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ve vědním oboru “Chemické vědy”

The development of synthetic methodology for the preparation and reactivity of fluorinated organic azides

Komise pro obhajoby doktorských disertací v oboru “Organická a bioorganická chemie”

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Ústav organické chemie a biochemie AV ČR

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Contents

Summary

Organic azides are widely used compounds in synthesis and also in biochemistry. α-Fluorinated azidoalkanes are a subgroup which has been regarded as a chemical curiosity and their chemistry has not been developed. In this work, we showed the synthetic access to a variety of fluorinated organic azides from CF_3N_3 to more elaborated ones and studied the factors influencing their stability, which opened up new possibilities for their application in organic synthesis. A photocatalytic nitrene formation gave access to nitrene reactive intermediates, useful in the synthesis of N-trifluoromethyl aziridines. [3+2] cycloaddition reactions of fluorinated azides afforded N-fluoroalkylated 1,2,3-triazoles. A study of denitrogenative processes of those triazoles allowed the preparation of a variety of structurally diverse nitrogen heterocycles and N-alkenyl compounds. A majority of those products showed a synthetic potential in follow-up derivatization reactions or resemble molecules used in the drug design. Yet unreported are reactions of fluorinated azides with nucleophiles, new reactivity of nitrenes, or metal-free cycloaddition for chemical biology applications. All of these research directions are being investigated in our laboratory.

1. Introduction

Nitrogen-containing organics, such as amides, amines, azides, and nitrogen heterocycles, are versatile building blocks in organic synthesis, essential components of biomolecules, such as proteins and nucleic acids, are prevalent in drug design and in agrochemicals. Their combination with fluorinated group has not been widely studied. This area of research has gained a momentum only recently leveraging the unique physicochemical properties of fluorinated molecular structures. Fluorinated groups are prevalent in medicinal chemistry and drug development due to their ability to modulate pharmacokinetic and pharmacodynamic properties, improve bioavailability, metabolic stability and binding affinity to biological targets, leading to more effective and safer pharmaceuticals.[1,2,3,4] In material science, fluorinated compounds find applications in the design and fabrication of advanced materials with tailored properties, ranging from high-tech polymers to organic semiconductors, sensors, imaging materials, contrast agents, and surfactants.[5]

The trifluoromethyl group is one of the most important moieties in fluorinated pharmaceuticals and agrochemicals.[6,7] A vast majority of active ingredients contain the trifluoromethyl group bound to carbon atom and few examples contain the trifluoromethyl group bound to oxygen or sulfur atoms. No approved drug or agrochemical contains the N-CF_3 functionality (amines, azoles) which is the result of their challenging synthesis.[8] The study of new classes of N-fluoroalkylated compounds is expected to open new possibilities in the development of advanced technologies and products.

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1 J. Wang, M. Sánchez-Roselló, J. L. Aceña, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok, H. Liu, *Chem. Rev.* **2014**, *114*, 2432.

2 Y. Zhou, J. Wang, Z. Gu, S. Wang, W. Zhu, J. L. Aceña, V. A. Soloshonok, K. Izawa, H. Liu, *Chem. Rev.* **2016**, *116*, 422.

3 A. A. Berger, J.-S. Völler, N. Budisa, B. Koksch, *Acc. Chem. Res.* **2017**, *50*, 2093.

4 M. Inoue, Y. Sumii, N. Shibata, *ACS Omega* **2020**, *5*, 10633.

5 R. Berger, G. Resnati, P. Metrangolo, E. Weber, J. Hulliger, *Chem. Soc. Rev.* **2011**, *40*, 3496.

6 P. V. Reddy, *Organofluorine Compounds in Biology and Medicine*; Elsevier: Amsterdam, The Netherlands, **2015**.

7 *Fluorine in Medicinal Chemistry and Chemical Biology*; Ojima, I., Ed.; Wiley-Blackwell: Chichester, U.K., **2009**.

8 S. Schiesser, H. Chepliaka, J. Kollback, T. Quennesson, W. Czechtizky, R. J. Cox, *J. Med. Chem.* **2020**, *63*, 13076.

To this end we set out to investigate fluorinated organic azides as precursors of a variety of N-fluoroalkylated compounds and other unprecedented structures. Organic azides play a crucial role in chemistry and biochemistry due to their unique reactivity and versatility.[9] These reactive but remarkably inert molecules under physiological conditions are widely employed as powerful and selective reagents in organic synthesis, particularly in the synthesis of pharmaceuticals and agrochemicals, and other complex organic molecules utilizing their ability to undergo diverse transformations, such as cycloadditions, nucleophilic substitutions, or nitrene formation.[10,11,12]

In biochemistry, organic azides are valuable tools in chemical biology and bioorthogonal chemistry. Bioorthogonal chemistry involves the selective labelling of biomolecules in living systems without interfering with native biological processes. Azide-based probes can be introduced into biological systems and selectively reacted with suitable partner molecules, facilitating the study and visualization of specific biomolecular interactions and processes. This bioorthogonal chemistry approach has become instrumental in understanding cellular events, drug development, and diagnostics.[13]

Before 2017 when we entered the field, fluorinated organic azides were regarded as chemical curiosities and their chemistry was virtually undeveloped.[14] Synthetic approaches to these compounds turned out to be challenging and nontrivial; however, the study of these derivatives proved rather fruitful.

2. Aims

The research work presented in this thesis is focused on the development of a new class of organic azides – fluorinated azidoalkanes and the study of their physicochemical properties, especially stability and reactivity. Organic aliphatic and aromatic azides are most commonly prepared by nucleophilic substitution

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9 S. Bräse, C. Gil, K. Knepper, V. Zimmermann, *Angew. Chem., Int. Ed.* **2005**, *44*, 5188.
10 K. Banert, S. Bräse, *Organic Azides: Syntheses and Applications*, John Wiley & Sons, **2009**.
11 B. Stanovnik, *Adv. Heterocycl. Chem.* **2020**, *130*, 145.
12 H.C. Kolb, K.B. Sharpless, *Drug Discov. Today* **2003,** *8*, 1128.
13 E. Kim, H. Koo, *Chem. Sci.* **2019**, *10*, 7835.
14 Review on fluorinated organic azides. O. Bakhanovich, P. Beier, *Chem. Eur. J.* **2020**, *26*, 773.

using azide salts. This approach is generally not available in the synthesis of α-fluorinated azidoalkanes and new synthetic approaches had to be devised. Of concern was also known limited stability and sometimes explosive character or organic azides, especially low molecular weight ones. This constraint limits their practical applicability and scale-up efforts. However, the situation is completely different for fluorinated azidoalkanes which proved to be markedly more stable and safer to use.

Another aim is the investigation of copper(I)-catalyzed azide-alkyne cycloaddition (CuAAC) to form N-fluoroalkylated 1,2,3-triazoles. A good part of our research focus was directed to the investigation of denitrogenation strategies of these triazoles for the formation of new N-alkenyl compounds or nitrogen heterocycles. Triazole denitrogenation strategies were extended to NH-triazoles via a new synthetic strategy involving acylation of triazoles. Azide protonation in superacid media and the formation of nitrenes from azides and follow-up chemistry were also investigated.

3. Methods

All methodologies are described in detail in the individual publications attached to this Thesis. All synthetic experiments were carried out in my group at IOCB. We made use of in-house MS and NMR service facilities. Investigation of protonation of fluorinated azides in superacids was performed in collaboration with Prof. S. Prakash and Prof. R. Haiges at the University of Southern California. Sensitivity to impact and sensitivity to heat experiments were conducted by Doc. R. Matyáš form the University of Pardubice. Prof. Petr Slavíček from UCT Prague performed *ab initio* calculations. Dr. Blanka Klepetářová (IOCB Prague) measured and solved crystal structures. Dr. Martin Dračínský performed advanced NMR experiments and quantum chemical calculations. Dr. Ján Tarábek performed EPR experiments. Dr. Lucie Bednárová measured kinetics by infrared spectroscopy. Dr. Tomáš Slanina, Dr. Lucie Ludvíková and Dr. Soňa Boháčová performed cyclic voltammetry and photochemistry experiments (time-correlated single photon counting spectroscopy, UV-vis absorption spectroscopy and transient absorption spectroscopy).

4. Results and discussion

The presented results were obtained since 2016 under my leadership and represent the work of myself, my group members and our collaborators. References in bold blue refer to our original publications in impacted international journals and in all of these references the candidate is listed as the corresponding author.

4.1 Synthesis of α-fluorinated azidoalkanes

Azidotrifluoromethane (CF_3N_3) was the only fluorinated azidomethane known before we started the project. It was prepared in two steps from toxic gaseous trifluoronitrosomethane using reagents and setup not suitable for laboratory synthesis.[15] Our approach focused on application of the Ruppert-Prakash reagent (CF_3TMS) as a nucleophilic trifluoromethylating reagent which was upon activation by cesium fluoride able to transfer the trifluoromethyl group to an electrophilic azide source, such as tosyl or nonaflyl azides (Scheme 1A).[16] Later we extended the methodology to higher analogues of CF_3TMS (Scheme 1B), used metastable organolithium (Scheme 1C), organopotassium (Scheme 1D),[17] or organomagnesium (Scheme 1E)[18] substrates in reactions with electrophilic azide sources for the preparation of various azido(per)fluoroalkanes. Access to azidodifluoromethane was achieved *via* the reaction of azide anion with electrophilic difluorocarbene generated by a known method from chlorodifluoromethane under aqueous basic conditions (Scheme 1F).[19] Azidofluoromethane was prepared by simple S_N2 chemistry starting from bromofluoromethane (Scheme 1G).[20] The propensity of fluorinated alkenes to undergo addition of nucleophiles including the azide anion was known[21,22,23] and

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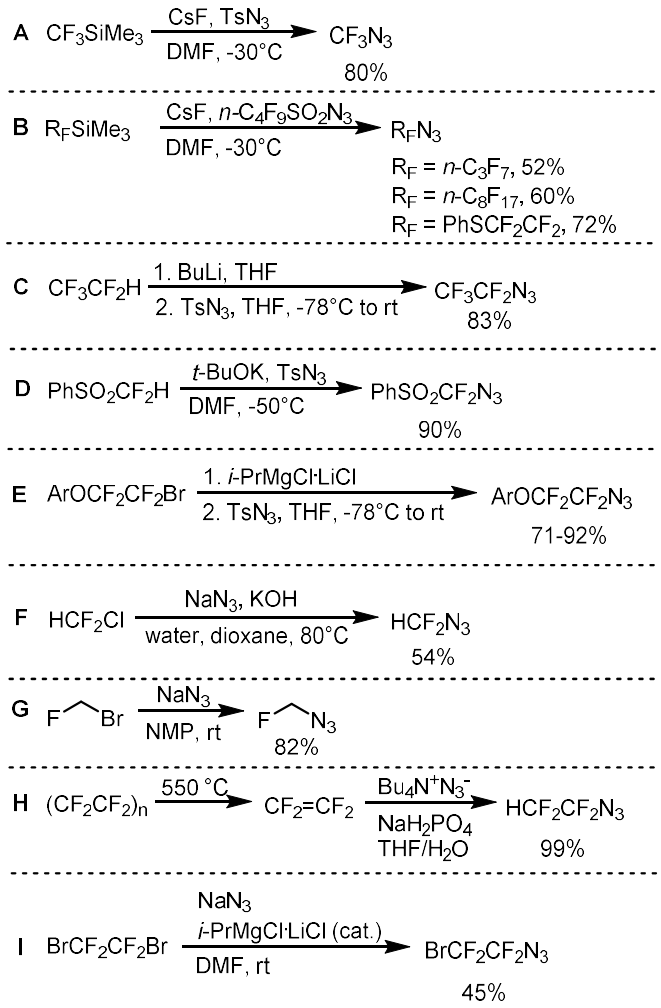
15 K. O. Christe, C. Schack, *J. Inorg. Chem.* **1981**, *20*, 2566.
16 Z. E. Blastik, S. Voltrová, V. Matoušek, B. Jurásek, D. W. Manley, B. Klepetářová, P. Beier, *Angew. Chem., Int. Ed.* **2017**, *56*, 346.
17 M. Ziabko, B. Klepetářová, P. Beier, *J. Org. Chem.* **2023**, *88*, 6939.
18 S. Voltrová, M. Museli, J. Filgas, V. Matoušek, B. Klepetářová, P. Beier, *Org. Biomol. Chem.* **2017**, *15*, 4962.
19 S. Voltrová, I. Putovný, V. Matoušek, B. Klepetářová, P. Beier, *Eur. J. Org. Chem.* **2018**, 5087.
20 S. Voltrová, J. Filgas, P. Slavíček, P. Beier, *Org. Chem. Front.* **2020**, *7*, 10.
21 C. G. Krespan, F. A. Van-Catledge, B. E. Smart, *J. Am. Chem. Soc.* **1984**, *106*, 5544.
22 J. Dai, Z. Li, T. Wang, R. Bai, *Org. Biomol. Chem.* **2016**, *14*, 4382.
23 R. E. Banks, D. Berry, M. J. McGlinchey, G. J. Moore, *J. Chem. Soc. (C)* **1970**, 1017.

we used this approach for the synthesis of azidotetrafluoroethane where tetrafluoroethylene was generated by the thermal depolymerization of PTFE, followed by addition of azide source in a buffered aqueous/organic solvent mixture (Scheme 1H).[24] A related approach is the synthesis of bromotetrafluoroethyl azide from 1,2-dibromotetrafluoroethane which is initiated by a bromophilic attack of a catalytic amount of TurboGrignard reagent, followed by in-situ formation of tetrafluoroethylene, which reacted with sodium azide, and finally closing the chain process by a bromophilic attack of the generated fluorinated carbanion to the starting halon (Scheme 1I).[25]

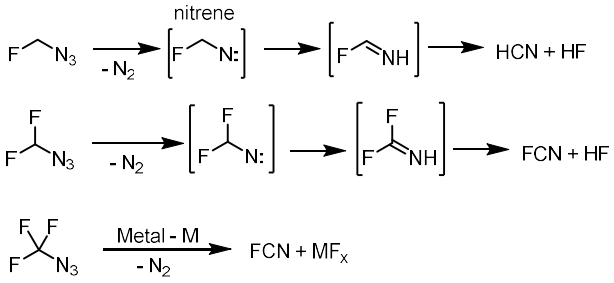


Scheme 1: Synthesis of azidofluoroalkanes in our group.

[24] E. Shaitanova, V. Matoušek, T. Herentin, M. Adamec, R. Matyáš, B. Klepetářová, P. Beier, *J. Org. Chem.* **2023**, *88*, 14969.
[25] D. Tichý, V. Košťál, V. Motornov, I. Klimánková, P. Beier, *J. Org. Chem.* **2020**, *85*, 11482.

4.2 Properties and stability of α-fluorinated azidoalkanes

One and two-carbon fluorinated azides are typically very volatile compounds (bp of CF_3N_3 and $HCF_2CF_2N_3$ are –28 °C and 30 °C, respectively) so we usually handle them in solution and purify them by distillation. Their thermal stability has been evaluated by heating their $CDCl_3$ solutions in a sealed NMR tube and observing the possible decomposition by ^1H and ^{19}F NMR spectroscopy or by the determination of sensitivity to impact (fall-hammer test) or sensitivity to intense heat (Koenen test). CF_3N_3, HCF_2N_3, $HCF_2CF_2N_3$, and $BrCF_2CF_2N_3$ are stable to at least 150 °C, while FCH_2N_3 decomposed in chloroform solution at ambient temperature. Based on experimental observation and quantum chemical calculations, the decomposition was found to take place by dinitrogen elimination to form a nitrene, 1,2-hydrogen shift from carbon to nitrogen, and ultimately fragmentation to form hydrogen cyanide (or FCN) and hydrogen fluoride (Scheme 2).[20] In the case of azidotrifluoromethane the thermal nitrogen elimination is difficult and the hydrogen shift cannot happen, which resulted in exceptional thermal stability of the azide. We patented[26] the preparation of key fluorinated azidoalkanes and commercialized some of them through a collaboration with our industrial partner. The synthesis and reactivity of α-fluorinated azidoalkanes have been reviewed recently.[14,27,28]

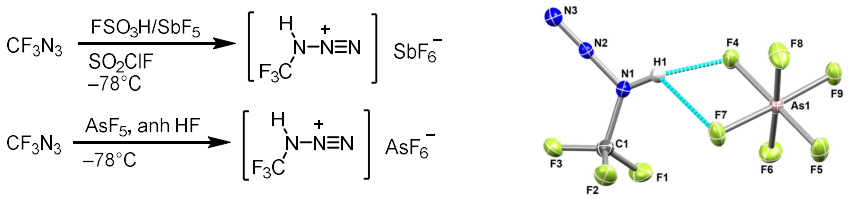


Scheme 2: Decomposition of azidofluoromethanes.

[26] P. Beier, V. Matoušek, Z. E. Blastik, S. Voltrová, US Patent US 10 590 091 B2, **2020**.
[27] P. Beier, *Synform* **2019**, *8*, A115.
[28] A. Markos, V. Matoušek, P. Beier, *Aldrichimica Acta* **2022**, *55*, 37.

4.3 Protonation of azidotrifluoromethane by superacids

In collaboration with Prof. S. Prakash and Prof. R. Haiges from the University of Southern California we investigated the protonation of CF_3N_3 in superacidic media. Magic acid (SbF_5 and FSO_3H) protonated CF_3N_3 to form trifluoromethylaminodiazonium hexafluoroantimonate which was fully characterized by NMR. The reaction of the azide with AsF_6 in anhydrous hydrogen fluoride afforded the corresponding hexafluoroarsenate salt whose crystal structure was determined, proving that the α-nitrogen was selectively protonated (Scheme 3).[29] A variable temperature ^{19}F NMR revealed that this salt possessed good thermal stability up to –32 °C. A ^{15}N labelling study and electronic structure calculations provided additional details. Attempted electrophilic amination of aromatics (benzene, toluene) with the diazonium salts were unsuccessful.



Scheme 3: Protonation of azidotrifluoromethane using superacids. Crystal structure of the hexafluoroarsenate salt.

4.4 Generation and reactivity of trifluoromethyl nitrene

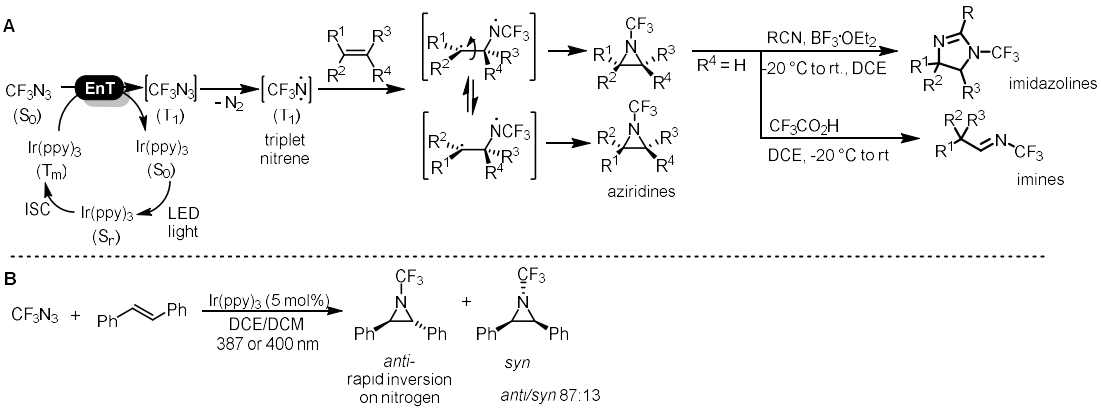
Nitrenes are highly reactive monovalent nitrogen species with electrophilic properties. Typically, they are generated by the thermolysis or photolysis of azides, reduction of nitro groups by phosphites, α-elimination, or by oxidation of amines by hypervalent iodine compounds. Nitrenes undergo C–C or C–H bond insertion, cycloaddition, or other reactions.[30,31] Trifluoromethyl or other fluoroalkyl nitrenes have not been generated before and the accomplishment of this process would

[29] T. Saal, Z. Blastik, R. Haiges, A. Nirmalchandar, A. F. Baxter, K. O. Christe, M. Vasiliu, D. A. Dixon, P. Beier, G. K. S. Prakash, *Angew. Chem., Int. Ed.* **2020**, *59*, 12520.
[30] C. Wentrup, *Angew. Chem., Int. Ed.* **2018**, *57*, 11508.
[31] C. Empel, R. M. Koenig, *Chem. Catal.* **2022**, *2*, 2506.

open up new opportunities for using N-trifluoromethyl compounds in synthetic chemistry and in life science.

After a considerable amount of proof of concept experiments and optimization study we identified a transition metal photocatalyzed process for the generation of trifluoromethylnitrene from the corresponding azide. The unstable nitrene efficiently added to mono-, di-, tri- and tetra-substituted alkenes to afford previously unknown aziridines substituted with the trifluoromethyl group on nitrogen (Scheme 4A). The obtained aziridines were converted into either N-CF_3 imidazolines, *via* a formal [3+2] cycloaddition with nitriles, mediated by a Lewis acid, or into N-CF_3 aldimines, *via* ring opening and aryl group migration, mediated by trifluoroacetic acid (Scheme 4A). A series of spectroscopic (EPR, NMR, time-correlated single photon counting, transient absorption spectroscopy), cyclic voltammetry, and quantum chemical calculations done in collaboration with our partners (for details, see Section 3 Methods) identified the details of the reaction mechanism and explained the product stereoselectivity. In short, the iridium photocatalyst was excited by a blue light, transferred energy of its triplet state to CF_3N_3 which eliminated dinitrogen and generated triplet nitrene. This reactive intermediate added to alkenes *via* biradical intermediates, and after intersystem crossing and C–C bond formation afforded N-trifluoromethylaziridines. 1,2-Disubstituted alkene products provided a mixture of the major *anti*-isomer of the aziridine with a rapid inversion on nitrogen and the minor *syn*-isomer in its less strained form (Scheme 4B).[32]

[32] N. Baris, M. Dračínský, J. Tarábek, J. Filgas, P. Slavíček, L. Ludvíková, S. Boháčová, T. Slanina, B. Klepetářová, P. Beier, *Angew. Chem., Int. Ed.* **2024**, *63*, e202315162.



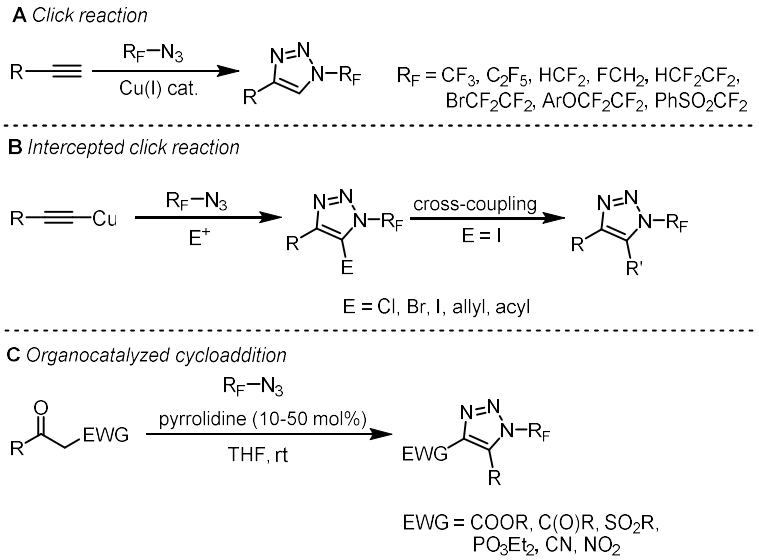
Scheme 4: Generation and reactivity of trifluoromethyl nitrene with alkenes.

4.5 [3+2] Cycloaddition of azidofluoroalkanes with alkynes and activated ketones

1,2,3-Triazole scaffold occurs in a number of bioactive compounds,[33] it is used in drug design as a bioisostere of an amide bond,[34] and in biochemistry as a ligation unit.[35,36,37] We utilized CuAAC for the synthesis of functionalized N-fluoroalkyl-4-substituted triazoles using terminal alkynes (Scheme 5A).[16-20,24,25] The reaction is regioselective, high yielding and of wide scope. A range of Cu(I) catalysts can be used but we prefer to use THF soluble copper(I) 3-methylsalicylate (CuMeSal). Using stoichiometric copper acetylides and various electrophiles we were able to perform so called intercepted click reaction and introduce various substitutions into position 5 of the triazole ring (Scheme 5B).[16,19,38] In the case of 5-iodotriazoles which are not too electron-poor, cross-coupling reactions represent a good strategy to modify the position with various carbon substituents.[18-20] Furthermore, fluorinated azidoalkanes undergo metal-fee, enamine-mediated [3+2]

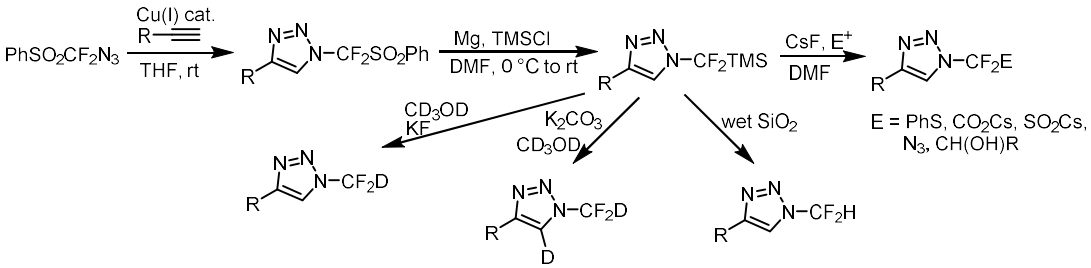
[33] L. Da S. M. Forezi, C. G. S. Lima, A. A. P. Amaral, P. G. Ferreira, M. C. B. V. de Souza, A. C. Cunha, F. de C. da Silva, V. F. Ferreira, *Chem. Rec.* **2021**, *21*, 2782.
[34] E. Bonandi, M. S. Christodoulou, G. Fumagalli, D. Perdicchia, G. Rastelli, D. Passarella, *Drug Discov. Today* **2017**, *22*, 1572
[35] J. M. Baskin, J. A. Prescher, S. T. Laughlin, N. J. Agard, P. V. Chang, I. A. Miller, A. Lo, J. A. Codelli, C. R. Bertozzi, *Proc. Natl. Acad. Sci. U. S. A.* **2007**, *104*, 1679.
[36] S. T. Laughlin, J. M. Baskin, S. L. Amacher, C. R. Bertozzi, *Science* **2008**, *320*, 664.
[37] J. Dommerholt, F. P. J. T. Rutjes, F. L. van Delft, *Top. Curr. Chem.* **2016**, *374*, 16.
[38] L. Janecký, A. Markos, B. Klepetářová, P. Beier, *J. Org. Chem.* **2023**, *88*, 1155.

cycloaddition with activated ketones to form 4,5-disubstituted triazoles (Scheme 5C).[19,39]



Scheme 5: Synthesis of N-fluoroalkylated 1,2,3-triazoles by [3+2] cyclization.

N-Difluro(phenylsulfonyl)methyl-1,2,3-triazoles underwent reductive desulfonylation/silylation to provide N-CF_2TMS triazoles. Subsequent treatment with acid or a Lewis base (CsF) and various electrophiles gave products of substitution of the trimethylsilyl group (Scheme 6). In these reactions, the starting azidodifluoromethyl phenyl sulfone represented he synthetic equivalent of the azidodifluoromethyl anion.[17]



Scheme 6: Desulfonylation/silylation/substitution sequence.

[39] Z. E. Blastik, B. Klepetářová, P. Beier, *ChemSelect* **2018**, *3*, 7045.

4.6 Denitrogenative reactions of N-fluoroalkyl-1,2,3-triazoles

Thanks to the presence of stabilized aromatic ring, 1,2,3-triazoles are generally thermally and chemically stable compounds. However, certain ring-opening processes of 1,2,3-triazoles occur. A well-known Dimroth rearrangement is known in *N*-phenyl-5-amino-1,2,3-triazoles[40] and N-sulfonyl triazoles are amenable to ring opening in the presence of Rh(II) catalyst to form carbenoid species, key intermediates in transannulation reactions and insertions into C–H and X–H bonds.[41,42,43,44]

4.6.1 Thermal denitrogenation of N-fluoroalkyl-1,2,3-triazoles to ketenimines

The Wolff rearrangement is the reaction of α-diazo carbonyl compounds to ketenes. We developed a related 1,2-group shift in the aza variant which does not use the diazo substrates but N-fluoroalkyl triazoles. A microwave-assisted ring opening, dinitrogen elimination and concomitant group rearrangement formed stable N-fluoroalkylketenimines. The reaction mechanism was studied by *ab initio* calculations and the reaction is characterized by a wide scope and high efficiency. The ketenimines are unlike other known ketenimines stable and isolable compounds and underwent [2+2] cycloaddition reactions with alkynes or alkenes to novel cyclobutenimines or cyclobutanimines, respectively. The addition of nucleophiles to ketenimines gave new N-fluoroalkyl amidines and (thio)imidates (Scheme 7).[45]

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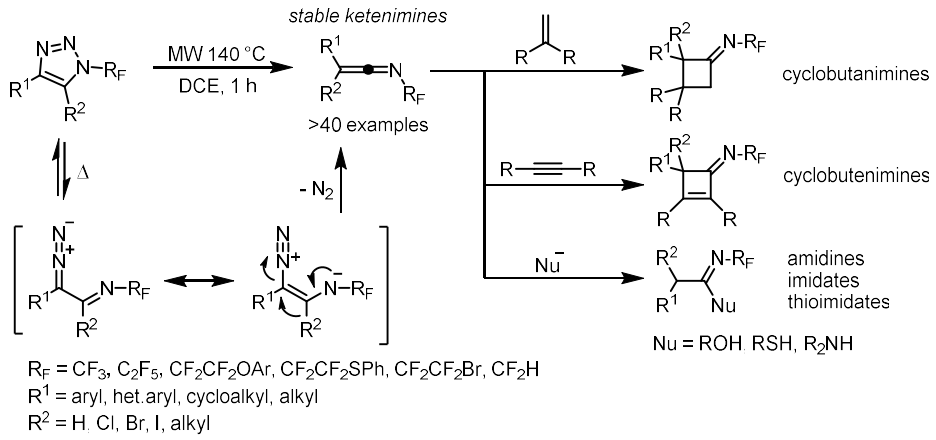
40 E. Lieber, T. S. Chao, C. N. Ramachandra Rao, *Org. Synth.* **1957**, *37*, 26.
41 B. Chattopadhyay, V. Gevorgyan, *Angew. Chem., Int. Ed.* **2012**, *51*, 862.
42 H. M. L. Davies, J. S. Alford, *Chem. Soc. Rev.* **2014**, *43*, 5151.
43 P. Anbarasan, D. Yadagiri, S. Rajasekar, *Synthesis* **2014**, *46*, 3004.
44 H. M. L. Davies, A. M. Walji, *Rhodium(II)-Stabilized Carbenoids Containing Both Donor and Acceptor Substituents. In Modern Rhodium-Catalyzed Organic Reactions*; P. A. Evans, Ed.; Wiley-VCH: Weinheim, Germany, **2005**; pp 301–340.
45 A. Kubíčková, A. Markos, S. Voltrová, A. Marková, J. Filgas, B. Klepetářová, P. Slavíček, P. Beier, *Org. Chem. Front.* **2023**, *10*, 3201.

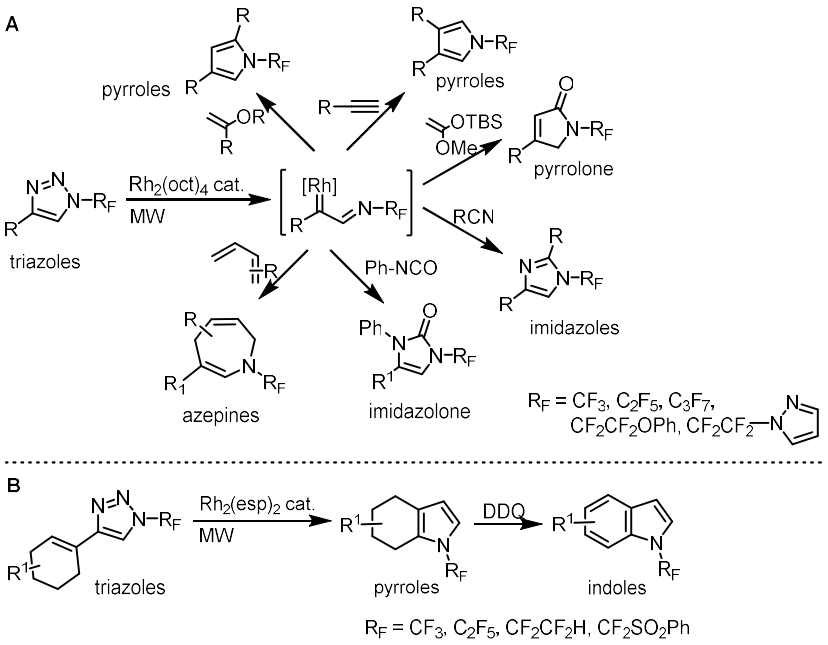


Scheme 7: Synthesis and reactivity of N-fluoroalkylketenimines from triazoles.

4.6.2 Rhodium(II)-catalyzed denitrogenation of N-fluoroalkyl-1,2,3-triazoles

Microwave-assisted heating of N-fluoroalkyl-1,2,3-triazoles in the presence of Rh(II) catalyst led to triazole denitrogenation and the formation of rhodium carbene intermediates. We conducted a variety of transannulation reactions using these reactive intermediates and for the first time prepared (per)fluoroalkyl nitrogen heterocycles, such as pyrroles, pyrrolones, imidazoles, imidazolones, azepines (Scheme 8A),[46,47,48] ring-fused pyrroles and indoles (Scheme 8B).[49] N-Trifluoromethylated 5-membered nitrogen heterocycles such as imidazoles and pyrazoles were recently found to possess favorable medicinal chemistry properties which make them attractive in the drug design.[8]

[46] V. Motornov, A. Markos, P. Beier, *Chem. Commun.* **2018**, *54*, 3258.
[47] V. Motornov, P. Beier, *J. Org. Chem.* **2018**, *83*, 15195.
[48] O. Bakhanovich, V. Khutorianskyi, V. Motornov, P. Beier, *Beilstein J. Org. Chem.* **2021**, *17*, 504.
[49] O. Bakhanovich, B. Klepetářová, P. Beier, *Org. Biomol. Chem.* **2023**, *21*, 7924.



Scheme 8: Transannulations of N-fluoroalkyl-1,2,3-triazoles catalyzed by Rh(II).

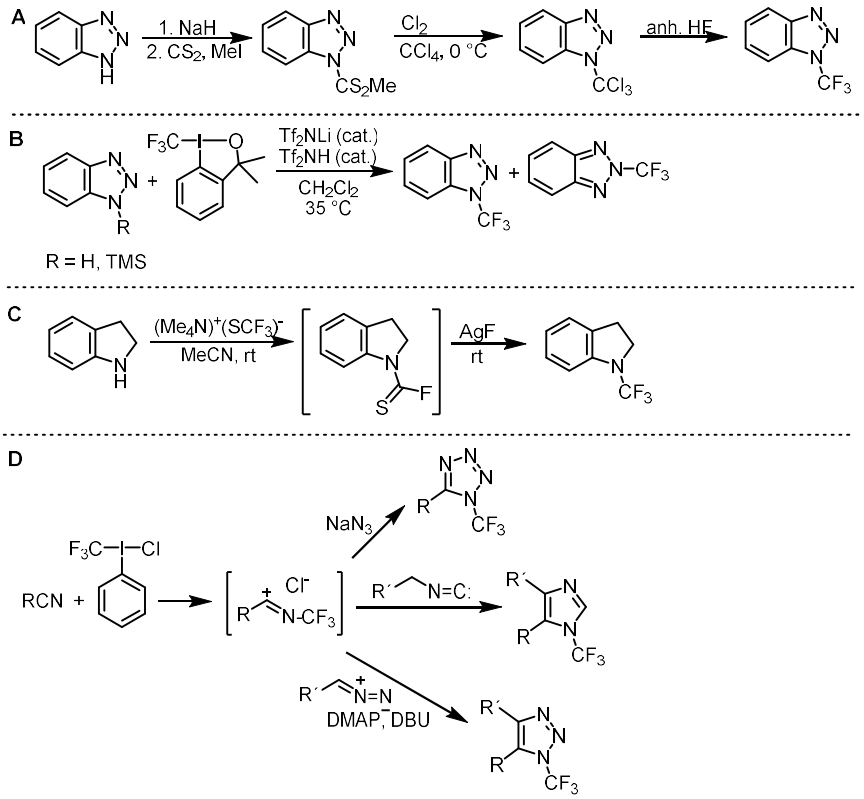
Current methods for the synthesis of N-trifluoromethyl nitrogen heterocycles are based on the halogen exchange of N-trichloromethyl-containing heterocycles (Scheme 9A),[50] non-regioselective electrophilic trifluoromethylation using hypervalent iodine compounds (Togni reagents) (Scheme 9B),[51] reaction of nitrogen nucleophiles with synthetic equivalents of fluorothiophosgene, followed by fluorodesulfurization mediated by silver fluoride (Scheme 9C),[52] or cyclization of N-trifluoromethylnitrilium ions prepared from nitriles (Scheme 9D).[53] Our method allows the preparation of not only N-trifluoromethylated but also N-fluoroalkylated heterocycles of various structures with good yields and regioselectivities.

50 L. Yagupolskii, D. V. Fedyuk, K. I. Petko, V. I. Troitskaya, V. I. Rudyk, V. V. Rudynyk, *J. Fluorine Chem.* **2000**, *106*, 181.

51 K. Niedermann, N. Früh, R. Senn, B. Czarniecki, R. Verel, A. Togni, *Angew. Chem. Int. Ed.* **2012**, *51*, 6511.

52 T. Scattolin, K. Deckers, F. Schoenebeck, *Angew. Chem. Int. Ed.* **2017**, *56*, 221.

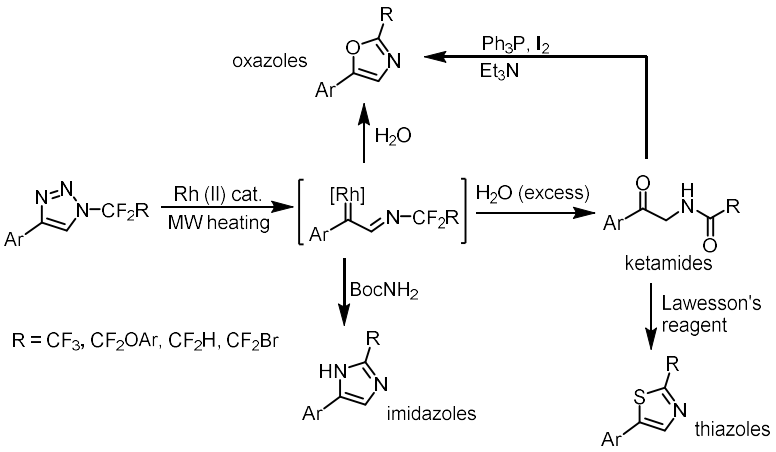
53 R. Z. Zhang, R. X. Zhang, S. Wang, C. Xu, W. Guan, M. Wang, *Angew. Chem. Int. Ed.* **2022**, *61*, e202110749.



Scheme 9: Alternative methods for the preparation of N-trifluoromethyl nitrogen heterocycles.

The rhodium carbenoid intermediates were found to react also with heteroatoms, such as with oxygen in water, or with $BocNH_2$ to form oxazoles or imidazoles respectively. During the process, the nitrogen-bound CF_2 group hydrolyzed and became the part of the new five-membered heterocycle. Ketamides were prepared using excess of water and thiazoles by their cyclization using the Lawesson's reagent (Scheme 10).[25,54]

[54] V. Motornov, V. Košťál, A. Markos, D. Täffner, P. Beier, *Org. Chem. Front.* **2019**, *6*, 3776.



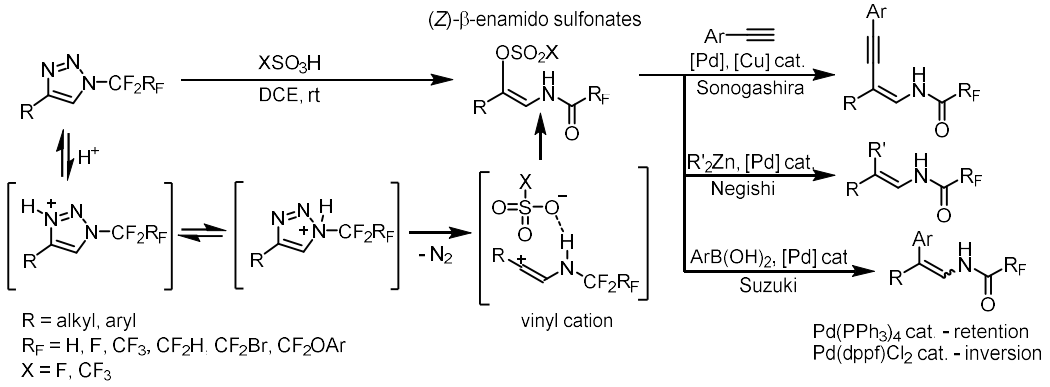
Scheme 10: Preparation of fluoroalkylated oxazoles, imidazoles and thiazoles.

4.6.3 Acid-mediated denitrogenation of N-fluoroalkyl-1,2,3-triazoles

Protonation of N-alkyl triazoles leads to the formation of stable triazolium salts. However, the behavior of N-fluoroalkyl triazoles under strongly acidic conditions was different. Triflic acid mediated denitrogenative transformation led to stable β-enamido triflates. Similarly, fluorosulfonic acid provided β-enamido fluorosulfonates. The mechanism of this new, metal-free, triazole opening process was investigated computationally and by deuterium labelling experiments. The reaction is initiated by triazole protonation, followed by ring opening of the N1-protonated intermediate, nitrogen elimination and vinyl cation formation which is captured by the conjugated base of the strong Brønsted acid. Another important feature is the stereoselectivity of the reaction, resulting from the hydrogen bonding of the NH group and the anion, thus delivering the anion to the vinyl cation sp hybridized center from the same side as the NH group and forming selectively (*Z*)-isomers of the products (Scheme 11).[55] Unlike in Rh(II)-catalyzed reaction, the strong acid-mediated process worked at room temperature and even with N-difluoromethylated triazole substrates. Enamido triflates exhibited excellent reactivity in cross-coupling reactions exemplified by Suzuki, Sonogashira, and Negishi reactions and leading to stereodefined enamides. The right choice of the palladium catalyst in the Suzuki reaction permitted the control of stereochemistry

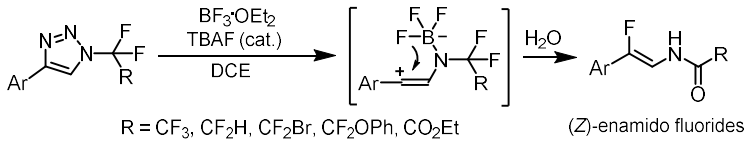
[55] A. Markos, S. Voltrová, V. Motornov, D. Tichý, B. Klepetářová, P. Beier, *Chem. Eur. J.* **2019**, *25*, 7640.

with retention or inversion of configuration of the C=C bond during the cross-coupling (Scheme 11).[56]



Scheme 11: Denitrogenation of N-fluoroalkyl-1,2,3-triazoles with triflic and fluorosulfonic acids and follow-up cross-coupling reactions.

The acid-mediated triazole denitrogenation strategy was extended to the use of Lewis acids. For example, BF_3-etherate promoted triazole ring opening to form enamido fluorides, again stereoselectivity and *via* a vinyl cation (Scheme 12).[57]

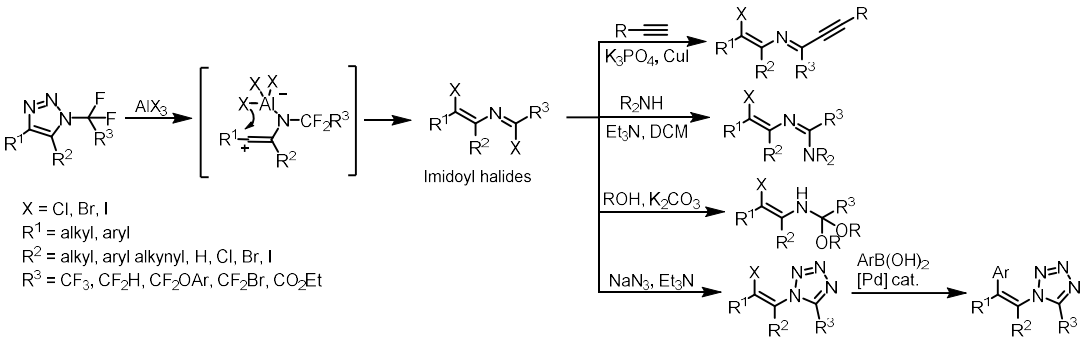


Scheme 12: Denitrogenation of N-fluoroalkyl-1,2,3-triazoles with BF_3-etherate.

Similarly, aluminum halides mediated the conversion of our triazoles to imidoyl halides. In this case, the N-CF_2 group did not hydrolyze and imidoyl halides were isolated as stable products. The difference was caused by a fluorophilic character of aluminum which exchanged chloride, bromide and iodide ions for fluoride and by a better hydrolytic stability of imidoyl halides (Cl, Br, I) over imidoyl fluorides. The highly functionalized imidoyl halide products are useful building blocks for the synthesis of a variety of stereodefined N-alkenyl compounds. The halide atom of imidoyl halides can be substituted with nucleophiles, the imidoyl group can undergo

[56] T. Chvojka, A. Markos, S. Voltrová, R. Pohl, P. Beier, *Beilstein J. Org. Chem.* **2021**, *17*, 2657.
[57] A. Markos, L. Janecký, B. Klepetářová, R. Pohl, P. Beier, *Org. Lett.* **2021**, *23*, 4224.

cyclization to a tetrazole, or the vinyl halide can engage in cross-coupling reactions (Scheme 13). Using this methodology, derivatives of zuclomiphene and enclomiphene drugs were prepared.[58]

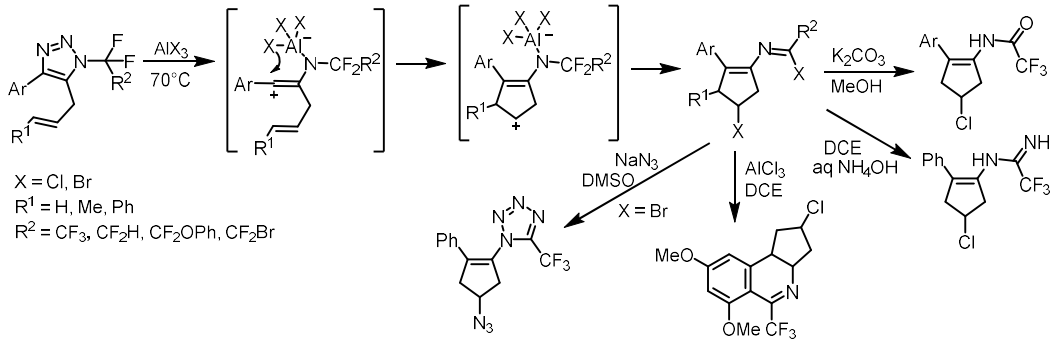


Scheme 13: Denitrogenation of N-fluoroalkyl-1,2,3-triazoles with aluminum halides.

N-Alkenyl compounds such as enamides and N-alkenyl imidoyl halides are versatile building blocks used in the synthesis of prominent classes of natural products, pharmaceuticals and agrochemicals. Our newly developed methods might contribute to streamlined syntheses of new products featuring these moieties.

The vinyl cation intermediate generated by acid-mediated triazole denitrogenation can be utilized in the intramolecular C–C bond formation (cyclization). Thus, we prepared N-fluoroalkyl 4-substituted-5-allylated 1,2,3-triazoles by the intercepted click reaction (Scheme 5B) and treated them with aluminum trihalides. Cyclization to halogenated cyclopentenes took place and further follow-up reactions creating structural diversity were showcased (Scheme 14).[38]

[58] A. Markos, L. Janecký, T. Chvojka, T. Martinek, H. Martinez-Seara, B. Klepetářová, P. Beier, *Adv. Synth. Catal.* **2021**, *363*, 3258.

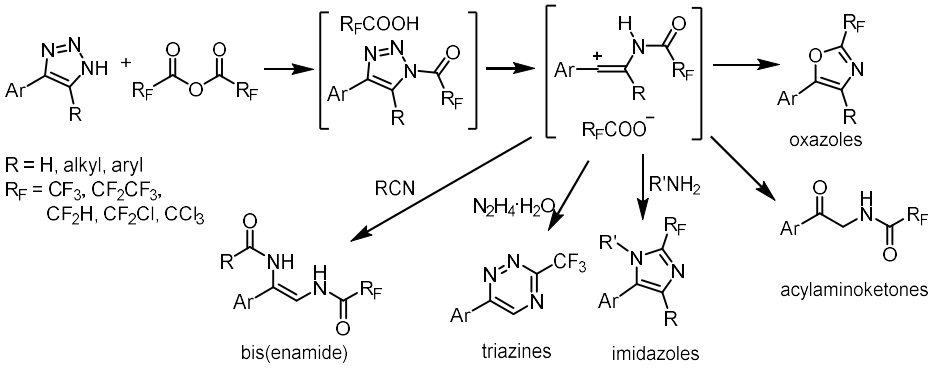


Scheme 14: AlX_3-mediated denitrogenation/cyclization of 4-allylated triazoles.

4.7 Denitrogenation reactions of NH-1,2,3-triazoles

During our investigations on denitrogenation reactions of N-fluoroalkylated triazoles we realized that under the right circumstances the presence of N-fluoroalkyl group on nitrogen N1 was not required for the ring opening to occur. The prerequisites for triazole denitrogenation are the presence of an electron-acceptor group on N1 and the use of sufficiently strong acid. Both requirements are met when NH-triazoles are acylated with highly electrophilic acid anhydrides, such as trifluoroacetic anhydride. In this reaction, N-trifluoroacetyl triazole and one equivalent of trifluoacetic acid would form leading to the triazole ring opening. Thus, we developed a denitrogenation of NH-triazoles using anhydrides and proceeding *via* a vinyl cation. These intermediates can be transformed to 2-fluoroalkylated oxazoles or acylamino ketones when treated with aqueous base. The addition of primary amine caused ring closing to 2-fluoroalkylimidazoles and the addition of hydrazide led to 1,2,4-triazines. In the presence of a nitrile a Ritter-type process operated yielding bis(enamide) in (*Z*) stereochemistry (Scheme 15).[59,60]

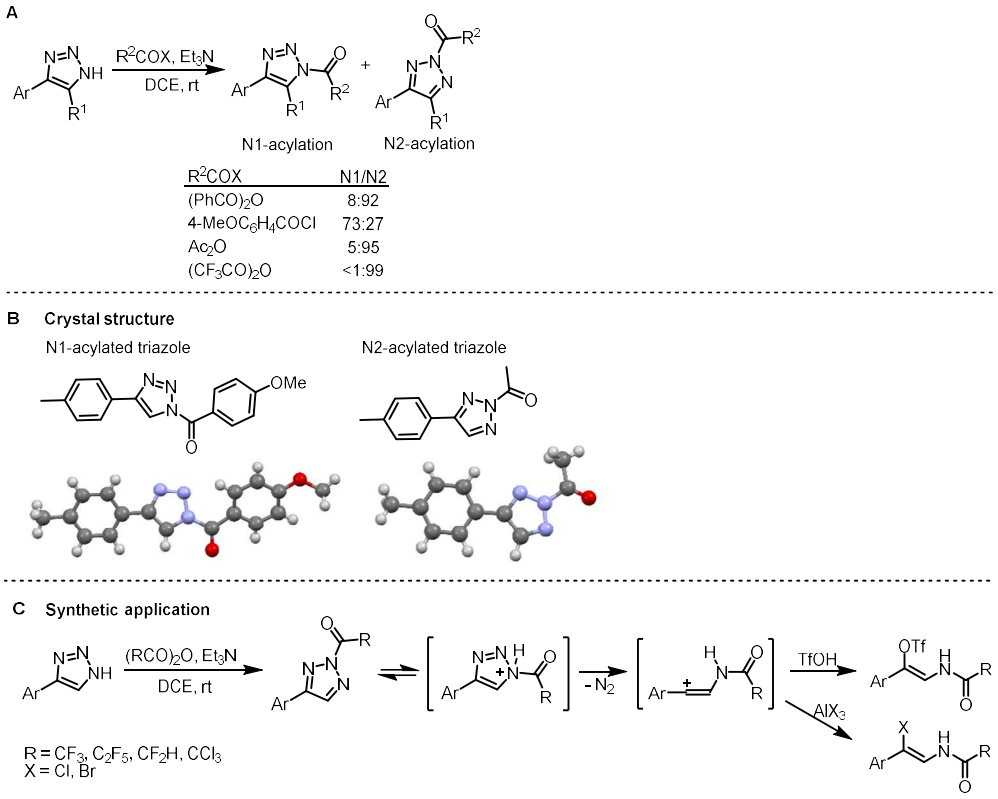
[59] V. Motornov, P. Beier, *Org. Lett.* **2022**, *24*, 1958.
[60] V. Motornov, P. Beier, *New. J. Chem.* **2022**, *46*, 14318.



Scheme 15: Denitrogenation of NH-1,2,3-triazoles using fluorinated acid anhydrides.

Subsequently, we studied acylation of NH-triazoles with various acylating reagents and found that the acylation regioselectivity can be achieved. Strongly electrophilic acylating reagents preferred acylation on N2 of the triazole, while less electrophilic and bulky ones preferred acylation on N1 (Scheme 16A). We were able to isolate and fully characterize (including X-ray structure) both isomers of acylated triazoles which were previously regarded as unstable intermediates (Scheme 16B). We also demonstrated their interconversion by heating or by the treatment with acid (Scheme 16C). Thus, in situ prepared N2 acylated triazoles were converted to denitrogenated products using triflic acid or aluminum trihalide. This work identified acylated triazoles as key intermediates in triazole denitrogenation reactions.[61]

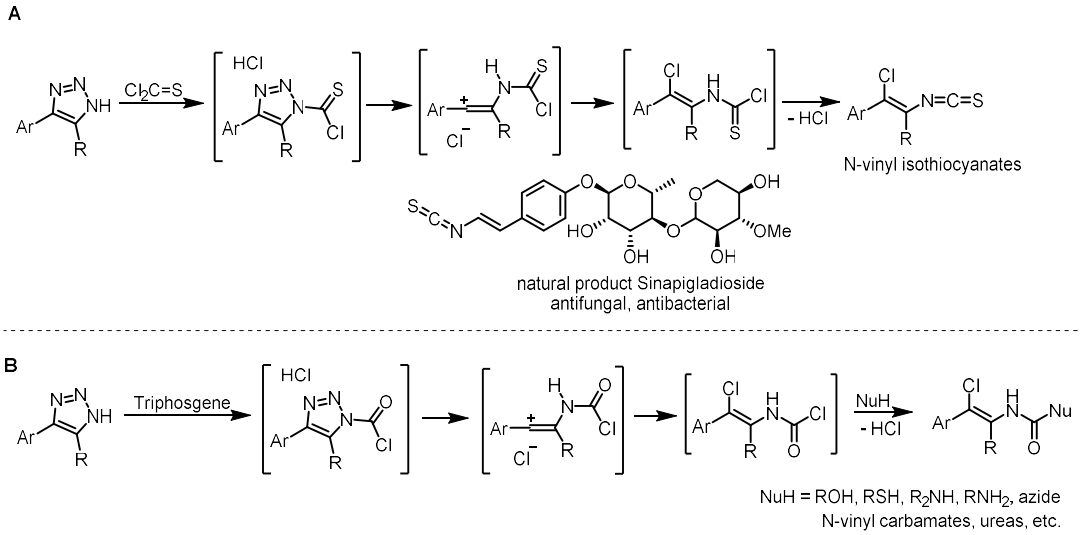
[61] V. Motornov, R. Pohl, B. Klepetářová, P. Beier, *Chem. Commun.* **2023**, *59*, 9364.



Scheme 16: Synthesis and conversion of acylated triazoles.

One-carbon acylating reagent thiophosgene acylated NH-triazoles and led to N-vinylated ring cleavage product N-vinylisothiocyanates. The vinyl isothiocyanate moiety is present in natural products, such as in Sinapigladioside with antibacterial and antifungal activity (Scheme 17A). The use of triphosgene as an acylating reagent on NH-triazoles provided after denitrogenation and follow-up reactions with nucleophiles N-vinylcarbamates, unsymmetrical vinylureas, carbamothioates and similar products (Scheme 17B).[62]

[62] V. Motornov, P. Beier, *Org. Biomol. Chem.* **2023**, *21*, 1143.



Scheme 17: Acylation of NH-triazoles with thiophosgene and triphosgene.

We recently reviewed denitrogenative transformations of NH-triazoles.[63]

5. Conclusions

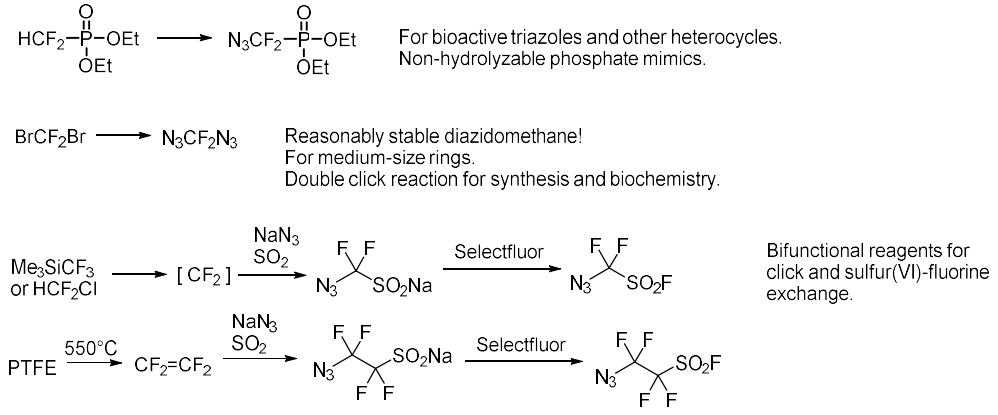
Fluorinated azidoalkanes developed by us are now easily available reagents with unusually high stability. They represent convenient reagents for the synthesis of a wide range of N-fluoroalkylated nitrogen heterocycles, such as triazoles, imidazoles, oxazole, azepines, indoles, and other. [3+2] Cycloaddition of fluorinated azides leads to N-fluoroalkyl-1,2,3-triazoles, which can be further transformed using rhodium-catalyzed transannulations to new medicinally interesting heterocycles with fluoroalkyl groups on nitrogen or carbon atoms. Furthermore, various denitrogenative processes were developed, which proceed thermally to give ketenimines, using Brønsted acids to enamido sulfonates, or Lewis acids to enamido halides, imidoyl halides and enamides. The synthetic usefulness of these N-alkenyl compounds spans beyond organofluorine chemistry. A denitrogenative triazole ring opening was also demonstrated by acylation strategy of NH-triazoles providing new N-alkenyl compounds and heterocycles

[63] V. Motornov, P. Beier, *RSC Adv.* **2023**, *13*, 34646.

which hold promise in the realm of medicinal chemistry and the advancement of industrial synthetic processes.

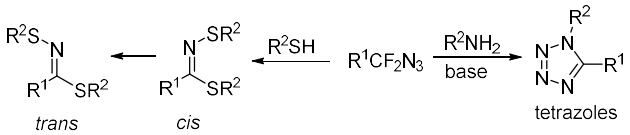
6. Future plans

Several research areas are pursued at the moment in our laboratory. We are developing new fluorinated azides and their synthetic applications (Scheme 18). For example, bifunctional azide-alkyne click and sulfur(VI)-fluorine exchange reagents will be useful in chemical biology applications.



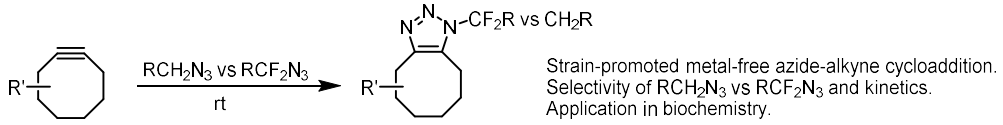
Scheme 18: Synthesis of new fluorinated azides.

The second area of research in this project is the investigation of reactions of fluoroalkyl azides with nucleophiles (Scheme 19). We found that the reaction with primary amines provides tetrazoles and the reaction with thiols new N–S-containing iminothioates. These processes and their application should be investigated in more detail.



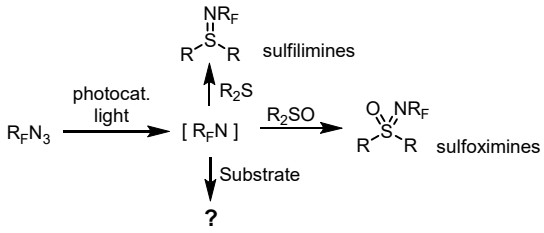
Scheme 19: Investigation of reactivity of fluorinated azides with nucleophiles.

We are also studying strain-promoted azide-alkyne cycloadditions (SPAAC) and the influence of fluorine substituents on the reaction rate of this metal-free click process with potential in applications in chemical biology (Scheme 20). We believe that with the right combination of azide and cyclooctyne reaction partners, good selectivity can be achieved for the reaction of either fluorinated or nonfluorinated organic azide.



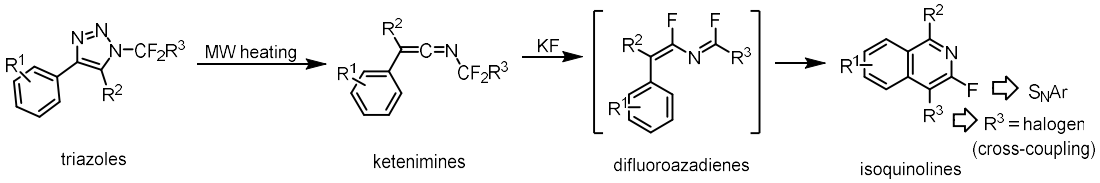
Scheme 20: SPAAC of fluorinated azides.

The photocatalytic generation of fluoroalkyl nitrenes is applied to other substrates than alkenes, to sulfides and sulfoxides with the aim to prepare new N-fluoroalkylated compounds (Scheme 21). The nitrene chemistry might also prove useful in C–H, X–H and C–C insertion reactions.



Scheme 21: Investigation of reactivity of fluorinated nitrenes.

Finally, a study of the synthetic use of ketenimines generated by thermal denitrogenation/rearrangement of triazoles is finishing up. Upon 1,2-fluorine shift of ketenimines and cyclization, new highly substituted isoquinolines are prepared efficiently (Scheme 22). This process represents a new and straightforward synthesis of isoquinolines which are compounds widely used in medicinal chemistry and in the development of agrochemicals.



Scheme 22: Synthesis of selectively-fluorinated and fluoroalkylated isoquinolines via ketenimines.

Abbreviations

Boc	tert-butyloxycarbonyl
CuAAC	copper(I)-catalyzed azide-alkyne cycloaddition
CuMeSal	copper(I) 3-methylsalicylate
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DCM	dichloromethane
DMAP	4-dimethylaminopyridine
dppf	1,1'-bis(diphenylphosphino)ferrocene
EPR	electron paramagnetic resonance
esp	α,α,α′,α′-tetramethyl-1,3-benzenedipropanoate
IOCB	Institute of Organic Chemistry and Biochemistry
MS	mass spectroscopy
NMR	nuclear magnetic resonance
nonaflyl	perfluorobutanesulfonyl
oct	octanoate
PTFE	poly(tetrafluoroethylene)
SPAAC	strain-promoted azide-alkyne cycloaddition
Tf	triflyl (trifluoromethanesulfonyl)

THF tetrahydrofuran

TMS trimethylsilyl

tosyl (Ts) *p*-toluenesulfonyl

UCT University of Chemistry and Technology

List of publications as a basis of this thesis

1. Z. E. Blastik, S. Voltrová, V. Matoušek, B. Jurásek, D. W. Manley, B. Klepetářová, P. Beier, *Angew. Chem., Int. Ed.* **2017**, *56*, 346.

2. S. Voltrová, M. Muselli, J. Filgas, V. Matoušek, B. Klepetářová, P. Beier, *Org. Biomol. Chem.* **2017**, *15*, 4962.

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4. Z. E. Blastik, B. Klepetářová, P. Beier, *ChemSelect* **2018**, *3*, 7045.

5. S. Voltrová, I. Putovný, V. Matoušek, B. Klepetářová, P. Beier, *Eur. J. Org. Chem.* **2018**, 5087.

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