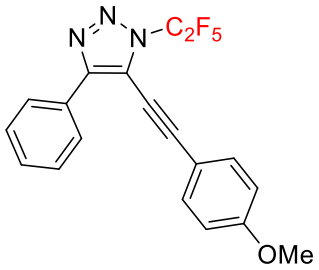



**Yield**: 49 mg (78%), white crystalline solid;

**m.p.** 112–114 °C; **$^{1}$H NMR** (600 MHz, $CDCl_3$) δ = 7.53–7.51 (m, 2H), 7.31–7.25 (m, 7H), 2.46 (s, 3H); **$^{13}$C NMR** (150.9 MHz, $CDCl_3$) δ = 145.9, 140.8, 134.4, 130.1, 129.9, 129.2, 128.8, 128.7, 127.3, 117.2 (qt, $^{1}J_{C\text{-}F}$ = 287.7 Hz, $^{2}J_{C\text{-}F}$ = 39.5 Hz, $CF_3$), 111.3 (tq, $^{1}J_{C\text{-}F}$ = 269.9 Hz, $^{2}J_{C\text{-}F}$ = 42.8 Hz, $CF_2$), 21.6; **$^{19}$F NMR** (376 MHz, $CDCl_3$) δ = -82.2 (s, 3F), -93.5 (s, 2F); **HRMS** ($EI^+$) *m/z* calcd for $C_{17}H_{13}N_3F_5$ $[M + H]^+$: 354.10241, found 354.10250.

### 8.3.4.3. Synthesis of 5-[(4-methoxyphenyl)ethynyl]-1-(pentafluoroethyl)-4-phenyl-1*H*-1,2,3-triazole (**68br**)

To a 10 mL screw-cap glass tube containing 5-iodo-1-(pentafluoroethyl)-4-phenyl-1*H*-1,2,3-triazole (**68bp**) (117 mg, 0.3 mmol, 1.0 equiv), 4-ethynylanisole (40 mg, 0.3 mmol, 1.0 equiv), potassium carbonate (138.2 mg, 1 mmol, 3.3 equiv), and palladium(II) acetate (2.5 mg, 0.01 mmol, 3.3%), dry DMA (1.0 mL) and copper(I) 3-methylsalicylate (1.1 mg, 0.005 mmol, 1.6%) were added. The reaction mixture was stirred at 50 °C in the closed vial for 16 h (UPLC-MS control), then poured into 5% HCl (10 mL) and extracted with $Et_2O$. The ethereal solution was dried over $MgSO_4$ and chromatographed on silica gel to obtain **68br**.




**Yield**: 98 mg (83%), white crystalline solid;

**m.p.** 60–61 °C; **$^1$H NMR** (600 MHz, $CDCl_3$) δ = 8.24–8.22 (m, 2H), 7.53–7.51 (m, 2H), 7.52–7.50 (m, 2H), 7.46–7.44 (m, 1H), 3.87 (s, 3H); **$^{13}$C NMR** (150.9 MHz, $CDCl_3$) δ = 161.3, 148.5, 133.6, 129.6, 129.0, 128.9, 126.8, 117.3 (qt, $^1J_{C\text{-}F}$ = 288.0 Hz, $^2J_{C\text{-}F}$ = 40.0 Hz, $CF_3$), 117.3, 114.6, 112.9, 111.0 (tq, $^1J_{C\text{-}F}$ = 271.7 Hz, $^2J_{C\text{-}F}$ = 43.4 Hz, $CF_2$), 104.9, 72.3, 55.5; **$^{19}$F NMR** (376 MHz, $CDCl_3$) δ = -82.9 (s, 3F), -97.5 (s, 2F); **HRMS** ($EI^+$) *m/z* calcd for $C_{19}H_{13}ON_3F_5$ $[M + H]^+$: 394.09733, found 394.09739.

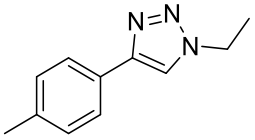
## 8.3.5. Competition experiment of $C_2F_5N_3$ and $C_2H_5N_3$ in the CuAAC

### 8.3.5.1. Preparation of azidoethane

Sodium azide (598 mg, 9.2 mmol) and bromoethane (327 mg, 3.0 mmol) were stirred in dry DMF (5 mL) at 60 °C for 23 h (GC-MS control). After cooling to laboratory temperature, the reaction mixture was poured into brine (20 mL) and extracted to THF (2 × 20 mL). The combined organic layers were washed with 5% LiCl solution (15 mL) and dried over $MgSO_4$. The content of azidoethane was calculated from $^1$H NMR spectra. The concentration of the resulting THF solution was 0.06M (42% yield).

### 8.3.5.2. Synthesis of 1-ethyl-4-(*p*-tolyl)-1*H*-1,2,3-triazole (**70**)

Copper(I) 3-methylsalicylate (2.1 mg, 0.01 mmol) was added to a 15 mL screw-cap glass tube containing THF solution of azidoethane (8 g, 0.55 mmol) and 4-ethynyltoluene (58 mg, 0.5 mmol), the flask was closed and stirred at rt for 16 h (UPLC-MS control). The reaction mixture was then poured into water (10 mL) and extracted with $Et_2O$. The ethereal solution was dried over $MgSO_4$ and evaporated. After crystallization from ethanol, a white crystalline material was obtained.



**Yield**: 77 mg (83%), white crystalline solid;

**m.p.** 69–72 °C (Ref.[178] 70–71 ºC); **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 7.71 (s, 1H), 7.72–7.70 (m, 2H), 7.23–7.21 (m, 2H), 4.43 (q, *J* = 7.3 Hz, 2H), 2.37 (s, 3H), 1.58 (t, *J* = 7.3 Hz, 3H); **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 147.0, 137.0, 128.6, 127.0, 124.7, 117.7, 44.4, 20.4, 14.7; **HRMS** ($EI^+$) *m/z* calcd for $C_{11}H_{13}N_3$ $[M]^+$: 187.1109, found 187.1107.

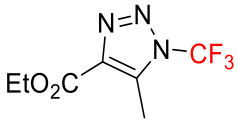
#### 8.3.5.3. Competition experiment

To a 15 mL round-bottom flask containing cold THF solution of azidoethane (0.36 mmol), perfluoroazidoethane (0.36 mmol) and 4-ethynyltoluene (41.6 mg, 0.36 mmol) was added copper(I) 3-methylsalicylate (2.1 mg, 0.01 mmol), the flask was closed with septum and stirred at rt. The content of concurrent triazoles was determined with UPLC-MS analysis. For calculation of the content of the triazoles **68bb** and **70** the calibrated $UV_{280}$ signal was chosen. Figure 5 shows the composition of the reaction mixture (molar % of both triazoles and alkyne) in dependence on reaction time.

## 8.4. Synthesis of N-perfluoroalkyl 1,2,3-triazoles in the organocatalytic azide-ketone cycloaddition

In a 10 mL screw-cap glass tube, with a cold solution of azidoperfluoroalkane (**56**) in THF (0.55-0.70 mmol, 2-3 mL), ketone (0.5 mmol) and pyrrolidine (4.2 µL, 0.05 mmol) were added and the mixture was stirred at rt for 18 h. THF was removed under reduced pressure, $Et_2O$ (2 × 15 mL) was added, the organic phase was washed with water (10 mL) and aqueous LiCl solution (1M, 10 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by column chromatography on silica gel.

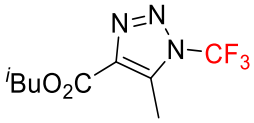
**Ethyl 5-methyl-1-(trifluoromethyl)-1*H*-1,2,3-triazole-4-carboxylate (71a)**




**Yield**: 87 mg (78%), light yellow liquid;

***R<sub>f</sub>*** (cyclohexane:EtOAc, 95:5) = 0.17; **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 4.47 (q, $^3J_{H-H}$ = 7.1 Hz, 2H), 2.79 (q, $^5J_{H-F}$ = 1.3 Hz, 3H), 1.44 (t, $^3J_{H-H}$ = 7.1 Hz, 3H); **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 160.6, 139.2, 137.8 (q, $^3J_{C-F}$ = 1.4 Hz), 118.0 (q, $^1J_{C-F}$ = 269.6 Hz, $CF_3$), 61.8, 14.3, 9.0 (q, $^4J_{C-F}$ = 2.2 Hz, $CH_3$); **$^{19}$F NMR** (376 MHz, $CDCl_3$) δ = -58.3 (s); **HRMS** (EI) *m/z* calcd for $C_7H_8N_3O_2F_3$ $[M]^+$: 223.0569, found 223.0571.

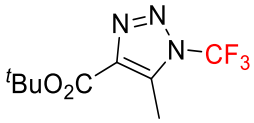
**Isobutyl 5-methyl-1-(trifluoromethyl)-1*H*-1,2,3-triazole-4-carboxylate (71b)**



**Yield**: 83 mg (66%), colorless liquid;

***R<sub>f</sub>*** (pentane:EtOAc, 99:1) = 0.16; **$^{1}$H NMR** (400 MHz, $CDCl_3$) δ = 4.18 (d, $^{3}J_{H\text{-}H}$ = 6.8 Hz, 2H), 2.78 (q, $^{5}J_{H\text{-}F}$ = 1.3 Hz, 3H), 2.13 (sep, $^{3}J_{H\text{-}H}$ = 6.7 Hz, 1H), 1.03 (d, $^{3}J_{H\text{-}H}$ = 6.7 Hz, 6H); **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 160.7, 139.0, 137.9 (q, $^{3}J_{C\text{-}F}$ = 1.7 Hz), 118.0 (q, $^{1}J_{C\text{-}F}$ =269.7 Hz, $CF_3$), 71.7, 27.9, 19.2, 9.1 (q, $^{4}J_{C\text{-}F}$ = 2.2 Hz, $CH_3$); **$^{19}$F NMR** (376 MHz, $CDCl_3$) δ = -58.3 (s); **HRMS** (EI) *m/z* calcd for $C_9H_{12}N_3O_2F_3$ $[M]^+$: 251.0882, found 251.0883.

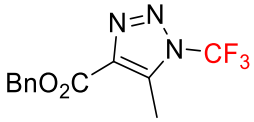
***tert*-Butyl 5-methyl-1-(trifluoromethyl)-1*H*-1,2,3-triazole-4-carboxylate (71c)**



**Yield**: 99 mg (79%), light yellow liquid;

***R<sub>f</sub>*** (pentane:EtOAc, 99:1) = 0.13; **$^{1}$H NMR** (400 MHz, $CDCl_3$) δ = 2.74 (q, $^{5}J_{H\text{-}F}$ = 1.3 Hz, 3H), 1.62 (s, 9H); **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 159.8, 139.0 (q, $^{3}J_{C\text{-}F}$ = 1.8 Hz), 138.5, 118.0 (q, $^{1}J_{C\text{-}F}$ = 269.3 Hz, $CF_3$), 83.3, 28.3, 9.1 (q, $^{4}J_{C\text{-}F}$ = 2.2 Hz, $CH_3$); **$^{19}$F NMR** (376 MHz, $CDCl_3$) δ = -58.4 (s); **HRMS** (EI) *m/z* calcd for $C_9H_{12}N_3O_2F_3$ $[M]^+$: 251.0882, found 251.0877.

**Benzyl 5-methyl-1-(trifluoromethyl)-1*H*-1,2,3-triazole-4-carboxylate (71d)**

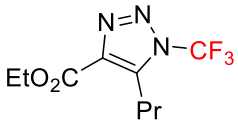


**Yield**: 116 mg (81%), colorless liquid;

***R<sub>f</sub>*** (pentane:EtOAc, 97:3) = 0.45; **$^{1}$H NMR** (400 MHz, $CDCl_3$) δ = 7.51–7.44 (m, 2H), 7.42–7.31 (m, 3H), 5.43 (s, 2H), 2.76 (q, $^{5}J_{H\text{-}F}$ = 1.3 Hz, 3H); **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 160.5, 139.4, 137.7 (q, $^{3}J_{C\text{-}F}$ = 1.7 Hz), 135.3, 128.8, 128.7, 128.7, 118.0 (q,

$^{1}J_{C\text{-}F}$ = 269.9 Hz, $CF_3$), 67.4, 9.1 (q, $^{4}J_{C\text{-}F}$ = 2.2 Hz, $CH_3$); **$^{19}$F NMR** (376 MHz, $CDCl_3$) δ = -58.3 (s); **HRMS** (EI) *m/z* calcd for $C_{12}H_{10}N_3O_2F_3$ $[M]^+$: 285.0725, found 285.0721.

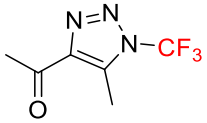
**Ethyl 5-propyl-1-(trifluoromethyl)-1*H*-1,2,3-triazole-4-carboxylate (71e)**




**Yield**: 82 mg (65%, 20 mol% pyrrolidine), yellow liquid;

***R*$_f$** (pentane:EtOAc, 99:1) = 0.28; **$^{1}$H NMR** (400 MHz, $CDCl_3$) δ = 4.46 (q, $^{3}J_{H\text{-}H}$ = 7.2 Hz, 2H), 3.16–3.11 (m, 2H), 1.74–1.65 (m, 2H), 1.44 (t, $^{3}J_{H\text{-}H}$ = 7.2 Hz, 3H), 1.03 (t, $^{3}J_{H\text{-}H}$ = 7.4 Hz, 3H); **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 160.5, 143.5, 137.6 (q, $^{3}J_{C\text{-}F}$ = 1.6 Hz), 118.1 (q, $^{1}J_{C\text{-}F}$ = 269.6 Hz, $CF_3$), 61.7, 25.1 (q, $^{4}J_{C\text{-}F}$ = 1.8 Hz), 22.6, 14.3, 13.9; **$^{19}$F NMR** (376 MHz, $CDCl_3$) δ = -57.6 (s); **HRMS** (EI) *m/z* calcd for $C_9H_{13}N_3O_2F_3$ $[M + H]^+$: 252.0954, found 252.0955 and for $C_9H_{12}N_3O_2F_3Na$ $[M + Na]^+$: 274.0774, found 274.0774.

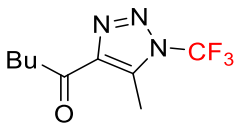
**1-(5-Methyl-1-(trifluoromethyl)-1*H*-1,2,3-triazol-4-yl)ethan-1-one (71f)**




**Yield**: 47 mg (49%), light yellow liquid;

***R*$_f$** (cyclohexane:EtOAc, 95:5) = 0.25; **$^{1}$H NMR** (400 MHz, $CDCl_3$) δ = 2.78 (q, $^{5}J_{H\text{-}F}$ = 1.3 Hz, 3H), 2.74 (s, 3H); **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 193.7, 144.0 (q, $^{3}J_{C\text{-}F}$ = 1.3 Hz), 137.8, 118.1 (q, $^{1}J_{C\text{-}F}$ = 270.0 Hz, $CF_3$), 28.3, 9.0 (q, $^{4}J_{C\text{-}F}$ = 2.2 Hz, $CH_3$); **$^{19}$F NMR** (376 MHz, $CDCl_3$) δ = -58.3 (s); **HRMS** (EI) *m/z* calcd for $C_6H_6N_3OF_3$ $[M]^+$: 193.0463, found 193.0464.

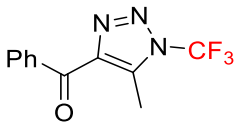
**1-(5-Methyl-1-(trifluoromethyl)-1*H*-1,2,3-triazol-4-yl)pentan-1-one (71g)**



**Yield**: 87 mg (74%), light yellow liquid;

***R<sub>f</sub>*** (pentane:$Et_2O$, 99:1) = 0.24; **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 3.16 (t, $^3J_{H-H}$ = 7.5 Hz, 2H), 2.78 (q, $^5J_{H-F}$ = 1.3 Hz, 3H), 1.78–1.66 (m, 2H), 1.50–1.33 (m, 2H), 0.95 (t, $^3J_{H-H}$ = 7.3 Hz, 3H); **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 196.5, 143.8 (q, $^3J_{C-F}$ = 1.3 Hz), 137.7, 118.1 (q, $^1J_{C-F}$ = 269.7 Hz, $CF_3$), 40.4, 26.0, 22.5, 14.0, 9.1 (q, $^4J_{C-F}$ = 2.2 Hz, $CH_3$); **$^{19}$F NMR** (376 MHz, $CDCl_3$) δ = -58.2 (s); **HRMS** (EI) *m/z* calcd for $C_9H_{12}N_3OF_3$ $[M]^+$: 235.0932, found 235.0929.

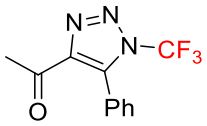
**(5-Methyl-1-(trifluoromethyl)-1*H*-1,2,3-triazol-4-yl)(phenyl)methanone (71h major)**




**Yield**: 77 mg (60%), colorless liquid;

***R<sub>f</sub>*** (pentane:$Et_2O$, 97:3) = 0.37; **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 8.30–8.26 (m, 2H), 7.66–7.62 (m, 1H), 7.56–7.51 (m, 2H), 2.85 (q, $^5J_{H-F}$ = 1.2 Hz, 3H); **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 186.7, 144.1 (q, $^3J_{C-F}$ = 1.5 Hz), 140.1, 136.7, 133.7, 130.7, 128.6, 118.2 (q, $^1J_{C-F}$ = 269.8 Hz, $CF_3$), 9.5 (q, $^4J_{C-F}$ = 2.2 Hz, $CH_3$); **$^{19}$F NMR** (376 MHz, $CDCl_3$) δ = -58.1 (s); **HRMS** (EI) *m/z* calcd for $C_{11}H_8N_3OF_3$ $[M]^+$: 255.0619, found 255.0617.

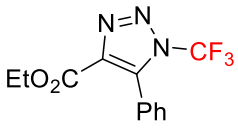
**1-(5-Phenyl-1-(trifluoromethyl)-1*H*-1,2,3-triazol-4-yl)ethan-1-one (71h minor)**




**Yield**: 7 mg (6%), colorless liquid;

***R<sub>f</sub>*** (pentane:$Et_2O$, 97:3) = 0.15; **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 7.59–7.54 (m, 1H), 7.53–7.49 (m, 2H), 7.40–7.37 (m, 2H), 2.70 (s, 3H); **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 191.8, 144.3 (q, $^3J_{C-F}$ = 1.4 Hz), 139.5, 131.1, 129.6, 128.7, 123.6, 118.0 (q, $^1J_{C-F}$ = 271.5 Hz, $CF_3$), 28.7; **$^{19}$F NMR** (376 MHz, $CDCl_3$) δ = -55.4 (s); **HRMS** (EI) *m/z* calcd for $C_{11}H_8N_3OF_3$ $[M]^+$: 255.0619, found 255.0618.

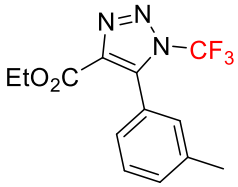
**Ethyl 5-phenyl-1-(trifluoromethyl)-1*H*-1,2,3-triazole-4-carboxylate (71i)**



**Yield**: 100 mg (70%), colorless crystalline solid;

**m.p.** 106 °C, ***R*$_f$** (pentane:$Et_2O$, 95:5) = 0.11; **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 7.60–7.56 (m, 1H), 7.54–7.50 (m, 2H), 7.42–7.39 (m, 2H), 4.30 (q, $^3J_{H-H}$ = 7.1 Hz, 2H), 1.23 (t, $^3J_{H-H}$ = 7.1 Hz, 3H); **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 159.7, 141.2, 138.5 (q, $^3J_{C-F}$ = 1.8 Hz), 131.0, 129.6, 128.6, 123.7, 117.8 (q, $^1J_{C-F}$ = 271.3 Hz, $CF_3$), 61.8, 14.1; **$^{19}$F NMR** (376 MHz, $CDCl_3$) δ = -55.6 (s); **HRMS** (EI) *m/z* calcd for $C_{12}H_{10}N_3O_2F_3$ $[M]^+$: 285.0725, found 285.0724.

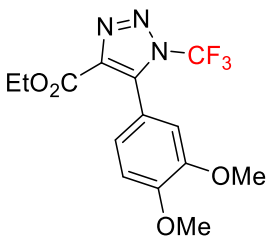
**Ethyl 5-(*m*-tolyl)-1-(trifluoromethyl)-1*H*-1,2,3-triazole-4-carboxylate (71j)**



**Yield**: 79 mg (52%), white crystalline solid;

**m.p.** 41-42 °C, ***R*$_f$** (pentane:EtOAc, 97:3) = 0.28; **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 7.43–7.34 (m, 2H), 7.21–7.15 (m, 2H), 4.31 (q, $^3J_{H-H}$ = 7.1 Hz, 2H), 2.42 (q, $^8J_{H-F}$ = 0.7 Hz, 3H), 1.24 (t, $^3J_{H-H}$ = 7.1 Hz, 3H); **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 159.7, 141.3, 138.4, 131.8, 130.1, 128.4, 126.7, 123.5, 117.8 (q, $^1J_{C-F}$ = 271.2 Hz, $CF_3$), 61.7, 21.4 (q, $^7J_{C-F}$ = 2.6 Hz, $CH_3$), 14.0; **$^{19}$F NMR** (376 MHz, $CDCl_3$) δ = -55.6 (s); **HRMS** (EI) *m/z* calcd for $C_{13}H_{12}N_3O_2F_3$ $[M]^+$: 299.0882, found 299.0884.

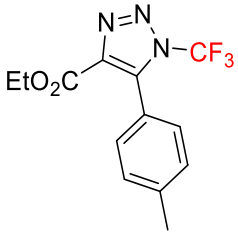
**Ethyl 5-(3,4-dimethoxyphenyl)-1-(trifluoromethyl)-1*H*-1,2,3-triazole-4-carboxylate (71k)**



**Yield**: 102 mg (59%), white crystalline solid;

**m.p.** 104-106 °C, $R_f$ (pentane:EtOAc, 9:1) = 0.20; **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 7.03–6.99 (m, 2H), 6.92–6.91 (m, 1H), 4.36 (q, $^3J_{H-H}$ = 7.1 Hz, 2H), 3.98 (s, 3H), 3.91 (s, 3H), 1.32 (t, $^3J_{H-H}$ = 7.1 Hz, 3H); **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 159.9, 151.2, 148.9, 141.2, 138.2 (q, $^3J_{C-F}$ = 1.6 Hz), 123.0, 117.9 (q, $^1J_{C-F}$ = 271.1 Hz, $CF_3$), 115.2, 112.6, 110.9, 61.8, 56.2, 56.1, 14.2; **$^{19}$F NMR** (376 MHz, $CDCl_3$) δ = -55.6 (s); **HRMS** (ESI) *m/z* calcd for $C_{14}H_{15}N_3O_4F_3$ $[M]^+$: 346.1009, found 346.1010 and $[M + Na]^+$: 368.0829, found 368.0829.

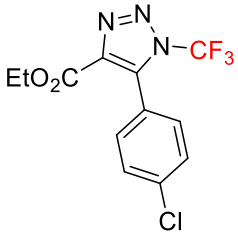
**Ethyl 5-(*p*-tolyl)-1-(trifluoromethyl)-1*H*-1,2,3-triazole-4-carboxylate (71l)**




**Yield**: 109 mg (73%), white crystalline solid;

**m.p.** 74-75 °C, $R_f$ (pentane:$Et_2O$, 95:5) = 0.16; **$^1$H NMR** (401 MHz, $CDCl_3$) δ = 7.33–7.27 (m, 4H), 4.32 (q, $^3J_{H-H}$ = 7.1 Hz, 2H), 2.45 (s, 3H), 1.27 (t, $^3J_{H-H}$ = 7.1 Hz, 3H); **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 159.8, 141.5, 141.4, 138.4 (q, $^3J_{C-F}$ = 1.6 Hz), 129.5, 129.3, 120.5, 117.9 (q, $^1J_{C-F}$ = 271.1 Hz, $CF_3$), 61.8, 21.7, 14.2; **$^{19}$F NMR** (376 MHz, $CDCl_3$) δ = -55.6 (s); **HRMS** (EI) *m/z* calcd for $C_{13}H_{12}N_3O_2F_3$ $[M]^+$: 299.0882, found 299.0883.

**Ethyl 5-(4-chlorophenyl)-1-(trifluoromethyl)-1*H*-1,2,3-triazole-4-carboxylate (71m)**

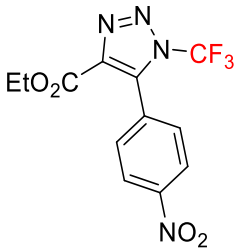



**Yield**: 72 mg (45%), colorless crystalline solid;

**m.p.** 129-130 °C, $R_f$ (pentane:EtOAc, 95:5) = 0.58; **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 7.54–7.48 (m, 2H), 7.40–7.31 (m, 2H), 4.33 (q, $^3J_{H-H}$ = 7.1 Hz, 2H), 1.28 (t, $^3J_{H-H}$ = 7.1

Hz, 3H); **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 159.6, 140.0, 138.6 (q, $^3J_{C\text{-}F}$ = 1.7 Hz), 137.6, 131.1, 129.1, 122.0, 117.8 (q, $^1J_{C\text{-}F}$ = 271.4 Hz, $CF_3$), 62.0, 14.1; **$^{19}$F NMR** (376 MHz, $CDCl_3$) δ = -55.5 (s); **HRMS** (EI) *m/z* calcd for $C_{12}H_9N_3O_2F_3Cl$ $[M]^+$: 319.0335, found 319.0334.

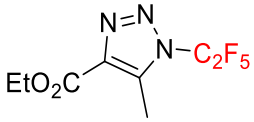
**Ethyl 5-(4-nitrophenyl)-1-(trifluoromethyl)-1*H*-1,2,3-triazole-4-carboxylate (71n)**




**Yield**: 63 mg (38%, 20 mol% pyrrolidine), pale yellow solid;

**m.p.** 73-74 °C, ***R*$_f$** (pentane:EtOAc, 97:3) = 0.09; **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 8.44–8.35 (m, 2H), 7.67–7.59 (m, 2H), 4.33 (q, $^3J_{H\text{-}H}$ = 7.1 Hz, 2H), 1.28 (t, $^3J_{H\text{-}H}$ = 7.2 Hz, 3H); **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 159.3, 149.5, 138.9, 138.7, 131.1, 130.2, 123.7, 117.7 (q, $^1J_{C\text{-}F}$ = 272.0 Hz, $CF_3$), 62.2, 14.1; **$^{19}$F NMR** (376 MHz, $CDCl_3$) δ = -55.4 (s); **HRMS** (EI) *m/z* calcd for $C_{12}H_9N_4O_4F_3$ $[M]^+$: 330.0576, found 330.0571.

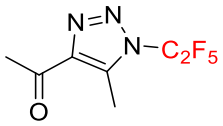
**Ethyl 5-methyl-1-(perfluoroethyl)-1*H*-1,2,3-triazole-4-carboxylate (71o)**




**Yield**: 107 mg (78%, 20 mol% pyrrolidine), yellowish liquid;

***R*$_f$** (pentane:EtOAc, 99:1) = 0.12; **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 4.46 (q, $^3J_{H\text{-}H}$ = 7.1 Hz, 2H), 2.79 (t, $^5J_{H\text{-}F}$ = 1.9 Hz, 3H), 1.44 (t, $^3J_{H\text{-}H}$ = 7.1 Hz, 3H); **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 160.6, 140.7 (t, $^3J_{C\text{-}F}$ = 1.6 Hz), 137.8, 117.1 (qt, $J_{C\text{-}F}$ = 287.6, 39.9 Hz, $CF_3$), 111.2 (tq, $J_{C\text{-}F}$ = 271.0, 43.3 Hz, $CF_2$), 61.8 (t, $J$ = 6.2 Hz, $CH_2CH_3$), 14.3 (q, $J$ = 4.6 Hz, $CH_2CH_3$), 9.7–8.9 (m, $CH_3$); **$^{19}$F NMR** (376 MHz, $CDCl_3$) δ = -83.1 (s, 3F), -97.6 (q, $^3J_{F\text{-}F}$ = 1.8 Hz, 2F); **HRMS** (EI) *m/z* calcd for $C_8H_8N_3O_2F_5$ $[M]^+$: 273.0537, found 273.0535.

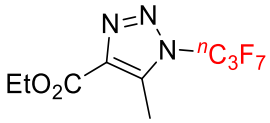
**1-(5-Methyl-1-(perfluoroethyl)-1*H*-1,2,3-triazol-4-yl)ethan-1-one (71p)**



**Yield**: 83 mg (68%, 20 mol% pyrrolidine), colorless liquid;

***R<sub>f</sub>*** (pentane:EtOAc, 99:1) = 0.24; **$^{1}$H NMR** (400 MHz, $CDCl_3$) δ = 2.79 (t, $^{5}J_{H\text{-}F}$ = 1.8 Hz, 3H), 2.73 (s, 3H); **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 193.7, 143.8, 139.3 (t, $^{3}J_{C\text{-}F}$ = 1.7 Hz), 117.2 (qt, $J_{C\text{-}F}$ = 287.7, 39.8 Hz, $CF_3$), 111.3 (tq, $J_{C\text{-}F}$ = 270.7, 43.2 Hz, $CF_2$), 28.5, 9.4 (t, $^{4}J_{C\text{-}F}$ = 3.9 Hz, $CH_3$); **$^{19}$F NMR** (376 MHz, $CDCl_3$) δ = -83.1 (s, 3F), -97.5 (q, $^{3}J_{F\text{-}F}$ = 1.9 Hz, 2F); **HRMS** (EI) *m/z* calcd for $C_7H_6N_3OF_5$ $[M]^+$: 243.0431, found 243.0434.

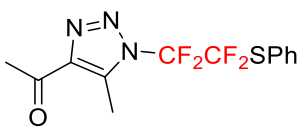
**Ethyl 5-methyl-1-(perfluoropropyl)-1*H*-1,2,3-triazole-4-carboxylate (71q)**



**Yield**: 69 mg (43%, 20 mol% pyrrolidine), yellowish liquid;

***R<sub>f</sub>*** (pentane:EtOAc, 99:1) = 0.09; **$^{1}$H NMR** (400 MHz, $CDCl_3$) δ = 4.46 (q, $^{3}J_{H\text{-}H}$ = 7.1 Hz, 2H), 2.77 (t, $^{5}J_{H\text{-}F}$ = 2.0 Hz, 3H), 1.44 (t, $^{3}J_{H\text{-}H}$ = 7.1 Hz, 3H); **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 160.7, 140.9 (t, $^{3}J_{C\text{-}F}$ = 1.4 Hz), 137.8, 117.3 (qt, $J_{C\text{-}F}$ = 287.9, 33.1 Hz, $CF_3$), 112.9 (tt, $J_{C\text{-}F}$ = 274.2, 32.0 Hz, $CF_2$), 107.8 (tq, $J_{C\text{-}F}$ = 270.1, 40.0 Hz, $CF_2$), 61.9, 14.4, 9.5 (tt, $J_{C\text{-}F}$ = 4.0, 1.6 Hz, $CH_3$); **$^{19}$F NMR** (376 MHz, $CDCl_3$) δ = -80.9 (t, $^{3}J_{F\text{-}F}$ = 9.2 Hz, 3F), -95.1 to -95.3 (m, 2F), -126.8 (s, 2F); **HRMS** (EI) *m/z* calcd for $C_9H_8N_3O_2F_7$ $[M]^+$: 323.0505, found 323.0504.

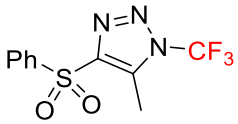
**1-(5-Methyl-1-(1,1,2,2-tetrafluoro-2-(phenylthio)ethyl)-1*H*-1,2,3-triazol-4-yl)ethan-1-one (71r)**



**Yield**: 163 mg (98%, 20 mol% pyrrolidine), white crystalline solid;

**m.p.** 49-50 °C, ***R*$_f$** (pentane:EtOAc, 99:1) = 0.14; **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 7.68–7.61 (m, 2H), 7.53–7.46 (m, 1H), 7.44–7.37 (m, 2H), 2.74–2.71 (m, 6H); **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 193.9, 143.7, 139.4 (t, $^3J_{C\text{-}F}$ = 1.5 Hz), 137.3, 131.2, 129.6, 122.8 (t, $^3J_{C\text{-}F}$ = 2.8 Hz), 122.5 (tt, $J_{C\text{-}F}$ = 291.6, 38.8 Hz, $CF_2$), 114.6 (tt, $J_{C\text{-}F}$ = 273.6, 36.5 Hz, $CF_2$), 28.4, 9.6 (tt, $J_{C\text{-}F}$ = 4.1, 1.9 Hz, $CH_3$); **$^{19}$F NMR** (376 MHz, $CDCl_3$) δ = -88.6 (t, $^3J_{F\text{-}F}$ = 6.4 Hz, 2F), -94.2 to -94.2 (m, 2F); **HRMS** (ESI) *m/z* calcd for $C_{13}H_{11}N_3OF_4NaS$ $[M + Na]^+$: 356.0451, found 356.0453.

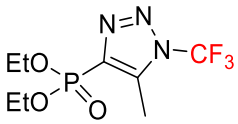
**5-Methyl-4-(phenylsulfonyl)-1-(trifluoromethyl)-1*H*-1,2,3-triazole (71s)**




**Yield**: 122 mg (84%, 50 mol% pyrrolidine), pale yellow oil;

***R*$_f$** (pentane:EtOAc, 9:1) = 0.20; **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 8.16–8.02 (m, 2H), 7.73–7.64 (m, 1H), 7.63–7.54 (m, 2H), 2.81 (q, $^5J_{H\text{-}F}$ = 1.3 Hz, 3H); **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 146.3 (q, $^3J_{C\text{-}F}$ = 1.6 Hz), 139.9, 137.0, 134.5, 129.6, 128.2, 117.8 (q, $^1J_{C\text{-}F}$ = 271.1 Hz, $CF_3$), 8.7 (q, $^4J_{C\text{-}F}$ = 2.3 Hz, $CH_3$); **$^{19}$F NMR** (376 MHz, $CDCl_3$) δ = -58.2 (s); **HRMS** (ESI) *m/z* calcd for $C_{10}H_8N_3O_2F_3SNa$ $[M + Na]^+$: 314.0182, found 314.0182 and for $C_{10}H_9N_3O_2F_3S$ $[M + H]^+$: 292.0362, found 292.0363.

**Diethyl (5-methyl-1-(trifluoromethyl)-1*H*-1,2,3-triazol-4-yl)phosphonate (71t)**




**Yield**: 126 mg (88%, 50 mol% pyrrolidine), pale yellow liquid;

***R*$_f$** (pentane:$Et_2O$, 1:1) = 0.25; **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 4.31–4.16 (m, 4H), 2.74 (dq, $^4J_{H\text{-}P}$ and $^5J_{H\text{-}F}$ = 1.3 Hz, 3H), 1.38 (td, $^3J_{H\text{-}H}$ = 7.1 Hz and $^4J_{H\text{-}P}$ = 0.7 Hz, 6H); **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 141.5 (d, $^2J_{C\text{-}P}$ = 34.6 Hz), 136.7 (d, $^1J_{C\text{-}P}$ = 236.5 Hz), 118.1 (q, $^1J_{C\text{-}F}$ = 270.0 Hz, $CF_3$), 63.5 (d, $^2J_{C\text{-}P}$ = 5.9 Hz), 16.3 (d, $^3J_{C\text{-}P}$ = 6.6 Hz), 8.8 (q, $^4J_{C\text{-}F}$ = 2.4 Hz, $CH_3$); **$^{19}$F NMR** (376 MHz, $CDCl_3$) δ = -58.2 (s); **$^{31}$P NMR** (162 MHz, $CDCl_3$)

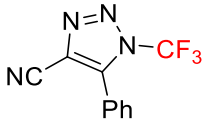
δ = 5.2 (p, $^{3}J_{P-H}$ = 7.7 Hz); **HRMS** (EI) *m/z* calcd for $C_8H_{13}N_3O_3F_3P$ $[M]^+$: 287.0647, found 287.0646.

**Diethyl (5-phenyl-1-(trifluoromethyl)-1*H*-1,2,3-triazol-4-yl)phosphonate (71u)**

**Yield**: 96 mg (55%, 50 mol% pyrrolidine), yellow liquid;

***R*$_f$** (pentane:EtOAc, 6:4) = 0.42; **$^{1}$H NMR** (401 MHz, $CDCl_3$) δ = 7.62–7.56 (m, 1H), 7.56–7.50 (m, 2H), 7.50–7.46 (m, 2H), 4.25–4.05 (m, 4H), 1.24 (td, $^{3}J_{H-H}$ = 7.1 Hz and $^{4}J_{H-P}$ = 0.7 Hz, 6H); **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 142.9 (d, $^{2}J_{C-P}$ = 32.7 Hz), 138.5 (d, $^{1}J_{C-P}$ = 238.8 Hz), 131.1, 129.8, 128.6, 117.9 (q, $^{1}J_{C-F}$ = 271.0 Hz, $CF_3$), 63.5 (d, $^{2}J_{C-P}$ = 6.0 Hz), 16.2 (d, $^{3}J_{C-P}$ = 6.6 Hz); **$^{19}$F NMR** (377 MHz, $CDCl_3$) δ = -55.3 (s); **$^{31}$P NMR** (162 MHz, $CDCl_3$) δ = 4.9 (p, $^{3}J_{P-H}$ = 8.3 Hz); **HRMS** (ESI) *m/z* calcd for $C_{13}H_{15}N_3O_3F_3PNa$ $[M + Na]^+$: 372.0695, found 372.0697.

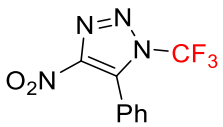
**5-Phenyl-1-(trifluoromethyl)-1*H*-1,2,3-triazole-4-carbonitrile (71v)**



**Yield**: 42 mg (35%, 50 mol% pyrrolidine), pale yellow liquid;

***R*$_f$** (cyclohexane:$Et_2O$, 9:1) = 0.39; **$^{1}$H NMR** (400 MHz, $CDCl_3$) δ = 7.69–7.65 (m, 1H), 7.63–7.59 (m, 2H), 7.55–7.51 (m, 2H); **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 144.3, 132.5, 129.7, 129.1 (q, $^{3}J_{C-F}$ = 1.2 Hz), 122.7 (q, $^{3}J_{C-F}$ = 2.4 Hz), 121.2, 117.7 (q, $^{1}J_{C-F}$ = 272.0 Hz, $CF_3$), 110.4; **$^{19}$F NMR** (376 MHz, $CDCl_3$) δ = -55.5 (s); **HRMS** (EI) *m/z* calcd for $C_{10}H_5N_4F_3$ $[M]^+$: 238.0466, found 238.0467.

**4-Nitro-5-phenyl-1-(trifluoromethyl)-1*H*-1,2,3-triazole (71w)**



**Yield**: 52 mg (40%, 50 mol% pyrrolidine), yellow oil;

***R*$_f$** (pentane:EtOAc, 99:1) = 0.08; **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 7.69–7.63 (m, 1H), 7.62–7.55 (m, 2H), 7.49–7.42 (m, 2H); **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 136.0, 132.1, 129.5 (q, $^3J_{C\text{-}F}$ = 1.0 Hz), 129.2, 121.1, 117.5 (q, $^1J_{C\text{-}F}$ = 273.4 Hz, $CF_3$); **$^{19}$F NMR** (376 MHz, $CDCl_3$) δ = -55.8 (s); **HRMS** (EI) *m/z* calcd for $C_9H_5N_4O_2F_3$ $[M]^+$: 258.0365, found 258.0367.

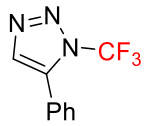
### 8.4.1. Cycloaddition of azidotrifluoromethane with pyrrolidinyl enamine of ethyl acetoacetate

Pyrrolidinyl enamine of ethyl acetoacetate was prepared according to literature.[179] To the cold solution of $CF_3N_3$ in THF (0.5 mmol in 2.5 mL), enamine (92 mg, 0.5 mmol) was added and the mixture was stirred at rt for 18 h. After workup (*vide infra*), the crude product was obtained in 82%.

### 8.4.2. Synthesis of N-perfluoroalkyl 1,5-disubstituted 1,2,3-triazoles *via* hydrolysis and decarboxylation

In a 10 mL round-bottom flask, previously synthesized triazole **71** (0.29 mmol) was dissolved in THF (1 mL). After the addition of $LiOH{\cdot}H_2O$ (0.58 mmol in 0.5 mL $H_2O$), the solution was stirred at rt for 45 min. Addition of HCl solution (0.85 mL, 1M) resulted in the formation of the carboxylic acid which was extracted with $Et_2O$ (2 × 15 mL), washed with water (10 mL) and aqueous LiCl solution (1M, 10 mL). The organic phase was then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to yield the pure carboxylic acid. Upon heating the acid to temperature slightly above the melting point (100-150 °C, oil bath temperature) for 10 min, the acid decarboxylated to give the pure 1,5-disubstituted triazole **77**.

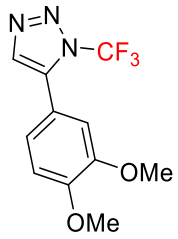
**5-Phenyl-1-(trifluoromethyl)-1*H*-1,2,3-triazole (77i)**



**Yield**: 51 mg (82%), yellow oil;

***R*$_f$** (pentane:$Et_2O$, 99:1) = 0.08; **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 7.74 (q, $^5J_{H-F}$ = 0.9 Hz, 1H), 7.57–7.48 (m, 3H), 7.45–7.42 (m, 2H); **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 138.3, 134.7 (q, $^3J_{C-F}$ = 1.7 Hz), 130.7, 129.2 (q, $^4J_{C-F}$ = 1.2 Hz), 129.0, 124.7, 118.3 (q, $^1J_{C-F}$ = 269.2 Hz, $CF_3$); **$^{19}$F NMR** (376 MHz, $CDCl_3$) δ = -55.6 (s); **HRMS** (EI) *m/z* calcd for $C_9H_6N_3F_3$ $[M]^+$: 213.0514, found 213.0512.

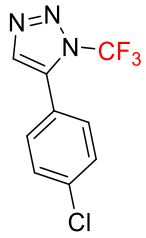
**5-(3,4-Dimethoxyphenyl)-1-(trifluoromethyl)-1*H*-1,2,3-triazole (77k)**



**Yield**: 46 mg (58%), white crystalline solid;

**m.p.** 80-81 °C, ***R*$_f$** (pentane:$Et_2O$, 7:3) = 0.30; **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 7.70 (q, $^5J_{H-F}$ = 1.0 Hz, 1H), 7.03–6.95 (m, 2H), 6.90–6.89 (m, 1H), 3.95 (s, 3H), 3.90 (s, 3H); **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 151.0, 149.2, 138.3, 134.6 (q, $^3J_{C-F}$ = 1.5 Hz), 122.3 (q, $^4J_{C-F}$ = 1.2 Hz), 118.4 (q, $^1J_{C-F}$ = 269.0 Hz, $CF_3$), 116.8, 112.0 (q, $^4J_{C-F}$ = 1.3 Hz), 111.3, 56.2, 56.2; **$^{19}$F NMR** (376 MHz, $CDCl_3$) δ = -55.6 (s); **HRMS** (EI) *m/z* calcd for $C_{11}H_{10}N_3O_2F_3$ $[M]^+$: 273.0725, found 273.0724.

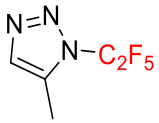
**5-(4-Chlorophenyl)-1-(trifluoromethyl)-1*H*-1,2,3-triazole (77m)**



**Yield**: 57 mg (79%), white crystalline solid;

**m.p.** 81-82 °C, $R_f$ (pentane:$Et_2O$, 97:3) = 0.32; **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 7.74 (q, $^5J_{H-F}$ = 0.9 Hz, 1H), 7.51–7.48 (m, 2H), 7.39–7.36 (m, 2H); **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 137.2, 137.2, 134.9 (q, $^3J_{C-F}$ = 1.6 Hz), 130.5 (q, $^4J_{C-F}$ = 1.0 Hz), 129.5, 123.1, 118.3 (q, $^1J_{C-F}$ = 269.3 Hz, $CF_3$); **$^{19}$F NMR** (376 MHz, $CDCl_3$) δ = -55.6 (s); **HRMS** (EI) *m/z* calcd for $C_9H_5N_3F_3Cl$ $[M]^+$: 247.0124, found 247.0126.

**5-Methyl-1-(perfluoroethyl)-1*H*-1,2,3-triazole (77o)**



**Yield**: 44 mg (76%), yellow liquid;

$R_f$ (pentane:$Et_2O$, 95:5) = 0.24; **$^1$H NMR** (400 MHz, $CDCl_3$) δ = 7.54 (dt, $^5J_{H-F}$ = 1.1 Hz, $^6J_{H-F}$ = 0.6 Hz, 1H), 2.50 (td, $^5J_{H-F}$ = 1.9 Hz, $^6J_{H-F}$ = 0.9 Hz, 3H); **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 135.2 (t, $^3J_{C-F}$ = 1.8 Hz), 134.5, 117.3 (qt, $^1J_{C-F}$ = 287.5 Hz, $^2J_{C-F}$ = 40.6 Hz, $CF_3$), 111.4 (tq, $^1J_{C-F}$ = 268.5 Hz, $^2J_{C-F}$ = 42.6 Hz, $CF_2$), 9.0 (t, $^4J_{C-F}$ = 3.9 Hz, $CH_3$); **$^{19}$F NMR** (376 MHz, $CDCl_3$) δ = -83.2 (s, 3F), -97.5 (q, $^3J_{F-F}$ = 1.7 Hz, 2F); **HRMS** (EI) *m/z* calcd for $C_5H_4N_3F_5$ $[M]^+$: 201.0325, found 201.0324.

### 8.4.3. Cycloaddition of azidotrifluoromethane with cyclic ketones

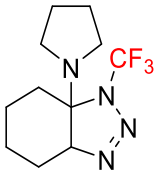
In a 10 mL screw-cap glass tube, with a cold solution of $CF_3N_3$ in THF (0.55-0.70 mmol, 2-3 mL), cyclohexanone (0.5 mmol) and pyrrolidine (63 µL, 0.75 mmol) were added and the mixture was stirred at -50 °C to -30 °C for 30 min. THF and unreacted pyrrolidine were removed under reduced pressure to give the crude triazoline **78**.

When the reaction was stirred overnight reaching room temperature, the formed triazoline decomposed to amide **79**. THF and pyrrolidine were removed under reduced pressure, $Et_2O$ (2 × 15 mL) was added, the organic phase was washed with water (10 mL) and aqueous LiCl solution (1M, 10 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude amide (**79**) was purified by column chromatography on silica gel.

When the reaction was quenched with aqueous HCl (1mL, 5%), the triazoline was converted to the mixture of amide **79** and triazole **84**. The workup of the reaction was accomplished as for amide **79**. The crude products were purified by column chromatography on silica gel.

When the reaction was quenched with TBDMSCl (75 mg , 0.5 mmol), the triazoline was transformed into triazole **84**. The workup of the reaction was accomplished as described before. The crude triazole (**84**) was purified by column chromatography on silica gel.

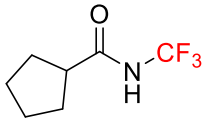
**7a-(Pyrrolidin-1-yl)-1-(trifluoromethyl)-3a,4,5,6,7,7a-hexahydro-1*H*-benzo[*d*][1,2,3]tria-zole (78)**



**Yield**: 125 mg (95%, $^{19}$F NMR yield), yellow liquid;

**$^{1}$H NMR** (400 MHz, $CDCl_3$) δ = 4.15 (t, $^{3}J_{H\text{-}H}$ = 7.3 Hz, 1H), 2.64–2.59 (m, 2H), 2.51–2.45 (m, 2H), 2.35–2.29 (m, 1H), 2.11–2.03 (m, 1H), 1.98–1.90 (m, 1H), 1.89–1.83 (m, 1H), 1.74–1.68 (m, 4H), 1.65–1.56 (m, 1H), 1.50–1.33 (m, 2H), 1.27–1.18 (m, 1H); **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 122.3 (q, $^{1}J_{C\text{-}F}$ = 261.5 Hz, $CF_3$), 83.4, 79.8 (d, $^{3}J_{C\text{-}F}$ = 10.6 Hz), 45.9–45.7 (m), 29.0 (q, $^{4}J_{C\text{-}F}$ = 1.6 Hz), 25.5, 24.3, 19.8, 19.4; **$^{19}$F NMR** (376 MHz, $CDCl_3$) δ = -57.2 (s, 3F); **HRMS** (ESI) *m/z* calcd for $C_{11}H_{18}N_4F_3$ $[M + H]^+$: 263.1478, found 263.1478.

***N*-(Trifluoromethyl)cyclopentanecarboxamide (79)**

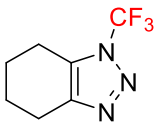


**Yield**: 24 mg (27%), white crystalline solid;

**$^{1}$H NMR** (400 MHz, $CDCl_3$) δ = 7.23 (br s, NH, 1H), 2.66 (p, $^{3}J_{H\text{-}H}$ = 7.9 Hz, 1H), 1.95–1.80 (m, 4H), 1.80–1.67 (m, 2H), 1.66–1.55 (m, 2H); **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 174.9, 118.8 (q, $^{1}J_{C\text{-}F}$ = 260.9 Hz, $CF_3$), 45.3, 30.0, 26.1; **$^{19}$F NMR** (376 MHz, $CDCl_3$)

δ = -57.5 (br s, 3F); **HRMS** (EI) *m/z* calcd for $C_7H_{10}NOF_3$ $[M]^+$: 181.0714, found 181.0717.

**1-(Trifluoromethyl)-4,5,6,7-tetrahydro-1*H*-benzo[*d*][1,2,3]triazole (84)**



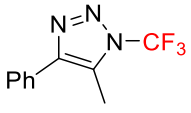
**Yield**: 31 mg (32%), yellow liquid;

**$^1$H NMR** (400 MHz, $CDCl_3$) δ = 2.81–2.77 (m, 4H), 1.93–1.82 (m, 4H); **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 144.8, 132.5, 118.4 (q, $^1J_{C\text{-}F}$ = 266.9 Hz, $CF_3$), 22.2, 22.1, 21.6, 20.5 (q, $^4J_{C\text{-}F}$ = 1.6 Hz); **$^{19}$F NMR** (376 MHz, $CDCl_3$) δ = -58.8 (s, 3F); **HRMS** (EI) *m/z* calcd for $C_7H_8N_3F_3$ $[M]^+$: 191.0670, found 191.0672.

### 8.4.4. Cycloaddition of $CF_3N_3$ with 1-phenylpropan-2-one

In a 10 mL screw-cap glass tube, with a cold solution of $CF_3N_3$ in THF (0.55-0.70 mmol, 2-3 mL), 1-phenylpropan-2-one (67 µL, 0.5 mmol) and pyrrolidine (8 µL, 0.1 mmol) were added and the mixture was stirred at rt for 18 h. THF was removed under reduced pressure, $Et_2O$ (2 × 15 mL) was added, the organic phase was washed with water (10 mL) and aqueous LiCl solution (1M, 10 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by column chromatography on silica gel.

**5-Methyl-4-phenyl-1-(trifluoromethyl)-1*H*-1,2,3-triazole (88)**



**Yield**: 18 mg (16%), yellow liquid;

**$^1$H NMR** (400 MHz, $CDCl_3$) δ = 7.68–7.65 (m, 2H), 7.53–7.47 (m, 2H), 7.46–7.41 (m, 1H), 2.62 (q, $^5J_{H\text{-}F}$ = 1.2 Hz, 3H); **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ = 146.4, 129.7, 129.5,

129.0, 128.9, 128.0, 118.4 (q, $^{1}J_{C\text{-}F}$ = 268.2 Hz, $CF_3$), 9.1 (q, $^{4}J_{C\text{-}F}$ = 2.4 Hz); **$^{19}$F NMR** (376 MHz, $CDCl_3$) δ = -58.4 (s, 3F); **HRMS** (EI) *m/z* calcd for $C_{10}H_8N_3F_3$ $[M]^+$: 227.0670, found 227.0672.

## 8.5. Protonation of azidotrifluoromethane

Azidotrifluoromethane was prepared using a modified reported procedure.

In a glovebox, CsF (1.82 g, 12 mmol) was weighed into a 50 mL round bottom flask. Dry DMF (22 mL) was added under nitrogen and the mixture was cooled to -60 °C while being stirred. A cold solution of $TMSCF_3$ (1.48 mL, 10 mmol) and $TsN_3$ (1.53 mL, 10 mmol) in dry DMF (3 mL) was added dropwise over 10 min, and then the reaction mixture was stirred at -60 °C to -30 °C for 4 h. The resulting mixture contained azidotrifluoromethane, fluoroform and fluorotrimethylsilane which were condensed into an NMR tube in a liquid $N_2$ bath. Cold $SO_2ClF$ (0.4 mL) was added at -78 °C and the NMR sample was measured on a Varian NMRS-400 spectrometer at -80 °C.

**Azidotrifluoromethane (56a)**

$CF_3N_3$

**$^{13}$C NMR** (100 MHz, acetone-$d_6$) δ = 121.9 (q, $^{1}J_{C\text{-}F}$ = 265.9 Hz); **$^{14}$N NMR** (36 MHz, $CH_3NO_2$) δ = -145.5 (s, N-3), -149.8 (s, N-2), -287.1 (br s, N-1);[174] **$^{19}$F NMR** (376 MHz, $SO_2ClF$) δ = -55.6 (s).

**Fluoroform**

$CF_3H$

**$^{1}$H NMR** (399 MHz, acetone-$d_6$) δ = 5.61 (q, $^{2}J_{H\text{-}F}$ = 77.8 Hz); **$^{13}$C NMR** (100 MHz, acetone-$d_6$) δ = 115.8 (q, $^{1}J_{C\text{-}F}$ = 275.8 Hz); **$^{19}$F NMR** (376 MHz, $SO_2ClF$) δ = -78.1 (d, $^{2}J_{H\text{-}F}$ = 79.3 Hz).

**Fluorotrimethylsilane**

TMSF

**$^{1}$H NMR** (399 MHz, acetone-$d_6$) δ = -0.42 (d, $^{2}J_{H-F}$ = 7.6 Hz); **$^{13}$C NMR** (100 MHz, acetone-$d_6$) δ = -1.2 (d, $^{2}J_{C-F}$ = 14.9 Hz); **$^{19}$F NMR** (376 MHz, $SO_2ClF$) δ = -156.7 (m).

To the cold $SO_2ClF$ solution of the $CF_3N_3$ (0.4 mL), freshly prepared magic acid ($FSO_3H/SbF_5$, 1:1, 0.1 mL) was added at -78 °C. The mixture was then shaken gently to obtain a homogenous solution which was analyzed by NMR at low temperatures. The NMR spectra were recorded at -80 °C.

**3-(Trifluoromethyl)triaz-1-yn-2-ium fluorosulfonylpentafluoroantimonate (89)**

$[CF_3NHN_2]^+ [FSO_3SbF_5]^-$

**$^{1}$H NMR** (399 MHz, acetone-$d_6$) δ = 10.37 (s); **$^{13}$C NMR** (100 MHz, acetone-$d_6$) δ = 116.3 (q, $^{1}J_{C-F}$ = 282.9 Hz); **$^{14}$N NMR** (36 MHz, $CH_3NO_2$) δ = -173.8 (br s, N-2), N-1 and N-3 were not observed; **$^{19}$F NMR** (376 MHz, $SO_2ClF$) δ = -54.8 (s). The anion is not characterized.

**Difluorodimethylsilane**

$Me_2SiF_2$

**$^{1}$H NMR** (399 MHz, acetone-$d_6$) δ = -0.46 (t, $^{3}J_{H-F}$ = 6.3 Hz, 6H); **$^{13}$C NMR** (100 MHz, acetone-$d_6$) δ = -5.2 (t, $^{2}J_{C-F}$ = 16.5 Hz); **$^{19}$F NMR** (376 MHz, $SO_2ClF$) δ = -129.6 (m).[180]

### 8.5.1. Protonation of $^{15}$N enriched azidotrifluoromethane

For the $^{15}$N NMR studies, $^{15}$N-labeled azidotrifluoromethane was prepared from 98%+ terminally enriched sodium azide.

First, tosyl azide was prepared according to literature procedure, with modified quantities and ratios.[181] A solution of $^{15}$N enriched sodium azide ($NaNN^{15}N$, 500 mg, 7.58 mmol, 1.03 equiv) in water (4 mL) was added dropwise over 15 min to a solution of tosyl chloride (1402 mg, 7.36 mmol, 1.0 equiv) in acetone (14.4 mL) at 0 °C. The reaction was allowed to warm up to room temperature and was stirred for 18 h. The acetone was removed under reduced pressure and the reaction mixture was extracted with diethyl ether

(2 × 7 mL). The combined organic layers were washed with water (2 × 7 mL), 5% $NaHCO_3$ (2 × 7 mL), water (2 × 7 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. $^{15}N$ enriched tosyl azide (a 1:1 mixture of $Tos^{15}NNN$ and $TosNN^{15}N$, 1.36 g) was obtained as a colorless oil in 93% yield.

In a glovebox, CsF (647 mg, 4.26 mmol) was weighed into a 25 mL round bottom flask. Dry DMF (7 mL) was added under nitrogen and the mixture was cooled to -60 °C while being stirred. A cold solution of $TMSCF_3$ (525 µL, 3.55 mmol) and $^{15}N$ enriched $TosN_3$ (544 µL, 3.55 mmol) in dry DMF (2 mL) was added dropwise over 10 min, and then the reaction mixture was stirred at -60 °C to -30 °C for 4 h. The resulting mixture contained $^{15}N$ enriched azidotrifluoromethane (a 1:1 mixture of $CF_3{}^{15}NNN$ and $CF_3NN^{15}N$), fluoroform and fluorotrimethylsilane which were condensed into an NMR tube in a liquid $N_2$ bath. Cold $SO_2ClF$ (0.4 mL) was added at -78 °C and the NMR sample was measured on a Varian NMRS-600 spectrometer at -50 °C.

To the cold $SO_2ClF$ solution of the $^{15}N$ enriched $CF_3N_3$ (0.4 mL), freshly prepared magic acid ($FSO_3H/SbF_5$, 1:1, 0.1 mL) was added at -78 °C. The mixture was then shaken gently to obtain a homogenous solution which was analyzed on a Varian NMRS-400 spectrometer at -75 °C.

$CF_3NN^{15}N$

**$^{13}$C NMR** (151 MHz, acetone-$d_6$) δ = 121.9 (q, $^1J_{C\text{-}F}$ = 265.8 Hz); **$^{15}$N NMR** (61 MHz, $CH_3NO_2$) δ = -145.4 (s, N-3); **$^{19}$F NMR** (564 MHz, $SO_2ClF$) δ = -56.1 (s).

$CF_3{}^{15}NNN$

**$^{13}$C NMR** (151 MHz, acetone-$d_6$) δ = 121.9 (qd, $^1J_{C\text{-}F}$ = 265.8 Hz, $^1J_{C\text{-}N}$ = 5.4 Hz); **$^{15}$N NMR** (61 MHz, $CH_3NO_2$) δ = -287.1 (q, $^2J_{N\text{-}F}$ = 22.3 Hz, N-1); **$^{19}$F NMR** (564 MHz, $SO_2ClF$) δ = -56.1 (d, $^2J_{N\text{-}F}$ = 21.3 Hz).

$[CF_3NHN^{15}N]^+ [FSO_3SbF_5]^-$

**$^1$H NMR** (399 MHz, acetone-$d_6$) δ = 10.37 (s); **$^{13}$C NMR** (100 MHz, acetone-$d_6$) δ = 116.4 (q, $^1J_{C\text{-}F}$ = 283.5 Hz); **$^{15}$N NMR** (40 MHz, $CH_3NO_2$) δ = -93.2 (s, N-3); **$^{19}$F NMR** (376 MHz, $SO_2ClF$) δ = -54.8 (s). The anion is not characterized.

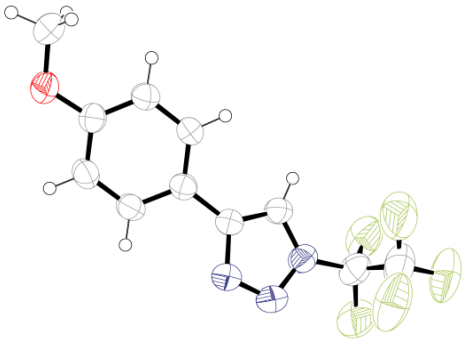
$[CF_3{}^{15}NHNN]^+ [FSO_3SbF_5]^-$

**$^1$H NMR** (399 MHz, acetone-$d_6$) δ = 10.37 (d, $^1J_{H\text{-}N}$ = 106.9 Hz); **$^{13}$C NMR** (100 MHz, acetone-$d_6$) δ = 116.4 (qd, $^1J_{C\text{-}F}$ = 283.5 Hz, $^1J_{C\text{-}N}$ = 22.7 Hz); **$^{15}$N NMR** (40 MHz, $CH_3NO_2$) δ = -272.2 (dq, $^1J_{H\text{-}N}$ = 106.2 Hz, $^2J_{N\text{-}F}$ = 25.4 Hz, N-1); **$^{19}$F NMR** (376 MHz, $SO_2ClF$) δ = -54.8 (d, $^2J_{N\text{-}F}$ = 25.6 Hz). The anion is not characterized.

## 8.6. Crystallographic data

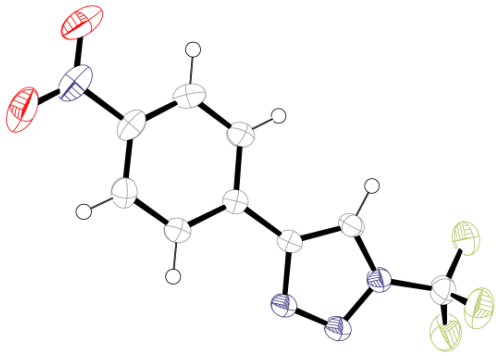
Crystallographic data for **68bc** and **71i** were measured on an Xcalibur X-ray diffractometer by monochromatized Cu(*Kα*) radiation (λ = 1.54180 Å) at 180 K. CrysAlisProCCD[182] was used for data collection, cell refinement and data reduction. Data for **68ae** were collected on a Bruker D8 VENTURE system employing Mo(*Kα*) radiation (λ = 0.71073 Å) at 180 K. Data collection and unit cell refinement were done with APEX3, data reduction with SAINT.[183] Structures were solved by direct methods with SIR92[184] and refined by full-matrix least-squares on F with CRYSTALS.[185] Non-hydrogen atoms were refined with anisotropic displacement parameters. Hydrogen atoms were found from a Fourier difference map and then recalculated into idealized positions and refined with riding constraints.

**4-(4-Methoxyphenyl)-1-(pentafluoroethyl)-1*H*-1,2,3-triazole (68bc)**



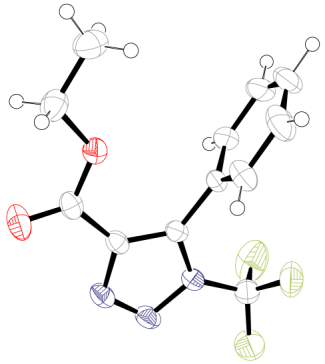
| | |
|---|---|
| Empirical formula | $C_{11}H_8F_5N_3O_1$ |
| Formula weight | 293.19 |
| Temperature (K) | 180 |
| Wavelength (Å) | 1.54180 |
| Crystal system | monoclinic |
| Space group | $P2_1/c$ |
| Unit cell dimensions: | |
| a (Å) | 22.4603(5) |
| b (Å) | 5.58481(15) |
| c (Å) | 9.6508(2) |
| β (°) | 91.619(2) |
| V (Å$^3$) | 1210.08(5) |
| Z | 4 |
| Crystal size (mm) | 0.14 × 0.31 × 0.59 |
| Reflections measured | 6752 |
| Independent reflections | 2410 |
| Data / parameters | 2068 / 181 |
| Goodness-on-fit | 1.085 |
| Final R indices [I > 2σ(I)] | R = 0.062, wR = 0.068 |
| CCDC | 1503411 |

**4-(4-Nitrophenyl)-1-(trifluoromethyl)-1*H*-1,2,3-triazole (68ae)**



| | |
|---|---|
| Empirical formula | $C_9H_5F_3N_4O_2$ |
| Formula weight | 258.16 |
| Temperature (K) | 180 |
| Wavelength (Å) | 0.71073 |
| Crystal system | monoclinic |
| Space group | $P2_1/c$ |
| Unit cell dimensions: | |
| a (Å) | 4.7355(2) |
| b (Å) | 14.7137(7) |
| c (Å) | 14.7503(7) |
| β (°) | 95.4092(15) |
| V (Å$^3$) | 1023.18(8) |
| Z | 4 |
| Crystal size (mm) | 0.14 × 0.20 × 0.59 |
| Reflections measured | 31383 |
| Independent reflections | 1939 |
| Data / parameters | 1658 / 164 |
| Goodness-on-fit | 1.044 |
| Final R indices [I > 2σ(I)] | R = 0.034, wR = 0.043 |
| CCDC | 1503412 |

**Ethyl 5-phenyl-1-(trifluoromethyl)-1*H*-1,2,3-triazole-4-carboxylate (71i)**



| | |
|---|---|
| Empirical formula | $C_{12}H_{10}F_3N_3O_2$ |
| Formula weight | 285.22 |
| Temperature (K) | 180 |
| Wavelength (Å) | 1.54180 |
| Crystal system | monoclinic |
| Space group | $P2_1/c$ |
| Unit cell dimensions: | |
| a (Å) | 8.9126(10) |
| b (Å) | 11.5321(13) |
| c (Å) | 12.9579(15) |
| β (°) | 91.619(2) |
| V (Å$^3$) | 107.205(4) |
| Z | 4 |
| Crystal size (mm) | 0.10 x 0.20 x 0.55 |
| Reflections measured | 30424 |
| Independent reflections | 2327 |
| Data / parameters | 2256 / 182 |
| Goodness-on-fit | 1.112 |
| Final R indices [I > 2σ(I)] | R = 0.037, wR = 0.040 |
| CCDC | 1821637 |

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