7th Fluorine Days

18-22 June 2023

Poznań, Poland

7th Fluorine Days

Book of Abstracts

Editorial office

Poznan Science and Technology Park
Professional Congress Organizer
Rubież 46, 61-612 Poznań, Poland
e-mail: bok@ppnt.poznan.pl

This volume has been compiled from files supplied by the Authors

Cover design

Akcygraf

DTP/Technical Editor

Reginaldo Cammarano

ISBN 978-83-950380-4-4

CONTENTS

7th Fluorine Days

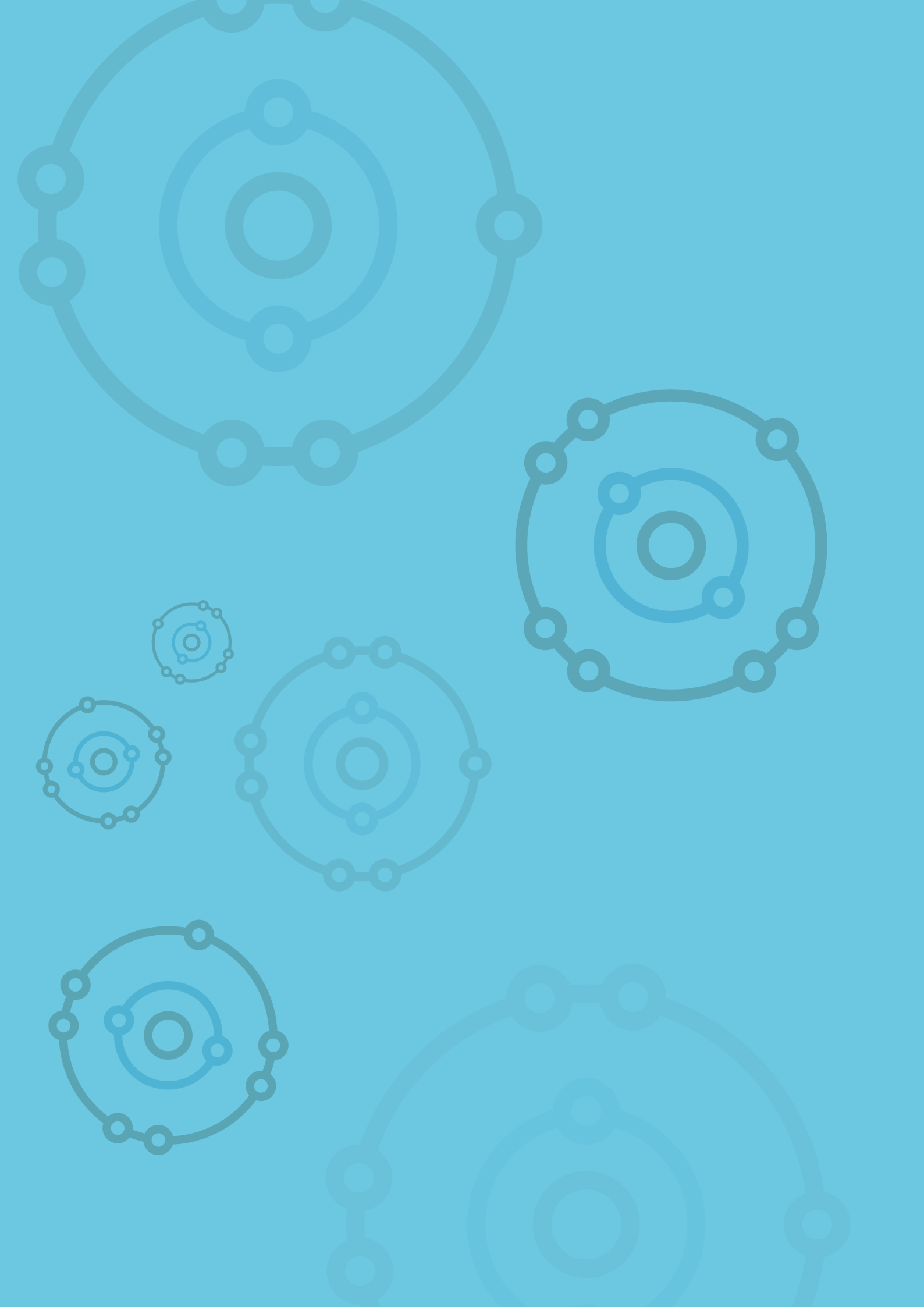
Plenary Session

Invited Lecture

Lectures

Poster Session

PLENARY SESSION



Polyhedral Perfluorocarbon Nanodroplets that Phase-Shift into Polyhedral Nanobubbles with Medical Potential

Marie Pierre Krafft[1], Hagop Abadian[1], Marc Schmutz[1], Delphine Felder-Flesh[2]

[1]*Institut Charles Sadron (ICS, CNRS), University of Strasbourg, 23 rue du Loess, 67034 Strasbourg, France*
[2]*Superbranche, Institut de Science et d'Ingénierie Supramoléculaires (ISIS), University of Strasbourg, 8, all. Gaspard Monge, 67000 Strasbourg, France*

E-mail: krafft@unistra.fr

The potential of perfluorocarbon (PFC)-stabilized microbubbles (MBs) for contrast ultrasound (US) diagnosis, therapy (focused US-mediated drug delivery and therapeutic energy delivery), and for sensitization of oxygen-dependent therapies (radio- and chemotherapy, dynamic photo(sono)therapy) is being intensively investigated [1, 2]. The micrometric size of the MBs that confines them to the vascular system and their short life-time in the circulation limit the scope of their uses. These issues can be circumvented by injecting nanodroplets (NDs, a nanoemulsion) of a liquid PFC that is subsequently vaporized to give birth to MBs by applying US pulses once their target (e.g., a tumor) is reached. Here, we report that a series of new amphiphilic oligo(ethylene glycol) alkylated dendrons [3] used in combination with phospholipids strongly stabilize perfluorohexane (*F*-hexane) NDs, as assessed by dynamic light scattering (DLS) (Fig. 1a). Remarkably, we found that the *F*-hexane NDs are not spherical immediately after preparation, but polyhedral, as demonstrated by cryogenic transmission electron microscopy (Cryo-TEM). Over time, the faceted NDs convert slowly into spherical ones (Fig. 1b), a phenomenon investigated by micro-differential scanning calorimetry (micro-DSC). Notably, the shelf stability of the *F*-hexane NDs is directly linked with the existence of the facets. Incorporation of the dendrons inhibits the faceted-to-spherical ND conversion, thus increasing stability dramatically (Fig. 1a, red curve). The interactions between DPPC and dendrons spread as Langmuir monolayers were investigated using the molecular area additivity rule. The potential of these faceted PFC NDs for acoustic droplet vaporization to MBs is discussed. The interest of polyhedral nanostructures, such as droplets and vesicles based on fluorinated compounds, is also presented from a fundamental viewpoint [4].

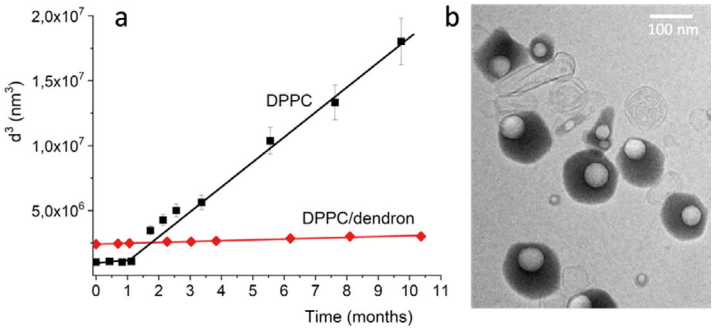


Figure 1: a) Variation of *F*-hexane droplet volume versus time; dipalmitoylphosphatidylcholine (DPPC, black)-stabilized *F*-hexane nanoemulsions start to become destabilized after ~1 month, which corresponds to their conversion to spherical morphologies. By contrast, nanoemulsions stabilized by DPPC/dendron combinations (molar ratio: 25:1) remain stable for at least 10 months. b) Cryo-TEM image showing polyhedral *F*-hexane nanodroplets (black) and nascent nanobubbles (white).

References

[1] M.P. Krafft, J.G. Riess, *Adv. Colloid Interface Sci.* **2021**, *294*, 102407.
[2] M.P. Krafft, *Curr. Opin. Pharmacol.* **2020**, *53*, 117-25.
[3] D. Felder-Flesch, B. Ayela, M. Rey, H. Abadian, S. El-Yakhlifi, M.P. Krafft, *Eur. Pat. n° 22305549.2* 14/04/2022.
[4] A. Gonzàlez-Pérez, M. Schmutz, G. Waton, M.J. Romero, M.P. Krafft, *J. Am. Chem. Soc.* **2007**, *129*, 756-7.

^{19}F-MRI Probes Based on Branched Fluorinated Residues

Pierangelo Metrangolo

Laboratory of Supramolecular and Bio-Nanomaterials (SBNLab), Department of Chemistry, Materials, and Chemical Engineering "Giulio Natta", Politecnico di Milano, Via L. Mancinelli 7, 20131 Milano, Italy.

E-mail: pierangelo.metrangolo@polimi.it

The ideal ^{19}F-MRI probe should bear as many as possible magnetically equivalent fluorine atoms and show optimal magnetic resonance relaxivity properties (*i.e.*, T1 and T2), which enable reduced acquisition time with the possibility to apply fast imaging methods. Moreover, it should be biocompatible with reduced tendency to bioaccumulate in tissues, which is one of the main drawbacks in using perfluorocarbons (PFCs), together with their difficulty to be chemically modified with functional groups. In fact, PFCs such as perfluorooctyl bromide (PFOB), perfluoro-15-crown-5-ether (PFCE), and linear perfluoropolyethers (PFPE) are currently the most used tracers in ^{19}F-MRI preclinical and clinical studies, with the above-mentioned limitations. In this regard, molecules bearing short branched fluorinated chains gained a lot of attention for their high number of equivalent fluorine atoms and expected capability of reducing bioaccumulation concerns. A valuable building block for branched fluorinated tracers is perfluoro-*tert*-butanol (PFTB), with nine magnetically equivalent fluorine atoms and easy availability and modification.

In this lecture, I will discuss the main challenges that ^{19}F-MRI has to overcome for increasing its clinical use, highlighting on one hand the need of developing customized fluorinated materials for increasing sensitivity and enabling multimodal properties, and, on the other hand, the importance of the ultrastructure of the final formulation for the final biological response (*i.e.*, clearance). In this context, my group has been focusing on the synthesis and development of branched fluorinated tracers, for which the originator is a molecule called PERFECTA (from suPERFluorinatEdContrasT Agent), bearing 36 equivalent ^{19}F atoms, which showed not only optimal relaxometry properties but also a very specific and intense Raman signal. Thus, PERFECTA and its derivatives represent a new family of multimodal tracers enabling multiscale analysis, from whole body imaging (^{19}F-MRI) to microscopic detection at the cellular/tissue level (Raman microscopy). I believe that our proposed PFTB strategy can strongly promote the production of increasingly effective ^{19}F-MRI materials with additional functionalities, facilitating the clinical translation of this imaging modality.

References

[1] Tirotta, I.; Mastropietro, A.; Cordiglieri, C.; Gazzera, L.; Baggi, F.; Baselli, G.; Bruzzone, M. G.; Zucca, I.; Cavallo, G.; Terraneo, G.; Baldelli Bombelli, F.; Metrangolo, P.; Resnati, G. *J. Am. Chem. Soc.* **2014**, *136*, 8524-8527.

[2] Chirizzi, C.; Morasso, C.; Caldarone, A. A.; Tommasini, M.; Corsi, F.; Chaabane, L.; Vanna, R.; Baldelli Bombelli, F.; Metrangolo P. *J. Am. Chem. Soc.* **2021**, *143*, 12253-12260.

[3] Bona, B. L.; Koshkina, O.; Chirizzi, C.; Dichiarante, V.; Metrangolo, P.; Baldelli Bombelli, F. *Acc. Mater. Res.* **2023,** *4*, 71-85.

Fluoride Extremists Separated by a Barrier

Wojciech Grochala[1], Łukasz Wolański[1], José Lorenzana[2]

[1]*Center of New Technologies, University of Warsaw, Zwirki i Wigury 93, 02089 Warsaw, Poland*
[2]*Institute for Complex Systems (ISC), Consiglio Nazionale delle Ricerche, Dipartimento di Fisica, Università di Roma "La Sapienza", 00185 Rome, Italy*

E-mail: w.grochala@cent.uw.edu.pl

Reactions between oxidizers and reductors are usually vigorous and complete, especially those between strong oxidizers and strong reductants. Take e.g. F_2, F atoms, KrF_2, AgF_2, or PtF_6 as one of the former, and alkali metals as the latter, and see what happens if you mix them together. In brief, you may expect to get a phone call from Lab Safety department or your institute director. Or it will be you who will be the first one calling the Firemen Support Unit of your University.

However, the matters become more interesting (and more controllable) if you separate the reactants by a nano-thin mechanical barrier which prevents them to enter into a direct contact. Just what will happen then will be explained in this account [1].

Figure 1: Mixing oxidizers and reductors together can be a lovely experience. Copyright: © 2012 Davin G Photography.

References

[1] A. Grzelak, J. Lorenzana, W. Grochala, *Angewandte Chemie International Edition in English* **2021**, *60*, 13892-13895.

Silyl Radical-mediated Cross-coupling Reactions of Organic Fluorides

Norio Shibata

Department of Nanopharmaceutical Sciences, Nagoya Institute of Technology, Nagoya, Japan.

E-mail: nozshiba@nitech.ac.jp

Recently, organofluorine compounds have become ubiquitous. This is due to the robust establishment of technologies for their synthesis. There are more than 340 registered fluoropharmaceuticals[1] and more than 425 registered fluoroagrochemicals.[2] In addition, 14.2 million commercially available compounds contain fluoroarene (Ar-F) moieties (SciFindern). A unique feature of organic fluorides is their stability and inertness. Fluorine is highly electronegative, making the C-F bond very strong and difficult to break. This property makes organic fluorides resistant to harsh reaction conditions such as high temperatures, strong acids or bases, and oxidizing or reducing agents. These facts led us to propose organic fluorides as valuable starting materials for synthesizing complex molecules via C-F bond cleavage/activation reactions. However, the chemical transformation of fluoro-organic compounds via cleavage of C-F bonds under very mild conditions can be challenging, as it often requires drastic conditions, such as high temperature, strong acids/bases, and organometallic reagents.

This presentation will report our recent progress on this topic based on the transformations of the C-F bond to other functional groups by silyl radical mediated cross-coupling reactions via C-F bond activation (Figure 1).[3]

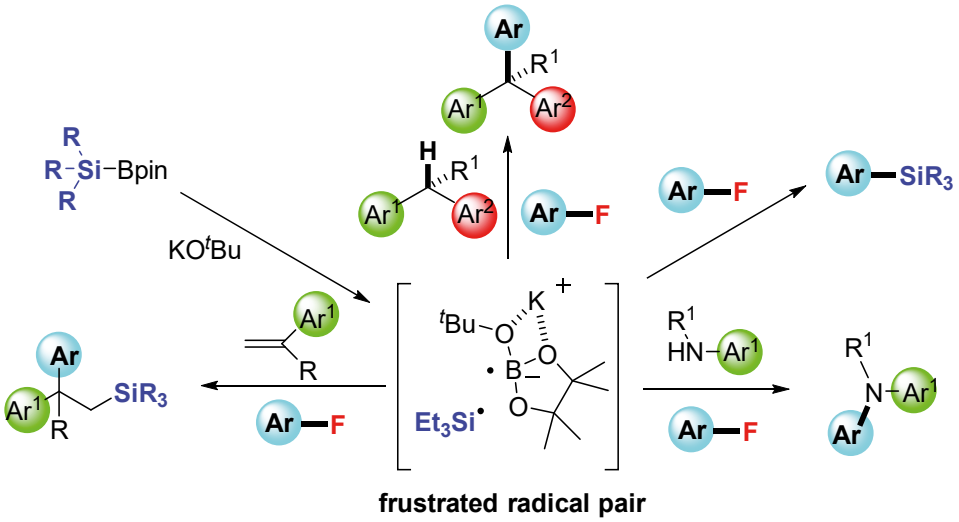


Fig 1. Silyl radical mediated cross-coupling reactions of organic fluorindes

Figure 1: Silyl radical mediated cross-coupling reactions of organic fluorindes

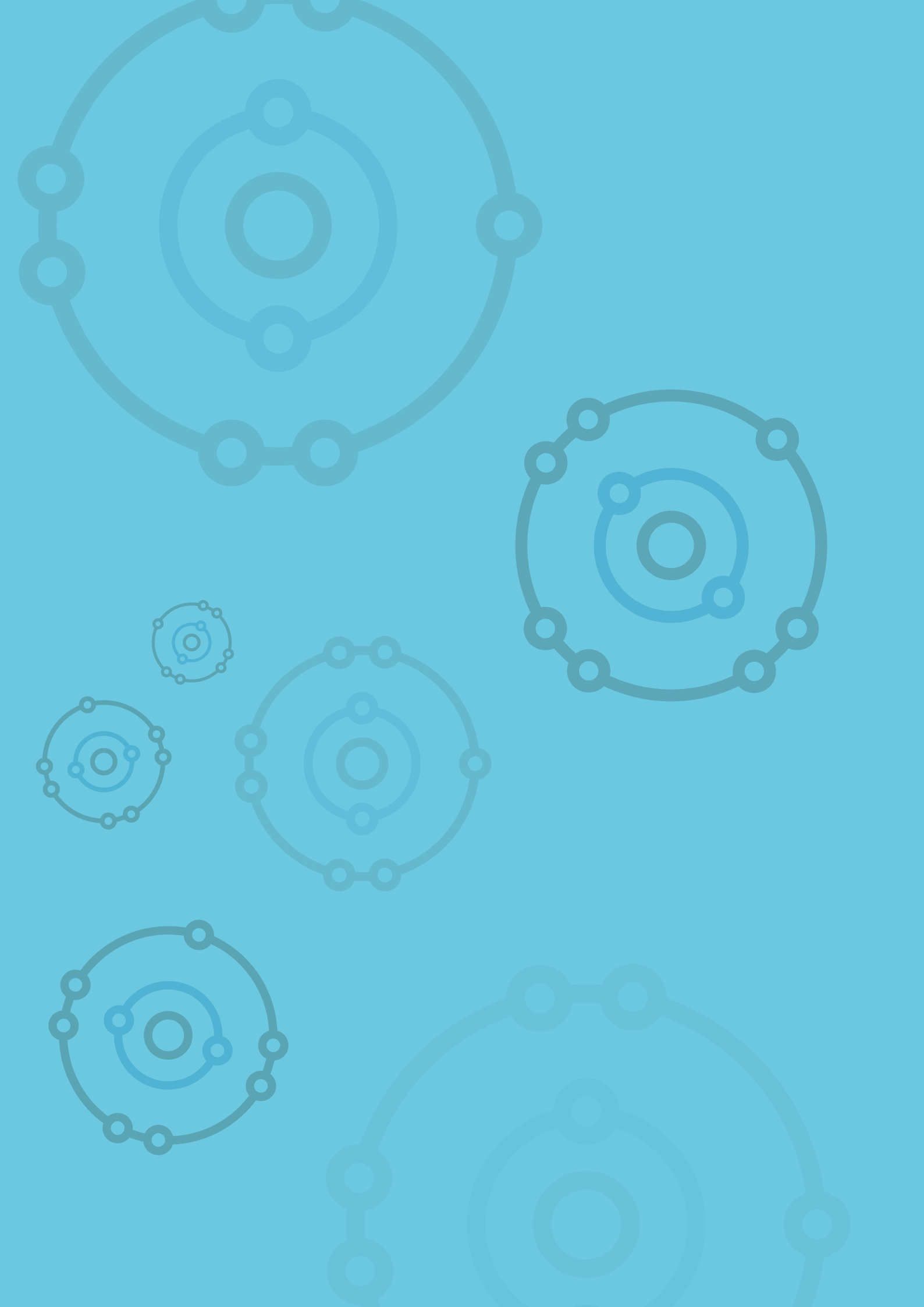
References

[1] Inoue, M., Sumii, Y., Shibata, N. *ACS Omega*, **2020**, *5*, 10633-10640.

[2] Ogawa, Y., Tokunaga, E., Kobayashi, O., Hirai, K., Shibata, N. *iScience* **2020**, *23*, 101467.

[3] a) Cui, B.; Jia, S.; Tokunaga, E.; Shibata, N. *Nat. Commun*. **2018**, *9*, 4393; b) Zhou, J.; Zhao, Z.; Shibata, N. *Front. Chem*. **2021**, *9*, 771473; c) Zhou, J.; Jiang, B.; Fujihira, Y.; Zhao, Z.; Imai, T.; Shibata, N. *Nat. Commun*. **2021**, *12*, 3749; d) Zhou, J.; Zhao, Z.; Jiang, B.; Yamamoto, K.; Sumii, Y.; Shibata, N. *Chem.Sci.* **2023**, *14*, 4248; e) Zhou, J.; Zhao, Z.; Shibata, N. *Nat. Commun*. **2023**, *14*, 1847.

INVITED LECTURE



Easy Access of *N*-CF_3 Amine and Hydrazine Derivatives

Benoît Crousse

BioCIS UMR 8076 CNRS-Université Paris Saclay, Bâtiment Henri MOISSAN, 17, Avenue des Sciences 91400 ORSAY, France.

E-mail: Benoit.crousse@universite-paris-saclay.fr

Fluorinated molecules are increasingly present in pharmaceuticals, materials, and polymers.[1] So it is still necessary to develop new methods incorporating fluorinated groups. In recent years, compounds with fluorinated groups on a heteroatom, such as RCF_2S and RCF_2O moieties, have attracted special interest.[2] Due to their high hydrophobic parameters,[3] these groups are potentially important targets and are now present in the pharmaceutical and agrochemical fields. [1,2]

However, the synthesis of fluorinated groups on nitrogen, such as *N*-CF_3, is understudied and remains a challenge. [4] Furthermore, these compounds should be markedly different from non-fluorinated analogues in order to exploit them wisely in various research fields.

In our interest in synthesizing original fluoro compounds and, particularly fluorinated peptidomimetics, we investigated the development of new *N*-fluorinated-containing scaffolds (Scheme 1). Thus, herein we report an efficient and economical approach to synthesizing *N*-CF_3 amines and hydrazines.[5] Also, in this line, the construction of new compounds will be described.

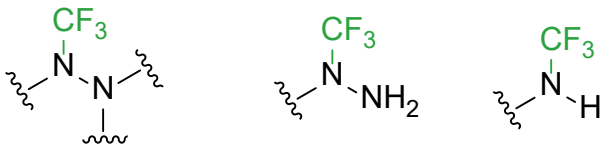


Figure 1: Example of *N*-fluorinated scaffolds.

References

[1] (a) S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev.* **2008**, *37*, 320. (b) K. L. Kirk, *J. Fluorine Chem.*, **2006**, *127*, 1013. (c) C. Thomas, *J. Curr. Top. Med. Chem.* **2006**, *6*, 1529. (d) K. Iseki, *Tetrahedron*, **1998**, *54*, 13887. (e) I. Ojima, *J. Org. Chem*. **2013**, *78*, 6358. (f) A. Meanwell, *J. Med. Chem*. **2018**, *61*, 5822-5880. (g) M. Inoue, Y. Sumii, N. Shibata, *ACS Omega*. **2020**, *5*, 10633-10640.

[2] (a) T. Fujita, J. Iwasa, C. Hansch, *J. Am. Chem. Soc.* **1964**, *86*, 5175. (b) F. Leroux, P. Jeschke, M. Schlosser, *Chem. Rev.* **2005**, *105*, 827. (c) P. Jeschke, E. Baston, F. R. Leroux, *Mini-Rev. Med. Chem.* **2007**, *7*, 1027.

[3] (a) A. Leo, C. Hansch, D. Elkins, *Chem. Rev.* **1971**, *71*, 525. (b) C. Hansch, A. Leo, S. H. Unger, K. H. Kim, D. Nikaitani, E. J. Lien, *J. Med. Chem.* **1973**, *16*, 1207.

[4] (a) T. Milcent, B. Crousse, *C. R. chimie*, **2018**, *21*, 771-778. (b) B. Crousse, *Chem. Rec.* **2023**, e202300011.

[5] (a) M. Mamone, R. S. B. Gonçalves, F. Blanchard, G. Bernadat, S. Ongeri, T. Milcent, B. Crousse *Chem. Commun.*, **2017**, *53*, 5024-5027. (b) T. Cao, P. Retailleau, T. Milcent, B. Crousse *Chem. Commun*., **2021**, *57*, 10351-10354.

Selective Fluorination of Some Highly Functionalized Cycloalkenes

Loránd Kiss[1], Melinda Nonn[2], Tamás Novák[1]

[1]*Stereochemistry Research Group, Institute of Organic Chemistry, Research Center for Natural Sciences, Magyar Tudósok krt. 2, H-1117 Budapest, Hungary*
[2]*MTA TTK Lendület Artificial Transporter Research Group, Institute of Materials and Environmental Chemistry, Research Center for Natural Sciences, Hungarian Academy of Sciences, Magyar Tudósok krt. 2, H-1117 Budapest, Hungary*

E-mail: kiss.lorand@ttk.hu

Organofluorine derivatives have had an increasing impact in synthetic organic chemistry, pharmaceutical chemistry, and drug research over the past two decades. Their syntheses and the development of novel synthetic strategies towards versatile fluorinated small molecular entities have generated high interest [1-3].

Our research group has designed various regio- and stereoselective and stereocontrolled methods for the construction of fluorine-containing small molecules, involving the transformation of various functionalized cycloalkenes through their ring olefin bond. The synthetic methodologies developed to access various pharmacologically interesting, fluorinated structural motifs with multiple chiral centers might be valuable protocols for the preparation of other, versatile classes of functionalized organic compounds as well.

The current work describes the most important achievements with respect to selective fluorinations of various substituted cycloalkenes (including cyclic amino acid derivatives, amines, esters, ketones etc.), followed by selective and substrate-dependent late-stage fluorinations [4].

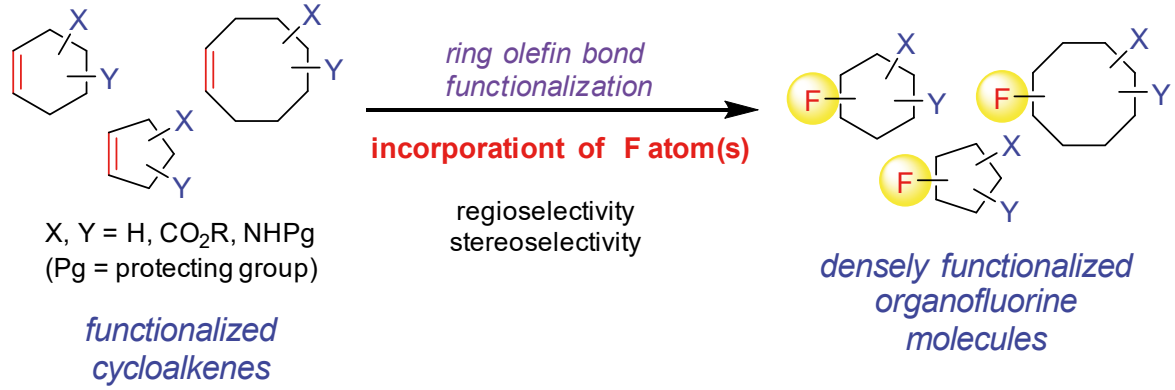


Figure 1: Synthesis of some densely functionalized, fluorine-containing molecules.

References

[1] J. Han, L. Kiss, H. Mei, A.M. Remete, M. Ponikvar-Svet, D.M. Sedgwick, R. Roman, S. Fustero, H. Moriwaki, V.A. Soloshonok, *Chem. Rev.* **2021**, *121*, 4678−4742.
[2] J. Han, A.M. Remete, L.S. Dobson, L. Kiss, K. Izawa, H. Moriwaki, V.A. Soloshonok, D. O'Hagan, *J. Fluorine Chem*. **2020**, *239*, 109639.
[3] R.A. Remete, M. Nonn, L. Kiss, *Chem. Eur. J.* **2022**, *28*, e202202076.
[4] M. Nonn, C. Paizs, L. Kiss, *Chem. Rec*. **2022**, *22*, e202200130.

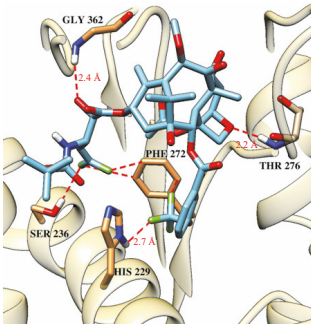
Fluorine-containing 3rd-Generation Taxoids as Potent Anticancer Agents

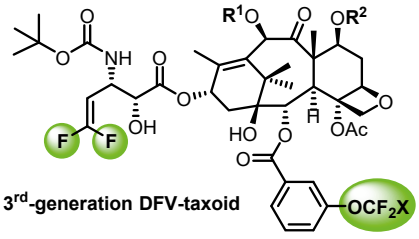
Iwao Ojima

Department of Chemisry and Institute of Chemical Biology and Drug Discovery, Stony Brook University– State University of New York, Stony Brook, NY 11794-3400, U.S.A.

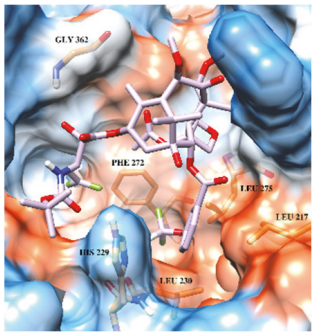
E-mail: iwao.ojima@stonybrook.edu

The incorporation of fluorine or organofluorine groups into pharmaceutical and agricultural drugs often induces desirable pharmacological properties through unique protein-drug interactions involving fluorine. We have reported separately remarkable effects of the 2,2-difluorovinyl (DFV) group at the C3' position of the 2nd- and 3rd-generation taxoids, including DFV-ortataxel [1,2], as well as those of the CF_3O and CHF_2O groups at the 3-position of the C2-benzoyl moiety of the 3rd-generation taxoids [3,4] on their potency and pharmacological properties. Accordingly, we investigated the combination of these two modifications in the 3rd-generation taxoids to examine whether these two modifications are cooperative at the binding site in the β-tubulin or not, as well as to see how these effects are reflected in the biological activities of the new 3rd-generation DFV-taxoids [5, 6]. Thus, we designed and synthesized new DFV-fluorotaxoids. These novel fluorotaxoids displayed remarkable cytotoxicity against drug-sensitive human breast, lung, colon, pancreatic and prostate cancer cell lines, and also exhibited 2-4 orders of magnitude greater potency against extremely drug-resistant cancer cell lines, LCC6-MDR (breast) and DLD-1 (colon), as compared to paclitaxel. The results indicate that these novel fluorotaxoids can overcome MDR caused by the overexpression of Pgp and other ABC cassette transporters. The cooperative effects of the combination of the 3'-DFV group and 3-CF_3O/CHF_2O-benzoyl moiety at the C2 position were investigated in detail by molecular docking analysis. Both the 3'-DFV moiety and the 3-CF_3O/3-CHF_2O group of the C2-benzoate moiety are found to be nicely accommodated to the deep hydrophobic pocket of the paclitaxel/taxoid binding site in the β-tubulin, enabling an enhanced binding mode through unique attractive interactions between fluorine/CF_3O/CHF_2O and the protein, which are reflected in the remarkable potency of the novel fluorotaxoids.





R^1 = Ac, *c*-PrCO, EtCO, Me_2NCO, Me, MeOCO;
R^2 = H, Me; **X** = F, H



References

[1] A. Pepe, L. Kuznetsova, L. Sun and I. Ojima, *Fluoro-Taxoid Anticancer Agents*, in *Fluorine in Medicinal Chemistry and Chemical Biology,* I. Ojima Ed., Wiley-Blackwell, 2009, Chichester; pp 117-139.

[2] L. Kuznetsova, L. Sun, J. Chen, X. Zhao, J. Seitz, M. Das, Y. Li, J. M. Veith, P. Pera, R. J. Bernacki, S. Xia, S. B. Horwitz and I. Ojima, *J. Fluor. Chem.* **2012**, 143, 177-188.

[3] D. Rong, C. Wang, X. Zhang, Y. Wei, M. Zhang, D. Liu, H. Farhan, S. A. M. Ali, Y. Liu, A. Taouil, W. Guo, Y. Wang, I. Ojima, S. Yang, H. Wang, *Cancer Lett.* **2020**, 491, 36-49.

[4] X. Zheng, C. Wang, Y. Xing, S. Chen, T. Meng, H. You, I. Ojima, Y. Dong, *Int. J. Oncol*., **2017**, 50, 893-902

[5] C. Wang, L. Chen, Y. Sun, W. Guo, A. K.Taouil, I. Ojima, *Bioorg. Chem.*, **2022**, 119, 105578.

[6] M. Wang, C. Wang, C. Feng, W. Guo, H. Chen, B. Liu, E. Li, W. Liu, A. Taouil, I. Ojima, P. Hou, *Endocrine.* **2022**, 75, 465-477.

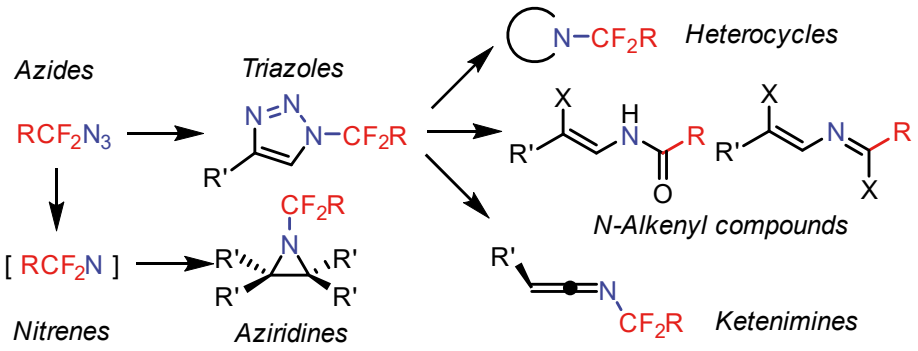
Fluorinated Organic Azides

Petr Beier

Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic, Flemingovo nám. 2, 166 10 Prague, Czech Republic

E-mail: beier@uochb.cas.cz

Organic azides are valuable building blocks in synthesis, biochemistry and material science. We developed the synthesis of a variety of novel α-fluorinated azidoalkanes and showed their unusual stability compared to non-fluorinated azidoalkanes. In this overview lecture, our latest development in the application of fluorinated azides in cycloaddition reactions, denitrogenative transformations of *N*-fluoroalkylated 1,2,3-triazoles, and trifluoromethyl nitrene formation and reactivity will be summarized (Scheme 1).[1-3] Fluorinated azidoalkanes are thus synthetically versatile compounds for the preparation of new heterocycles, *N*-fluoroalkylated and *N*-alkenyl compounds.



Scheme 1: Synthetic application of fluorinated azidoalkanes.

Acknowledgments
This work was financially supported by the Czech Science Foundation (23-04659S) and the Czech Academy of Sciences (RVO: 61388963).

References

[1] A. Markos, V. Matoušek, P. Beier, *Aldrichimica Acta* **2022**, *55*, 37.
[2] O. Bakhanovich, P. Beier, *Chem. Eur. J.* **2020**, *26*, 773.
[3] A. Markos, L. Janecký, T. Chvojka, T. Martinek, H. Martinez-seara, B. Klepetářová, P. Beier, *Adv. Synth. Catal.* **2021**, *363*, 3258.

Advanced Fluorinated Building Blocks for Drug Discovery

Ivan S. Kondratov,[1,2] Ivan G. Logvinenko,[1,2] Anton A. Homon,[1,2] Illiya O. Feskov,[1,2] Anton V. Chernykh,[1] Oleksandr O. Grygorenko[1,3]

[1]*V.P. Kukhar Institute of Bioorganic Chemistry & Petrochemistry, National Academy of Sciences of Ukraine, Murmanska Street 1, Kyïv 02660, Ukraine*
[2]*Enamine Ltd, Chervonotkatska Str. 78, Kyïv 02094, Ukraine*
[3]*Taras Shevchenko National University of Kyïv, Volodymyrska Street 60, Kyïv 01601, Ukraine*

E-mail: i.kondratov@enamine.net

Intensive application of Building Blocks for fast construction of more complex molecules became common practice in modern medicinal chemistry as well as agrochemistry and material science. Due to important role of Fluorine in the abovementioned disciplines access to diverse fluorine containing compounds is particularly important and therefore there are intensive investigations to extend the space of available fluorinated building blocks. During last decade our team has discovered diverse approaches to different fluorinated Building Blocks (Figure 1). and investigated their properties [1-7]. Results of several research projects will be presented during the lecture in detail.

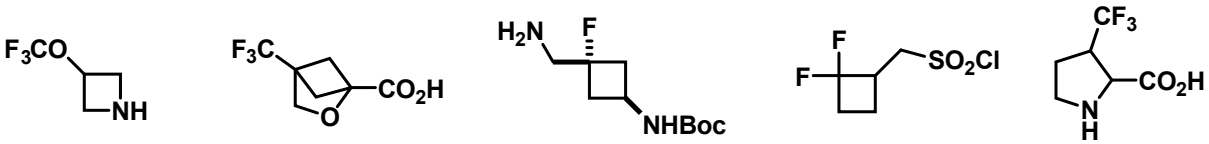


Figure 1: Examples of discovered fluorinated building blocks.

References

[1] A. V. Chernykh, D. Aloshyn, Yu. O. Kuchkovska, C. G. Daniliuc, N. A. Tolmachova, I. S. Kondratov, S. Zozulya, O. O. Grygorenko, G. Haufe *Org. Biomol. Chem.*, **2022**, *20*, 9337-9350.
[2] A. A. Homon, L. V. Shynder, O. P. Demchuk, O. V. Hryshchuk, I. S. Kondratov, I. I. Gerus, O. O. Grygorenko *J. Fluorine Chem.*, **2022**, 110041.
[3] I. G. Logvinenko, I. S. Kondratov, S. O. Pridma, N. A. Tolmachova, R. N. Morev, V. G. Dolovanyuk, A. L. Boretskyi, R. O. Stepanyuk, S. A. Trofimchuk, C. Mück-Lichtenfeld, C.-G. Daniliuc, G. Haufe, *J. Fluorine Chem.* **2022**, 109990
[4] A. A. Homon, O. V. Hryshchuk, O.V. Mykhailenko, B. V. Vashchenko, K. P. Melnykov, O. M. Michurin, C. G. Daniliuc, I. I. Gerus, V. O. Kovtunenko, I. S. Kondratov, O. O. Grygorenko *Eur. J. Org. Chem.* **2021**, *47*, 6580-6590
[5] I. O. Feskov, B. O. Golub, B. V. Vashchenko, V. V. Levterov, I. S. Kondratov, O. O. Grygorenko, G. Haufe *Eur. J. Org. Chem.* **2020**, *30*, 4755-4767
[6] A. V. Chernykh, K. P. Melnykov, N. A. Tolmacheva, I. S. Kondratov, D. S. Radchenko, C. G. Daniliuc, D. M. Volochnyuk, S. V. Ryabukhin, Y. O. Kuchkovska, O. O Grygorenko *J. Org. Chem.* **2019**, *84*, 8487-8496.
[7] N. A. Tolmachova, I. S. Kondratov, V. G. Dolovanyuk, S. O. Pridma, A. V. Chernykh, C. G. Daniliuc, G. Haufe *Chem. Commun.* **2018**, *54*, 9683-9686.

Taming Fluoride in the Coordination Sphere of Au and Pt to Control Fluorination Steps

Thomas Braun, Simon Rachor, Stefan Sander

Department of Chemistry, Humboldt University Berlin, Brook-Taylor-Str. 2, 12489 Berlin, Germany

E-mail: thomas.braun@cms.hu-berlin.de

Reactivity studies of Au(I) fluorido phosphine complexes towards alkynes and HF sources will be presented, in order to probe their behavior in hydrofluorination reactions.[1] Investigations on the formation of fluorovinyl complexes and on solvent coordination allowed for a further understanding of catalytic key-steps.[2,3] In addition, it was found that a Au(I) fluoroamido complex is accessible from a Au(I) fluorido phospineprecursor by reaction with NFSI.[4]
An unprecedented strategy for catalytic hydrofluorination reactions of alkynes on using Pt(II) complexes bearing cooperating indolyl phosphine ligands will also be reported.[5,6] Hydrogen bonding allows for the generation of electrophilic metal centres, whereas at the same time fluoride is stabilized in the coordination sphere and provided for reactivity (Figure).[6,7] Pt(II) (poly)fluorido complexes were applied for catalytic hydrofluorination reactions of internal alkynes to yield selectively (*Z*)-fluoroalkenes using $Et_3N{\cdot}3HF$ as mild HF source.

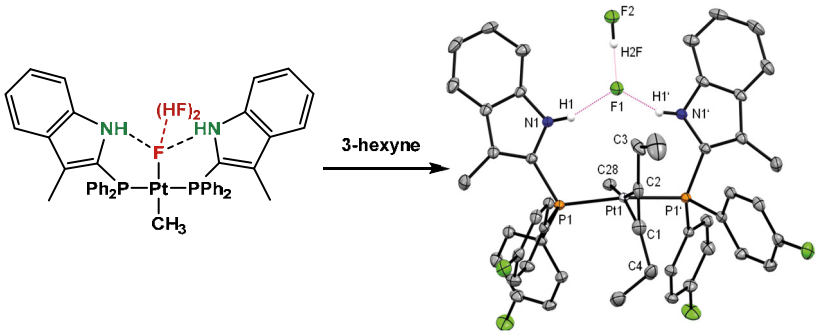


Figure 1: Coordination of an alkyne at a HF-stabilized fluorido complex.

References

[1] S. G. Rachor, R. Müller, P. Wittwer, M. Kaupp, T. Braun, *Inorg. Chem.* **2022**, *61*, 357-367.
[2] S. G. Rachor, R. Jaeger, T. Braun, *Eur. J. Inorg. Chem.* **2022**, *2022*, e20220015.
[3] S. G. Rachor, R. Müller, M. Kaupp, T. Braun, *Eur. J. Inorg. Chem.* **2023**, *26*, e202200668.
[4] S. G. Rachor, M. Ahrens, T. Braun, *Angew. Chem. Int. Ed.* **2022**, *61*, e202212858.
[5] S. Sander, R. Müller, M. Ahrens, M. Kaupp, T. Braun, *Chem. Eur. J.* **2021**, *27*, 14287-14298.
[6] S. Sander, T. Braun, *Angew. Chem. Int. Ed.* **2022**, *61*, e202204678.
[7] S. Sander, E. J. Cosgrove, R. Müller, M. Kaupp, T. Braun, *Chem. Eur. J.* **2023**, *29*, e202202768.

Novel Analytical Chemistry of Organofluorines in Complex Matrices and Overview with Environmental Case Studies

Joerg Feldmann[1], Viktoria Müller[1,2], Eleonora Matic[1], Raquel Gonzalez de Vega[1], David Clases[1]

[1]*Analytical Chemistry, University of Graz, Universitätsplatz 1, 8010 Graz, Austria*
[2]*James Hutton Institute, Craigiebuckler, Aberdeen, Scotland, UK*

E-mail: joerg.feldmann@uni-graz.at

The analysis of fluorine-containing compounds in a complex matrix such as biological and environmental as well as in processes is hampered by the fact that no routine fluorine-specific detectors for chromatography exists. Here in this lecture an overview is given about the recent development of fluorine-specific detection and its application to environmental chemistry applications.

Current routine method for the molecular determination of fluorine-containing compounds uses ^{19}F-NMR and LC-HR-MS for non-targeted analysis. ^{19}F-NMR is only applicable for high concentrations and relatively pure solutions, while LC-HR-MS can determine several F-containing compounds in a complex mixture but quantification is difficult without standards.

The detection of traces of F-containing compounds in environmental samples such as sewage water or biodegradation experiments or biological samples is difficult due to the plethora of F-containing pharmaceuticals, pesticides and PFAS. Hence, F-specific detection is desirable to find the needle in the haystack and to quantify these as well.

In this lecture the concept of sum parameters such as EOF using high-resolution graphite furnace molecular absorption spectrometry (HR GFMAS), combustion ion chromatography (CIC) and inductively-coupled plasma mass spectrometry (ICP-MS) will be explained.[1]

Furthermore, it will be explained how these fluorine-specific detectors aid in studies of organofluorines in biodegradation experiments[2] and in environmental studies such as PFAS and F-containing pharmaceuticals and pesticides in surface and sewage water[3]. Further will questions be answered which PFAS accumulate in the brains of stranded whales in Scotland, and if ski wax contaminates pristine Alpine soils.

References

[1] J. Feldmann, A. Raab, E.M. Krupp, Anal Bioanal Chem *2018,* **410**, 661-667.
[2] S. Heuckeroth, T.N. Nxumalo, A. Raab, J. Feldmann, Anal. Chem. *2021,* **93** (16), 6335-6341.
[3] T. Nxumalo, et al., Anal Bioanal Chem *2023,* **415**, 1195-1204.

Beyond Refrigerants – From ICI to Koura, an Industrial Perspective on Fluorine Chemistry

Claire N. Rees, Andrew. P. Sharratt

Koura Global, Thornton Science Park, Pool Lane, Ince, Cheshire, CH2 4NU, United Kingdom

E-mail: claire.rees@kouraglobal.com

Koura is Orbia's Fluorinated Solutions business whose fluoro-materials production heritage goes back to the 1960's when it was the fluorine division of ICI in the UK. Since this time, the company has undergone several changes in ownership and direction but has always maintained its historical R&D roots in the UK. Koura is now the only fully integrated fluoro-materials company outside of China and operates a 'mine to market' strategy. This is underpinned by its significant reserves of the key raw material CaF_2 from which a vast array of fluoroproducts are made globally via the intermediate HF - the lifeblood of the fluoro-products industry. Today, Koura is continuing to develop new products and processes in its quest to move further downstream, solving some of today's major global issues such as climate change, healthcare, and energy storage. As a result, fluorine chemists at Koura find themselves working on a diverse range of chemistries exploiting the many unique and valuable properties of fluorine.

This presentation will give an overview of Koura, what drives it, and an insight into the challenges faced by scientists working in this field. The manufacture of fluoro-materials often involves processes operating at the limits of process technology, particularly those involving anhydrous HF. In particular, it will describe how Koura's world class catalyst and process technology, originally developed for the manufacture of generation 2 refrigerants such as HFC-134a (1,1,1,2-tetrafluoroethane) as shown in Figure 1, [1] has been adapted and used for low GWP generation 3 HFO refrigerants.

Finally, an overview of the chemistry associated with new fluorinated products for application in energy materials and Li-ion batteries will be given.

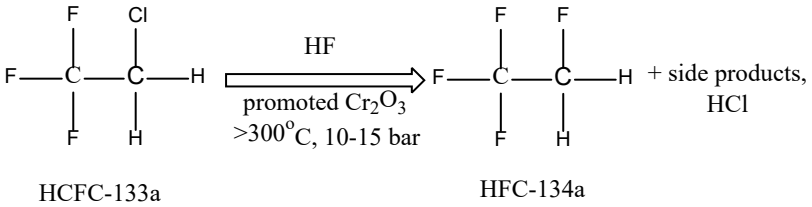


Figure 1: Example of a catalytic vapour-phase hydrofluorination reaction.

References

[1] A. P. Sharratt, *US Patent, priority 2008, Catalyst and Process Using the Catalyst,* US9556079 (B2).

DFT Calculations in the Study of Nucleophilic Fluorination Reagents. Successes and Controversies

Jaroslav Kvíčala[1], Adam Hroch[1], Michal Trojan[1], Šárka Bouzková[1], Vít Jeníček[1], Evelin Gruden[2], Gašper Tavčar[2], Markéta Rybáčková[1]

[1]*Department of Organic Chemistry, University of Chemistry and Technology, Prague, Technická 5, 166 28 Prague 6*
[2]*Department of Inorganic Chemistry and Technology, "Jožef Stefan" Institute, Jamova cesta 39, Ljubljana, Slovenia*

E-mail: kvicalaj@vscht.cz

Ab initio calculations and especially highly effective DFT methods are a powerful tool for studies of organic and inorganic structures and reaction mechanisms. During our work on new nucleophilic fluorination reagents, we employed DFT calculations in three independent studies.

First, we studied decomposition pathway to fluorosilane and ammonium fluoride of various tetramethylammonium difluorosilicates, bearing 0-3 aryl groups and 0-3 methyl groups, with aryl group modified optionally with electron-donating or electron-accepting groups. While TBAT bearing three phenyl groups is a stable and highly useful fluorination reagent, mechanism of its action is quite unknown. Moreover, structures reported by us and others as alkylaryldifluorosilicates [1,2] are highly probably erroneous and correspond to ammonium hydrogen difluorides, because their computed ^{19}F NMR values (-75 to 90 ppm) differ from the reported experimental values (-150 to 160 ppm). Calculations surprisingly imply that nucleophilic fluorination of alkyl bromides is highly endergonic process and, to proceed, must be coupled with unknown exergonic process (Figure 1).

Second, we studied equilibrium among fluoropyrrolidines and dihydropyrrolium fluorides (Scheme 1). Computations showed that for correct description, at least triple-ζ basis set has to be employed. Quite surprisingly, while computations imply that the equilibrium is shifted forward with ΔG = -12.5 kJ/mol, experimentally hydrogen difluoride **2** can be obtained only with difficulties and disproportionates readily into the mixture of **1** and **3**.

Third, decomposition of Ritter-type fluorophenoxyimidazoles to fluorophenol was studied.

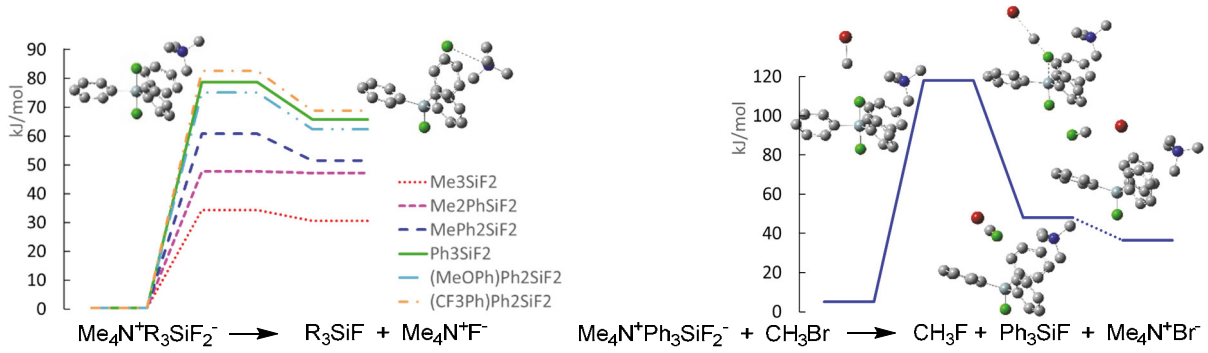
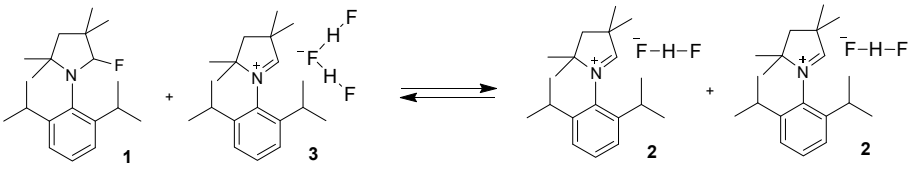
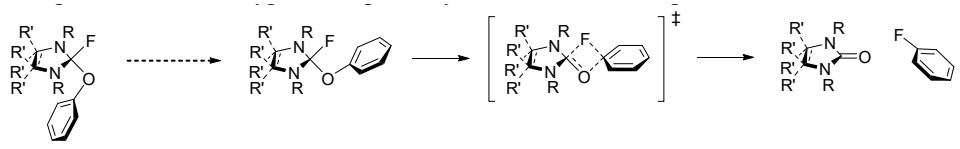


Figure 1: DFT study of difluorosilicates



Scheme 1: DFT study of isodesmic reaction among fluoropyrrolidines and dihydropyrrolium fluorides



Scheme 2: DFT study of decomposition of fluorophenoxyimidazoles

References

[1] M. Penso, D. Albanese, D. Landini, V. Lupi, *J. Mol. Catal. A Chem,* **2003**, *204-205*, 177-185.
[2] J. Kvíčala, P. Mysík, O. Paleta, *Synlett* **2001**, 547-549.

Synthesis and Reactivity of Halonium Ions

Sebastian Riedel

Institut für Chemie und Biochemie, Freie Universität Berlin, Fabeckstrasse 34/36, 14195 Berlin, Germany

E-mail: s.riedel@fu-berlin.de

Nowadays, it is well known that super acidic systems play an important role in different fields of fundamental as well as industrial chemistry. Many interesting and important reactions have been investigated in the last decades. Our group was recently involved in the preparation and investigation of novel super acidic systems. These systems have been prepared by simple one step synthesis of e.g. triethylaluminum and pentafluoroorthotelluric acid.[1,2] Depending on the stoichiometric amount of pentafluoroorthotelluric acid either the Lewis- or Brønsted-superacid can be synthesized and further used for the preparation of unusual compounds.[3-5]

Here we will present synthetic attempts to prepare fluorinated chloronium ions which can be used as alkylation reagents in organic reactions.

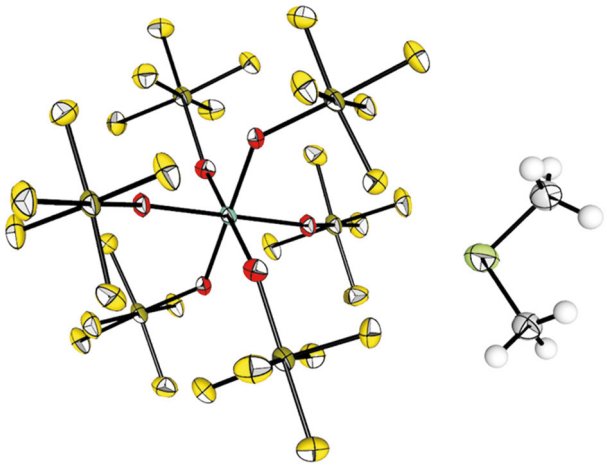


Figure 1: Structure of $[CH_3\text{-}Cl\text{-}CH_3][Sb(OTeF_5)_6]$

References

[1] K. F. Hoffmann, A. Wiesner, S. Steinhauer, S. Riedel, *Chem. Eur. J.* **2022**, *28*, e202201958.
[2] A. Wiesner, T. Gries, S. Steinhauer, H. Beckers, S. Riedel, *Angew. Chem. Int. Ed.* **2017**, *56*, 8263-8266.
[3] K. F. Hoffmann, D. Battke, P. Golz, S. M. Rupf, M. Malischewski, S. Riedel, *Angew. Chem. Int. Ed.* **2022**, *61*, e202203777.
[4] S. Hämmerling, G. Thiele, S. Steinhauer, H. Beckers, C. Müller, S. Riedel, *Angew. Chem. Int. Ed.* **2019**, *58*, 9807-9810.
[5] A. Wiesner, S. Steinhauer, H. Beckers, C. Müller, S. Riedel, *Chem. Sci.* **2018**, *9*, 7169-7173.

Main Group Fluorine Chemistry

Herbert W. Roesky, Zhi Yang

Department of Inorganic Chemistry University of Göttingen, Tammannstrasse 4, 37077 Göttingen, Germany

E-mail: hroesky@gwdg.de

In recent years my group concentrated the fluorine chemistry on the elements aluminum and silicon, due to the ubiqitous available of these elements in the earth's crust that allows a sustainable application. Moreover, we also investigated the lighter and heavier elements of these groups. For example $B(C_6F_5)_3$ is an interesting precursor for the preparation of five-membered aluminum compounds containing C_6F_5 substituents with surprising properties.

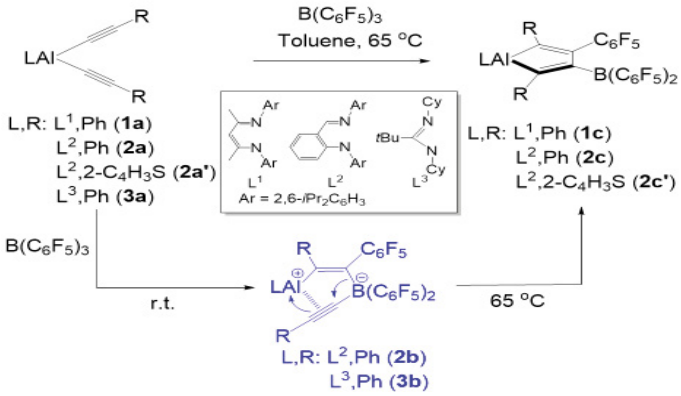


Figure 1: Preparation of five-membered Al-containing molecules.

β-Diketimine aluminum dihydride is easy converted to mono-substituted triflate species. The latter is a very interesting molecule that functions as a catalyst for various hydroboration reactions. An overview will be reported.

In silicon chemistry the para substituted F or CF_3 phenylisonitriles reacts each with two silylenes to generate the longest known C-N bond and an inverted tetrahedral carbon atom.

References

[1] B. Yan et.al. Dalton Trans, **2022**, 51, 6756-6765.
[2] C. Ni et al. Eur. J. Inorg. Chem. e202100929.
[3] J. Li et al. J.Am.Chem.Soc.**2021**, 143,8244.
[4] J. Li et al. Angew. Chem.Intern.Ed. **2020**, *59,* 10027-10031.

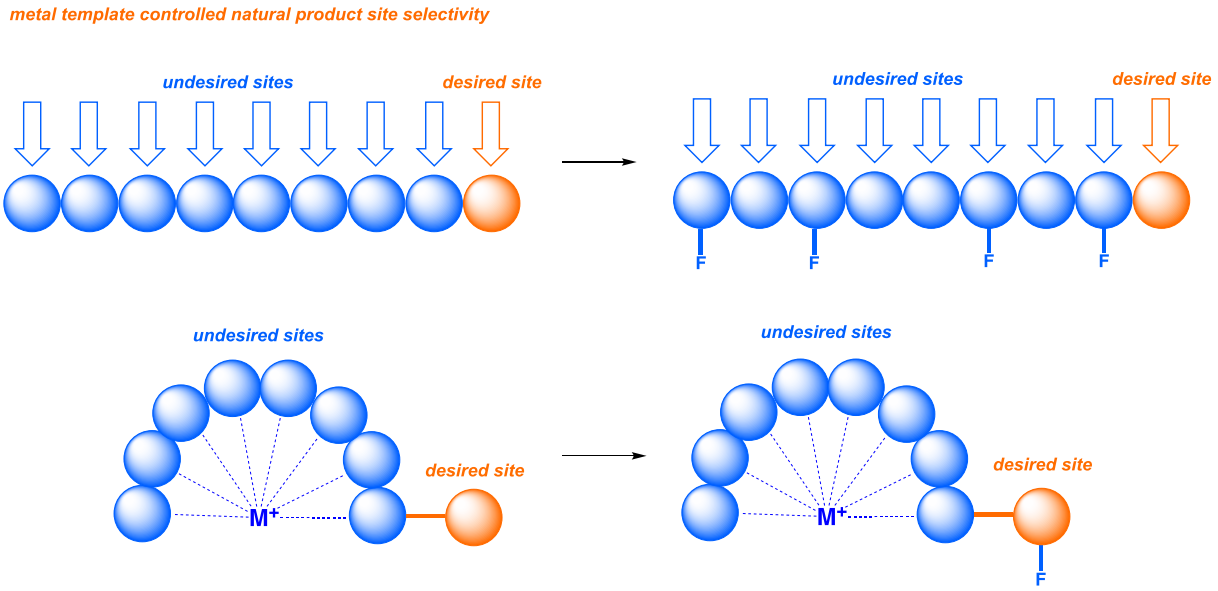
Metal Template Controlled Natural Product Site Selectivity

Thomas Lectka

Department of Chemistry, Johns Hopkins University, Baltimore, MD 21218, USA

E-mail: lectka@jhu.edu

Natural product functionalization is a complicated topic from any perspective, and combined with a radical fluorination the issue becomes especially challenging. We have recently found that the radical-based fluorination of polycyclic ionophoric natural products can be controlled by metal complexation. The metal ion deactivates unwanted sites though charge repulsion and stereoelectronic effects. The size of the metal ion is also a key factor.



Fluorochemicals with Important and Unique Applications in Electronics

Robert (Bob) G. Syvret

Fluorine Chemistry and Technology (F2ChemTech) LLC

E-mail: syvretrg@f2chemtech.com

Processing of semiconductor materials that are used in the fabrication of integrated circuits and computer chips is heavily dependent on the use of many different fluorochemical products employed at various critical stages throughout the fabrication lifecycle. For example, WF_6 is used for tungsten metal deposition; NF_3 and other fluorocarbons are used for chamber cleaning; and many different fluorocarbons, including fluoroalkanes and hydrofluorocarbons are used for various reactive-ion etching steps that collectively create the intricate electronic circuitry on a silicon wafer that results in a computer chip.

Beyond the "common" fluorochemicals traditionally used in electronics materials processing, there are a number of less common and/or emerging fluorochemicals currently under development for specific and unique applications that are enabling the continued advancement of semiconductor technology. Some of these recent advances will be highlighted in this presentation.

New Synthetic Route for a Perfluorinated Cyclic Sulfone and the Use of Perfluoro(2-propoxypropyl vinyl ether)

Gerd-Volker Röschenthaler[1], Sergey N. Tverdomed[1], Markus E. Hirschberg[2], Romana Pajkert[1], Klaus Hintzer[2]

[1]*Life Sciences & Chemistry, Jacobs University Bremen, Bremen, Germany*
[2,3]*M Advanced Materials Division, Dyneon GmbH, Burgkirchen, Germany*

E-mail: groeschenthaler@constructor.university

Previously unknown γ-fluorosulfonyl perfluoro-butanoic acid derivatives are undergoing thermal decarboxylation accompanied by the formation of a perfluorinated cyclic sulfone.[1] For the first time, parallel processes of decarboxylation and desulfonylation in one molecule were observed. In addition, the reversibility of the alkaline alcoholysis of perfluorocarbonyl fluorides and the possibility of their generation by the reaction of alkali metal carboxylates with inorganic fluorides under higher temperatures are presented. The reaction conditions, factors affecting reactivity and regioselectivity of the thermolysis process, as well as the pathways of main and side reactions are discussed. Furthermore the application of perfluoro(2-propoxypropyl vinyl ether) (PPVE-2) in the synthesis of perfluoro(propyl vinyl ether) (PPVE-1) is disclosed.[2-4]

References

[1] S. N. Tverdomed, M. E. Hirschberg, R. Pajkert, K. Hintzer, G.-V. Röschenthaler, *J. Fluorine Chem.,* **2020**, *233*, 109500.
[2] S. N. Tverdomed, M. E. Hirschberg, R. Pajkert, K. Hintzer, S. M. Smith, G.-V. Röschenthaler, *J. Fluorine Chem.,* **2020**, *233*,109508.
[3] K. Hintzer, M. Hirschberg, S. Tverdomed, R. Pajkert, G.-V. Röschenthaler (3M Dyneon, Burgkirchen), WO 2017112629 (A1), WO 2018211457 A2, EP 3394021 (A1) JP 2019500373 (A), US 2018370888.
[4] M. E. Hirschberg, K. Hintzer, W. M. Lamanna, S. M. Smith, G.-V. Röschenthaler, R. Pajkert, S. N Tverdomed, (3M Dyneon, Burgkirchen), WO 2019123342 A1, CN 111511711 A, EP 3728177 A1, US 20210070686 A1.

Enantioselective Synthesis of Trifluoromethylated Nitrogen-containing Compounds

Takahiko Akiyama

Department of Chemistry, Gakushuin University, Mejiro, Toshima-ku, Tokyo, JAPAN

E-mail: takahiko.akiyama@gakushuin.ac.jp

Construction of trifluoromethylated nitrogen-containing compounds in optically pure form continues to be an important issue in organic synthesis because of its interesting biological activity. As part of our continued interest in the chiral phosphoric acid catalysis, we wish to discuss enantioselective synthesis of trifluoromethylated nitrogen-containing compounds using chiral phosphoric acid as acid catalyst.

1. Friedel-Crafts alkylation of trifluoromethylated *N*-H ketimines with heteroarenes Trifluoromethylated *N*-H ketimines are known to be relatively stable among *N*-H ketimines. Nucleophilic addition toward trifluoromethyl *N*-H ketimine will provide straightforward method for the preparation of α-trifluoromethylated *N*-free amines because deprotection of the *N*-protecting group is obviated. We investigated Friedel-Crafts alkylation reaction of heteroarenes, such as indole and pyrrole, with trifluoromethylated *N*-H ketimines by means of chiral phosphoric acid. Corresponding α-trifluoromethylated amines were obtained in good yields and with good to excellent enantioselectivity (Figure 1-1).[1,2,3]

2. Friedel-Crafts alkylation of trifluoromethylated nitroalkenes with heteroarenes

We already reported Friedel-Crafts alkylation of indole with nitrostyrenes by means of chiral phosphoric acid.[4] CF_3-substituted nitroalkene was studied in combination with chiral phosphoric acid. Although chiral phosphoric acid itself was not effective, chiral calcium phosphate promoted the Friedel-Crafts alkylation reaction with indoles and pyrroles smoothly to give the adducts with high to excellent optical purity.[5,6]

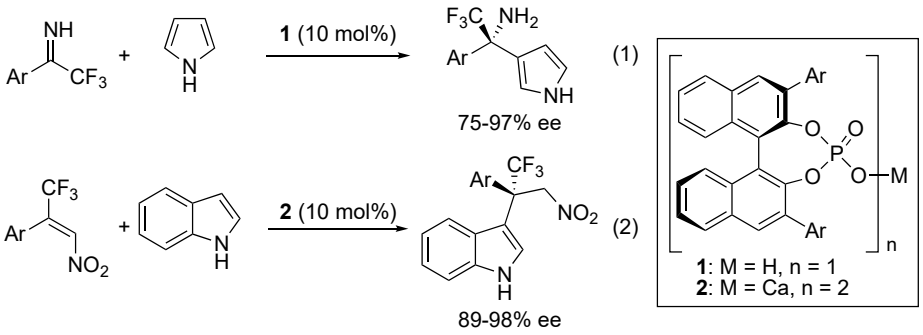


Figure 1: Friedel-Crafts alkylation reaction with heteroarenes

We will also discuss C-F bond activation reaction in the lecture.

References

[1] M. Miyagawa, M. Yoshida, Y. Kiyota, T. Akiyama, *Chem. Eur. J.* **2019**, *25*, 5677-5681.
[2] T. Uchikura, R. Suzuki, Y. Suda, T. Akiyama, *ChemCatChem* **2020**, *12*, 4784-4787.
[3] T. Uchikura, K. Aruga, R. Suzuki, T. Akiyama, *Org. Lett.* **2022**, *24*, 4699-4703.
[4] K. Mori, M. Wakazawa, T. Akiyama, *Chem. Sci.* **2014**, *5*, 1799-1803.
[5] I. Ibánez, M. Kaneko, Y. Kamei, R. Tsutsumi, M. Yamanaka, T. Akiyama, *ACS Catal.* **2019**, *9*, 6903-6909.
[6] T. Uchikura, S. Yokohama, M. Murakami, T. Akiyama, *Synthesis* **2022**, *54*, 3793-3800.

Light-mediated Perfluoroakylations of Alkenes and Alkynes

Jean-Marc Vincent

Institute of Molecular Sciences, University of Bordeaux –CNRS, 351 Crs de la libération, Talence, France

E-mail: jean-marc.vincent@u-bordeaux.fr

In the lecture, studies on the development of light-promoted radical processes for the trifluoromethylation and iodoperfluoroalkylations of non-activated terminal olefins will be presented. We will show that combinations of benzophenone or copper(II)/benzophenone with UVA and hydroalcoholic solvents are particularly effective to perform iodoperfluoroalkylations of alkenes/alkynes,[1] or to catalyze Heck-type trifluoromethylation of olefins.[2] The beneficial effect of catalytic amounts of chloride ions (NaCl) to promote the iodoperfluoroalkylation of alkenes/alkynes will also be described, with particular emphasis on the implication of halogen bonding to facilitate the direct photolysis of the RCF_2–I bond.[3]

References

[1] a) R. Beniazza, M. Douarre, D. Lastécouères, J.-M. Vincent, *Chem. Commun.* **2017**, *53*, 3547-3550, b) R. Beniazza, R. Atkinson, C. Absalon, F. Castet, S. A. Denisov, N. D. McClenaghan, D. Lastécouères, J.-M. Vincent, *Adv. Synth. Catal*. **2016**, *358*, 2949-2961.

[2] R. Beniazza, F. Molton, C. Duboc, A. Tron, N. D. McClenaghan, D. Lastécouères, J.-M. Vincent, *Chem. Commun.* **2015**, *51*, 9571-9574.

[3] R. Beniazza, L. Remisse, D. Jardel, D. Lastécouères, J.-M. Vincent, *Chem. Commun.* **2018**, *54*, 7451-7454.

Regioselectivity of Catalyst Free *N*-Arylation Reactions of Fluorobenzenes

Frederik Diness[1,2], Sergey Nikitin[1,2], Morten P. Meldal[1], Jonas Hansen[1], Niklas H. Fischer[1,2]

[1]*Department of Chemistry, University of Copenhagen, Universitetsparken 5, DK-2100 Copenhagen, Denmark*
[2]*Faculty of Natural Science and Environment, Roskilde University, Universitetsparken 1, DK-4000 Roskilde, Denmark*

E-mail: diness@ruc.dk

Arylation reactions of heteroatoms are essential organic chemical transformations. Commonly, these are carried out through transition-metal catalyzed cross coupling reactions. Albeit, cross couplings have some drawbacks as these are costly, oxygen sensitive and may leave toxic metal contaminants in the products. As an alternative, we have explored catalyst-free arylation by S_NAr reactions of fluorobenzene derivatives [1] with regard to scope, mechanism and applications [2,3,4,5]. Here we present our recent results of exploring the chemo- and regio-selectivity of these reactions when applying derivatives with multiple halogen substituents. This includes using ^{19}F-NMR spectroscopy for mapping the balance between the inductive withdrawing effect and the π-donating effect of substituents as well as the impact of their steric hindrance.

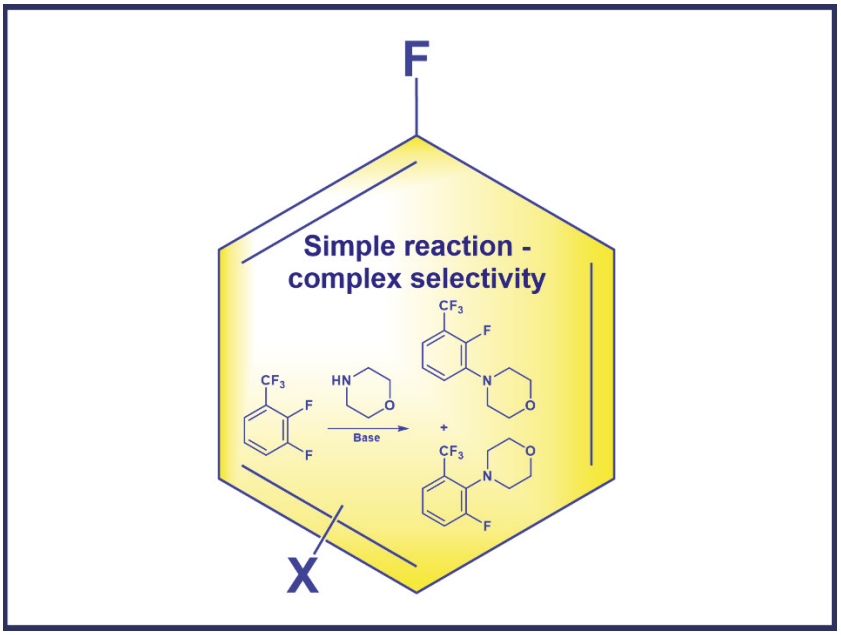


Figure 1: Products from a S_NAr reaction of 2,3-difluorobenzotrifluoride.

References

[1] H. Amii, K. Uneyama, *Chem. Rev.* **2009**, *106*, 2119
[2] F. Diness, D. P. Fairlie, *Angew. Chem. Int. Ed.* **2012**, 51, 8012
[3] F. Diness, M. Begtrup, *Org. Lett.* **2014**, *16*, 3130
[4] C B. Jacobsen, M. Meldal, F. Diness, *Chem. Eur. J.* **2017**, *23*, 846
[5] A. M. Embaby, S. Schoffelen, C. Kofoed, M. Meldal, F. Diness, *Angew. Chem. Int. Ed.* **2018**, *57*, 8022

Diversely Substituted Fluorinated Heterocycles Syntheses from Alkyne/Carbonyl Bifunctional Reagent

Roman Dembinski[1, 2]

[1]*Oakland University, Department of Chemistry, Rochester, Michigan 48309, USA*
[2]*Centre of Molecular and Macromolecular Studies, Polish Academy of Sciences, Division of Bioorganic Chemistry, 90-363 Łódź, Poland*

E-mail: dembinsk@oakland.edu

To incorporate fluorine into five- and seven-membered heterocyclic compounds, we accomplished developing their synthetic methods.The application of 1,4-disubstituted but-3-yn-1-ones as starting materials for the synthesis of fluoro-furans, bromo-fluoro-furans, iodo-fluorofurans, fluoro-benzodiazapines, will be summarized. The outcomes of these processes were confirmed by the X-ray structure determination (Figure 1).

In particular, the reaction of a bifunctional reagent, alk-3-yn-1-one, with *o*-phenylenediamine provides an effective synthetic method with high atom economy for the preparation of diversely substituted 3-fluoro-1,5-benzodiazepines. The reaction initially leads to the formation of conjugated enaminone (3-amino-2-alkenone), at room temperature, which constitutes a formal non-catalyzed hydroamination of the non-conjugated alkyne. The microwave-accelerated cascade reaction of *o*-phenylenediamines with fluoroalkynones in ethanol and the intramolecular cyclization of intermediate enaminones in ethanol/acetic acid lead to 3-fluoro-substituted 1,5-benzodiazepines with good yields. Aryl and methylene-aryl substituents are installed at C-2 and C-4 leading to non-symmetrical structures.

The results of this work provide new preparative avenues for reactions leading to diverse heterocycles with a fluorine substituent that are difficult to introduce by other means. Protocols with mild and environmentally friendly reaction conditions were elaborated.

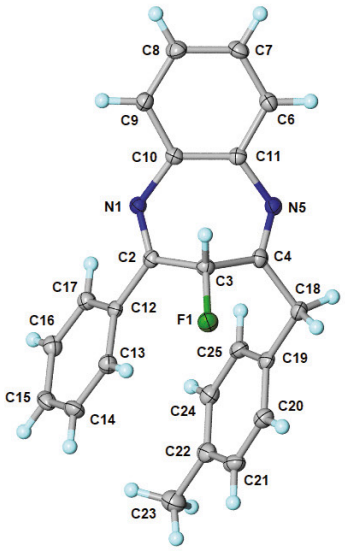


Figure 1: X-ray structure of 3-fluoro-substituted 1,5-benzodiazepine.

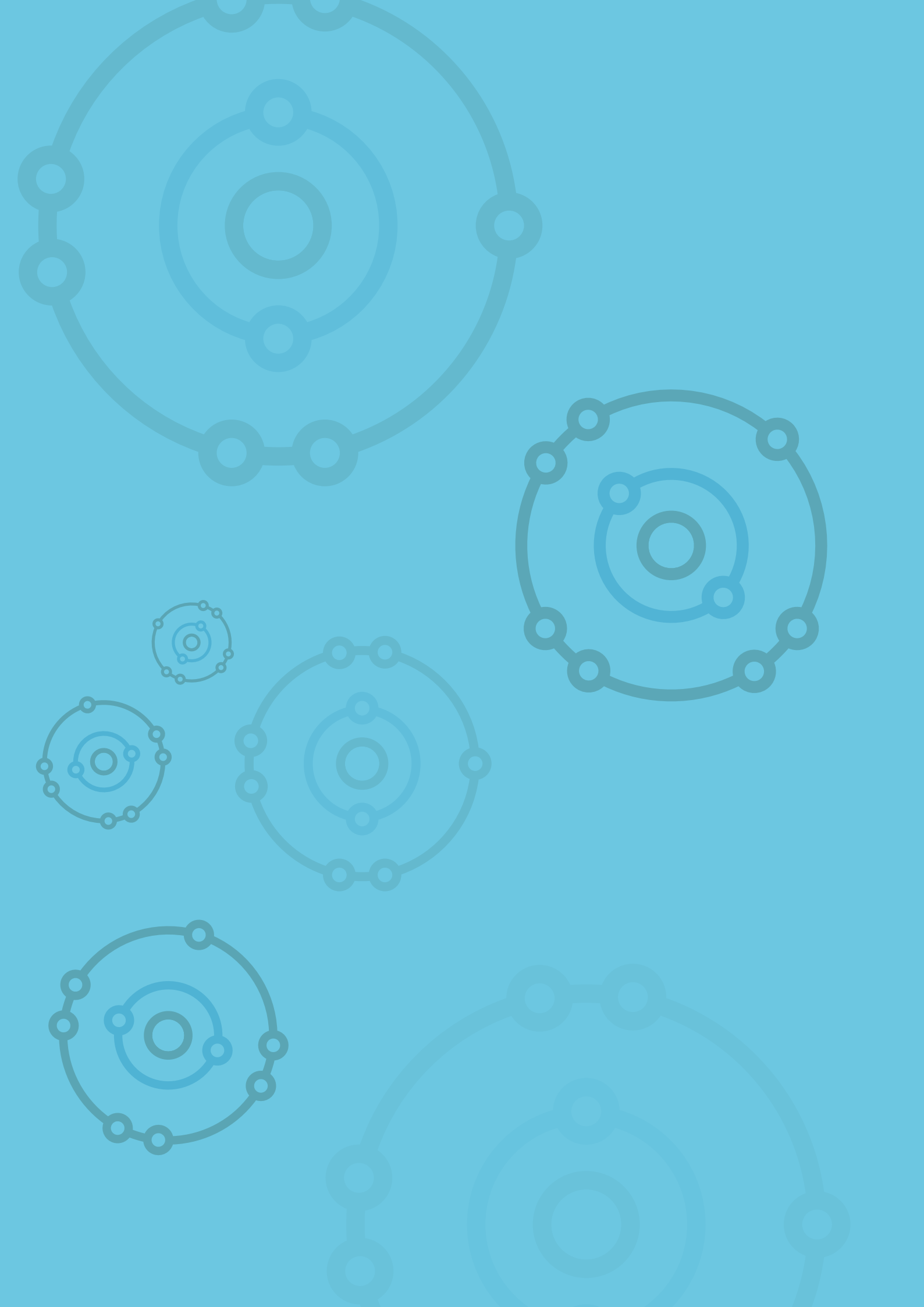
Compilation of the Industrial Usage of Fluorinated Products and Materials in the Past and Today

Rudi H. Feist

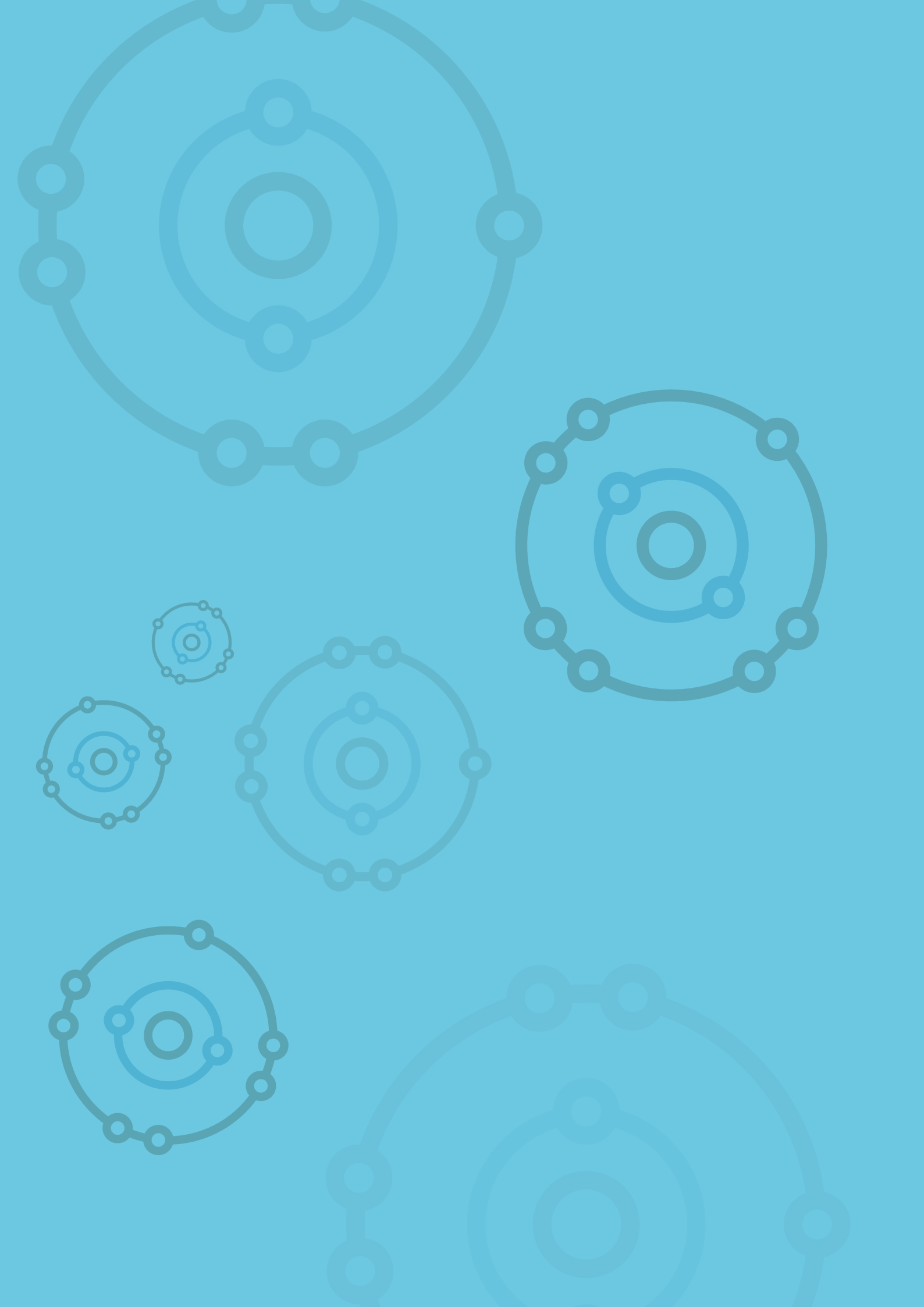
FLCI Sp.zo.o.

Rudi.feist@fluorochemika.pl

Unique properties of fluorinated products and materials being widely used for the manufacture of many products and materials like but not limited to polymers, pharmaceuticals, Lithium-ion batteries, semiconductors, oil- and gas exploration products and many further applications are based on their high electronegativity, stability and reactivity. While PFAS is controversially discussed Fluorine and fluorinated materials are and will remain essential for many products and applications. A review of such products and applications is provided.



LECTURES



Design of Fluorinated, Liquid Crystal-inspired Monolayers for Memory and Neuromorphic Computing

Peer Kirsch[1,2]

[1]*Merck Electronics KGaA, Frankfurter Str. 250, 64293 Darmstadt, Germany*
[2]*Department of Materials Science, Technical University of Darmstadt, Alarich-Weiss-Str. 2D, 64287 Darmstadt, Germany*

E-mail: peer.kirsch@merckgroup.com

Tunnel junctions based on fluorinated, liquid crystal-inspired self-assembled monolayers (SAM) show bistable and reversible resistance switching [1]. The monolayers are composed of phosphonic acids carrying a 2,3-difluorophenylene unit which is rotated by the application of an external electrical field, affecting a large change in tunnel current (Figure 1). SAMs with phosphonic acid anchoring groups can be easily grafted on TiN electrodes, and the resulting organic-inorganic hybrid devices show high thermal stability [2].
Originally, this technology was developed for non-volatile memory, but it also has potential for application in neuromorphic computing. Fabrication and processing of SAM-based devices is extremely simple since the complexity of their functionality can be designed into the molecular building blocks. Whereas the first generation of devices exhibited a very noisy electrical current-voltage characteristics, the design of a new molecular scaffold resulted in clean and reversible resistance switching, which is potentially suitable for multi-level or even analog operation. Future activities are directed towards integrating SAM-based tunnel junctions into neuromorphic computational architectures.

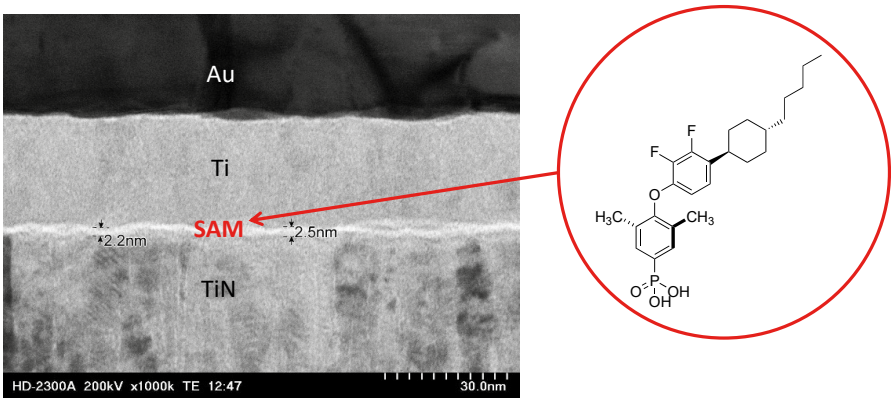


Figure 1: STEM micrograph of a cross section through a solid state tunnel junction (TiN/**SAM**/Ti/Au) containing a SAM composed of a dipolar phosphonic acid.

References

[1] J. M. Dlugosch, H. Seim, A. Bora, T. Kamiyama, I. Lieberman, F. May, F. Müller-Plathe, A. Nefedov, S. Prasad, S. Resch, K. Saller, C. Seim, M. Speckbacher, F. Voges, M. Tornow, P. Kirsch, *ACS Adv. Mater. Interfaces* **2022**, *14*, 31044-31053.
[2] X. Wan, I. Lieberman, A. Asyuda, S. Resch, H. Seim, P. Kirsch, M. Zharnikov, *J. Phys. Chem. C* **2020**, *124*, 2531-2542.

Mechanisms and Kinetics for the Decomposition Reaction of 1,3-Dioxo-2-difluoromethylene-4-trifluoromethoxy-5-difluoroammonium Acetate Dioxole

Ivan Diego Wlassics, Silvia Grossi, Domenico Giovinazzo, Stefano Millefanti

Solvay Specialty Polymers – Italy; Viale Lombardia, 20; 20021 Bollate (MI) - ITALY

ivan.wlassics@solvay.com

Recently, there has been a great strive to find new and efficient methods for the degradation or mineralization of perfluorinated alkylated substances[1,2,3,4].

In this research work, we present recent advancements and results in the mineralization of the surfactant "*c*-C_6O_4" (**I**) (1,3-dioxo-2-difluoromethylene-4-trifluoromethoxy-5-difluoroammonium acetate dioxole) which demonstrate that it can be efficiently degraded at 20°C.

The results of the DMSO induced decomposition, an innovative chemical strategy at mild temperatures, which decomposed and mineralized *c*-C_6O_4 **(I)** to CO_2 + HF/F^-, in many cases ≥ 99 mol%, will be discussed. All results will be supported by the respective kinetics, rates of reaction, thermodynamic reaction parameters, mechanisms of reaction, and decomposition products.

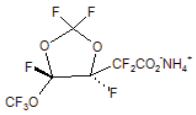


Figure 1: *c*C_6O_4 **(I)**

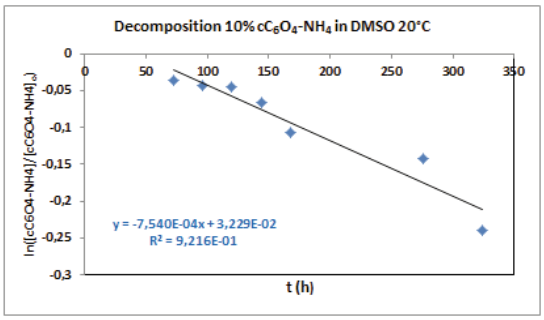


Figure 2: DMSO-induced decomposition of 10% cC_6O_4

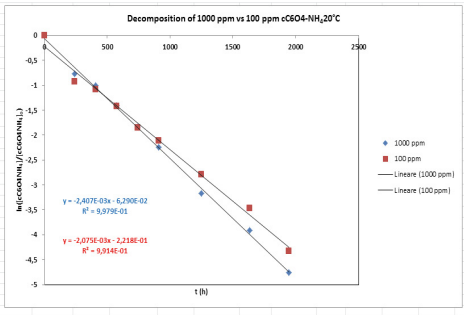


Figure 3: DMSO-induced decomposition of 100 ppm *c*C_6O_4

References

[1] A. Berham, I. Mutanda, J. Taolin, M.A. Qaria; Science of the Total Environment **2023**, *859*, 160010-160025.
[2] B. Cantoni, A. Turolla, J. Wellmitz, A.S. Ruhl, M. Antionelli; Science of the Total Environment **2021**, *795*, 148821-148832.
[3] L. Chu, C. Zhang, P. Chen, Q. Chu, X. Zhou, Y. Zhang; J. Water Process Engineering **2022**, *49*, 103070-103080.
[4] R. Daily, D. Minakata; Env. Sci. Water Res. Technol. **2022**, *8*, 543-574.

Establishing Fluorine-containing Amino Acids as an Orthogonal Tool in Peptide SelfAssembly

Thomas Hohmann, Beate Koksch

Institute of Chemistry and Biochemistry, Freie Universität Berlin, Arnimallee 20, 14195 Berlin, Germany

E-mail: thho@zedat.fu-berlin.de

The αhelical coiled coil (CC) is one of the best characterized and most widely applied protein motifs. CCs play an important role in many areas of peptide and protein chemistry, such as protein-protein interactions, intracellular transport, and the formation of supramolecular structures.[1,2] In this context, control of the CC assembly process is of crucial importance. Here, we demonstrate that fluorinated amino acids can be used as an orthogonal tool to control peptide self-assembly.[3] First, a combinatorial peptide library was studied with regard to thermal stability, oligomerization state, and orientation of each CC pair. These data formed the basis for a rational design approach to fluorinedirected peptide self-assembly. We could demonstrate that the formation of coiled coil dimers can be turned on and off depending on the stereochemistry of the specific fluorinated amino acid used in the hydrophobic core (Figure 1). This work demonstrates the exquisite specificity of interaction between fluorinated aliphatic amino acids to rationally control peptide self-assembly, providing a further tool, besides electrostatic and hydrophobic interactions, used by nature to direct and tune peptidepeptide interactions.

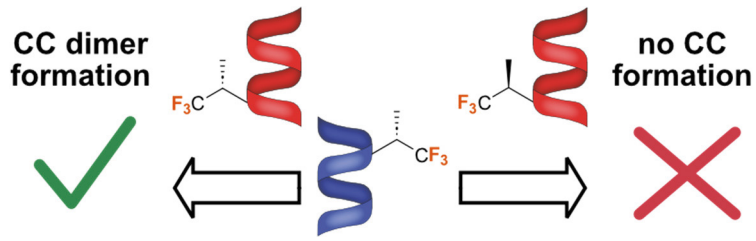


Figure 1: Fluorineinduced formation of coiled coil dimers.

References

[1] A. N. Lupas, J. Bassler, *Trends in Biochemical Sciences* **2017**, *42*, 130-140.
[2] D. N. Woolfson, G. J. Bartlett, M. Bruning, A. R. Thomson, *Curr. Opin. Struct. Biol.* **2012**, *22*, 432-441.
[3] T. Hohmann, P. Dubatouka, K. Pfeifer, B. Koksch, *Biomacromolecules* **2023**, *submitted*.

Improved Synthesis of 3′-Azido-2′,3′-dideoxy-5-fluorouridine and its Highly Cytotoxic 1,2,3-Triazole Conjugates with Cinchona Alkaloids

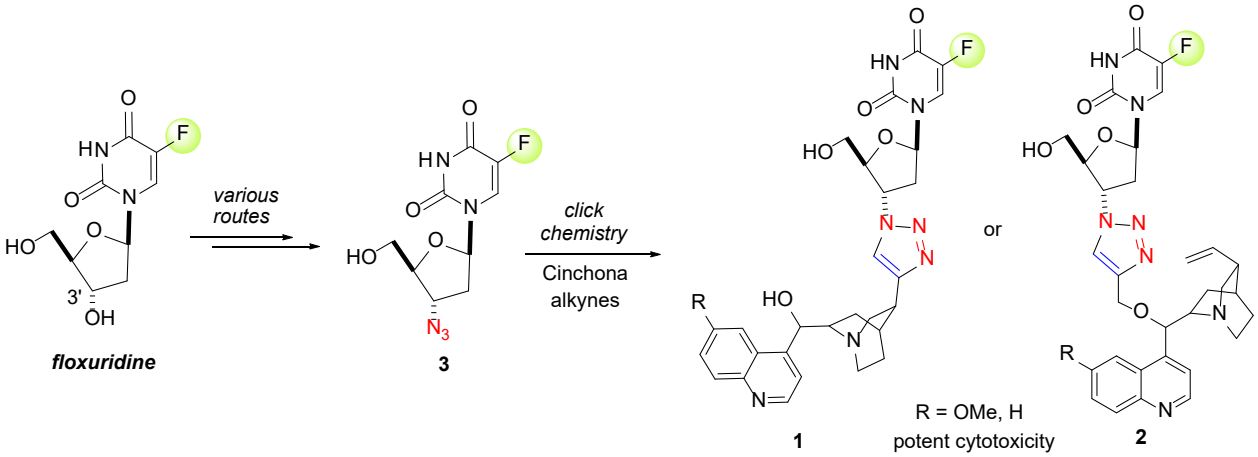
Karol M. Kacprzak[1], Lech Celewicz[1] and Piotr Ruszkowski[2]

[1]*Faculty of Chemistry, Department of Medicinal Chemistry, A. Mickiewicz University, ul. Uniwersytetu Poznańskiego 8, 61-614 Poznań, Poland*
[2]*Department of Pharmacology, Poznan University of Medical Sciences, Rokietnicka St 5a, 60-806 Poznan, Poland*

E-mail: Karol.kacprzak@gmail.com

Few years ago we began a research project comprising click chemistry conjugation of some azido-nucleosides with various alkynes toward new cytotoxic leads [1-3]. Among them we shown that AZT underwent easy click conjugation with either 10,11-didehydrocinchona alkaloids and 9-*O*-propargylcinchona ethers and resultant 1,2,3-triazoles exhibited remarkable level of cytotoxicity [1]. Replacement of AZT for 3'-azido-2',3'-dideoxy-5-fluorouridine (derivative of well-known drug floxuridine) led to strong increase of the cytotoxicity of the respective 1,2,3-triazoles **1** and **2** [2].

To assess in detail the commercial value of such conjugates, an easy access to 3'-azido-2',3'-dideoxy-5-fluorouridine **3** was mandatory and the completed optimization of its synthesis toward practical and scalable route will be presented (Scheme 1). On the other hand cytotoxic activity of best conjugates and their water soluble salts has also been screened on the panel of 9 common cancer cell lines. It was found that MCF-7, HeLa, K562, Caki1, HT1376, KATO i HCT116 lines were the most sensitive for conjugates action. In most cases conjugates were much more active than cytarabine drug used as a reference. SAR studies of conjugates will also be presented.



Scheme 1: General route to 1,2,3-triazole conjugates of 3'-azido-2',3'-dideoxy-5-fluorouridine and *Cinchona* alkaloid alkynes.

References

[1] B. Baraniak, K. Kacprzak, L. Celewicz Bioorg. Med. Chem. Lett., **2011**, *21*, 723-726.
[2] L. Celewicz, K. Kacprzak, P. Ruszkowski, D. Baraniak, M. Lewandowska, **2014**, PCT/PL2014/050009, USA pat. US9,388,209 B2, Jp. pat., 5894350, Canada pat. 2,887,039,
[3] M. Lewandowska, P. Ruszkowski, K. Chojnacka, N. Kleczewska, M. Hoffmann, K. Kacprzak, L. Celewicz, Bioorg. Med. Chem. **2016**, *24*, 2330-2341

Amino Acids with Fluorinated Olefinic Motif – Building Blocks for Peptide's Isosteres

Katarzyna Koroniak-Szejn, Katarzyna Salamon-Krokosz, Karolina Paszek, Henryk Koroniak

Faculty of Chemistry, Adam Mickiewicz University, Uniwersytetu Poznańskiego 8, 61-614 Poznań, Poland

E-mail: katarzyna.koroniak@amu.edu.pl

Peptide's isosters are compounds derived from peptides and obtained by structure modification using unnatural amino acids and/or conformational restraints. Modified fluorinated amino acids are of great interest as the building blocks for the preparation of peptidomimetics. Herein we would like to report the synthesis of fluorinated analogues of amino acids bearing olefinic moiety with the use of the synthetic sequence with Horner-Wadsworth-Emmons reaction as a key reaction. We have synthesized the examples of amino acids bearing monofluorovinyl moiety and interestingly we've found out that the cyclization of obtained products to yield fluorinated lactams proceeds easily in all studied cases (Fig.1). [1] Additionally we are studying the synthetic route for the preparation of analogous of amino acids bearing trifluorometylated olefinic moiety with the use of $TMSCF_3$ (Ruppert-Prakash reagent).

Organic compounds bearing fluorinated moiety have many favorable and unique physicochemical and biochemical properties that play a key role in materials engineering, agrochemistry and the pharmaceutical industry.[2]

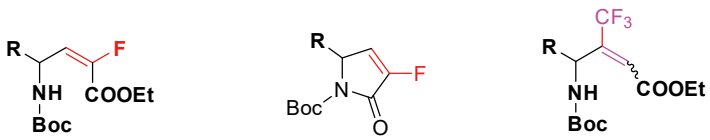


Figure 1. Fluorinated amino acids derivatives with olefinic moiety

References

[1] K. Salamon-Krokosz, M. Gołdyn, T. Siodła, E. Bartoszak-Adamska, H. Koroniak, K. Koroniak-Szejn, *Synthesis* **2022**, *54* (17): 3785-3792.
[2] R. Filler, Y. Kobayashi, L. M. Yagupolskii, *Organofluorine Compounds in Medicinal Chemistry and Biomedical Applications*; Elsevier: Amsterdam, **1993**.

Plasmachemical Syntheses of Binary Hexafluorides

Florian Kraus[1], Björn Koch[1], Tobias Chemnitz[2], Winfried Petry[2]

[1]*Fachbereich Chemie, Philipps-Universität Marburg, Hans-Meerwein-Str. 4, 35032 Marburg, Germany*
[2]*Forschungs-Neutronenquelle Heinz Maier-Leibnitz, TU München, Lichtenbergstraße 1, 85748 Garching, Germany*

E-mail: f.kraus@uni-marburg.de

Starting from the respective metal, we have synthesized the binary hexafluorides MF_6 of M = Mo, Os, Ir, Te, and U by the use of a remote fluorine plasma source using a mixture of Ar and NF_3 as the feed gas. The formation of the binary hexafluorides was confirmed by several different spectroscopic methods including IR, Raman, UV/VIS, and NMR spectroscopy.[1]

However, we could not synthesize the much more reactive hexafluorides MF_6 of M = Ru, Rh, and Pt. The syntheses of the hexafluorides RuF_6, RhF_6, and PtF_6 usually require very sophisticated methods and prove to be experimentally quite challenging. One preparation method is based on burning these metals in the form of powder or thin filaments in an atmosphere of elemental fluorine in a quartz reactor cooled with liquid nitrogen.[2–4] Another way of obtaining them is by burning the respective metal powders in a special designed autoclave at high temperature and pressure.[5]

These hexafluorides have not been accessible by the plasmachemical process described previously,[1] as the accessible temperature range proved to be too low. This obstacle could be overcome by the introduction of a laser-based heating system, which allows for a selective heating of the substrate material up to 1200 °C. At the same time, the reaction chamber can be held at a temperature below 100 °C which prevents corrosion.

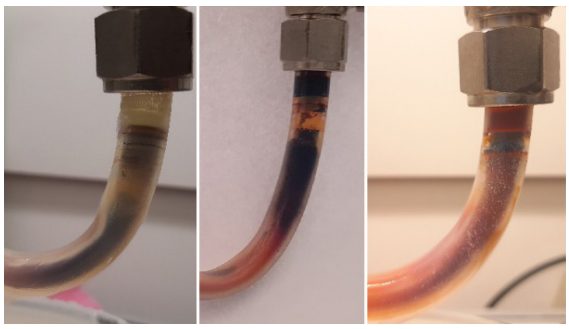


Figure 1: Photographs of RuF_6, RhF_6, and PtF_6.

References

[1] T. Chemnitz, M. R. Buchner, W. Petry, F. Kraus, *J. Fluorine Chem.* **2021**, *249*, 109862.
[2] H. H. Claassen, H. Selig, J. G. Malm, C. L. Chernick, B. Weinstock, *J. Am. Chem. Soc.* **1961**, *83*, 2390–2391.
[3] C. L. Chernick, H. H. Claassen, B. Weinstock, *J. Am. Chem. Soc.* **1961**, *83*, 3165–3166.
[4] B. Weinstock, H. H. Claassen, J. G. Malm, *J. Am. Chem. Soc.* **1957**, *79*, 5832–5832.
[5] A. K. Brisdon, P. J. Jones, W. Levason, J. S. Ogden, J. H. Holloway, E. G. Hope, G. Stanger, *J. Chem. Soc. Dalton Trans.* **1990**, 715–718.

Beyond SuFEx - Synthesis and Transformation of Sulfonyl Fluorides and Related Systems

Michał Barbasiewicz

Faculty of Chemistry, University of Warsaw, Pasteura 1, 02-093 Warsaw, Poland

E-mail: barbasiewicz@chem.uw.edu.pl

Invention of the 'click'-type and bioortogonal reactions was recognized in 2022 with Nobel Prize in Chemistry, awarded to Sharpless, Meldal and Bertozzi. After the 'first generation' azide-alkyne cycloadditions, a much broader concept of SuFEx − sulfur(VI) fluoride exchange reaction was formulated[1], and developed.[2] Unique properties of the parent class of sulfonyl fluorides combine stability and reactivity, which can be triggered on demand with activators, such as amidine bases, proton donors and silicon centers.

Following the interest our group explores synthesis[3,4] and transformations[5,6] of sulfonyl compounds. Recently, we developed olefination reaction, in which methanedisulfonyl fluoride reacts with aldehydes, giving βarylethenesulfonyl fluorides.[4] Further transformations of the latter in a stereo-controlled manner is now being explored (Figure 1).[6]

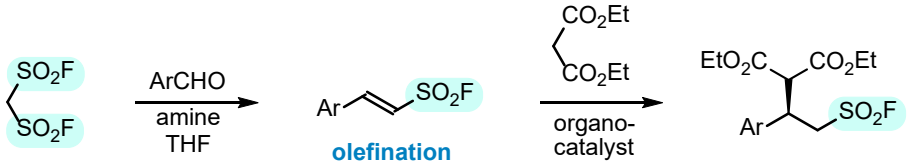


Figure 1: Synthesis and Michael-type addition to β-arylethenesulfonyl fluoride.

Interestingly, recent observations suggest that fluorocarbonyl compounds may display complementary reactivity, expanding set of well-addressable coupling reactions to increase molecular complexity.[7-9]

The project is financed from NCN, Poland (DEC-2018/31/B/ST5/01118).

References

[1] J. Dong, L. Krasnova, M. G. Finn, K. B. Sharpless, *Angew. Chem. Int. Ed.* **2014**, *53*, 9430-9448.
[2] T. Shing- Bong Lou, M. C. Willis, *Nature Chem Rev.* **2022**, *6*, 146-162.
[3] A. Talko, M. Barbasiewicz, *ACS Sustainable Chem. Eng.* **2018**, *6*, 6693-6701.
[4] A. Talko, D. Antoniak, M. Barbasiewicz, *Synthesis*, **2019**, 51, 2278-2286.
[5] M. Tryniszewski, D. Basiak, M. Barbasiewicz, *Org. Lett.*, **2022**, *24*, 4270-4274.
[6] M. Kopyt, M. Tryniszewski, M. Barbasiewicz, P. Kwiatkowski, in preparation.
[7] M. Tryniszewski, M. Barbasiewicz, *Synthesis*, **2022**, *54*, 1446-1460.
[8] J. Nowak, M. Tryniszewski, M. Barbasiewicz, in preparation.
[9] J. Dudziński, D. Antoniak, M. Barbasiewicz, in preparation.

Deoxyfluorination of Electron-deficient Phenols

Jan Jelen[1,2], Gašper Tavčar[1,2]

[1]Department of Inorganic Chemistry and Technology, Jožef Stefan Institute, Jamova cesta 39, 1000 Ljubljana, Slovenia
[2]Jožef Stefan International Postgraduate School, Jamova 39, 1000 Ljubljana, Slovenia

E-mail: jan.jelen@ijs.si

One of the promising methods developed in last decade for installing a C-F bond is deoxyfluorination, a nucleophilic substitution reaction between hydroxyl group and fluoride, since it uses readily available alcohols, phenols and carboxylic acids as starting materials [1,2,3]. In this study, we report a facile synthesis of 2-chloro-1,3-bis(2,6-diisopropylphenyl)imidazolium moiety, a crucial component in deoxyfluorination of phenols [1], by a one-step chlorination of readily available 2H-1,3-bis(2,6-diisopropylphenyl)imidazolium chloride using hypochlorite as chlorinating agent in aqueous media under ambient conditions (Scheme 1). Previous synthetic methods rely on a two-step chlorination via NHC intermediate using anhydrous solvents in an inert environment [1,2]. In addition, an air-stable and moisture-insensitive deoxyfluorination reagent based on poly[hydrogen fluoride] salt is presented, capable of converting electron-deficient phenols or aryl silyl ethers into corresponding aryl fluorides in the presence of DBU as a base, demonstrated on a broad substrate scope with good to excellent yields and high functional group tolerance. Work is summarized in Figure 1.

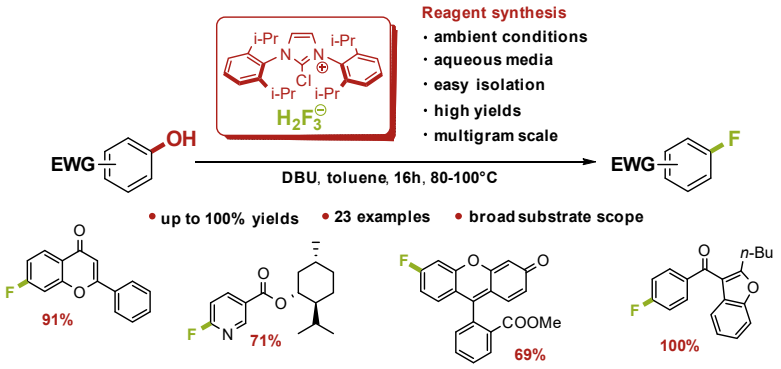
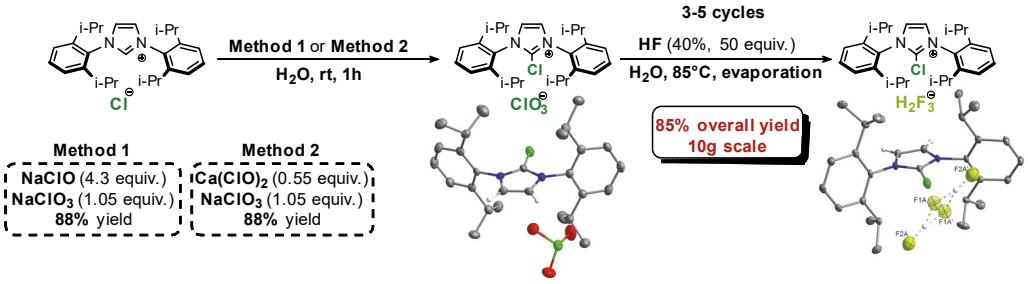


Figure 1: Deoxyfluorination of electron-deficient phenols.



Scheme 1: Synthesis of deoxyfluorination reagent.

References

[1] T. Fujimoto, T. Ritter, *PhenoFluorMix: Practical Chemoselective Deoxyfluorination of Phenols* **2015**, 17, 544–547.
[2] N. W. Goldberg, X. Shen, J. Li, T. Ritter, *AlkylFluor: Deoxyfluorination of Alcohols* **2016**, 18, 6102–6104.
[3] M. K. Nielsen, C. R. Ugaz, W. Li, A. G. Doyle, *PyFluor: A Low-Cost, Stable, and Selective Deoxyfluorination Reagent* **2015**, 137, 9571–9574.

Construction of Fluorine-containing Five-membered Heterocycles via Defluorinative Annulation of Fluorinated Small Molecules

Junji Ichikawa

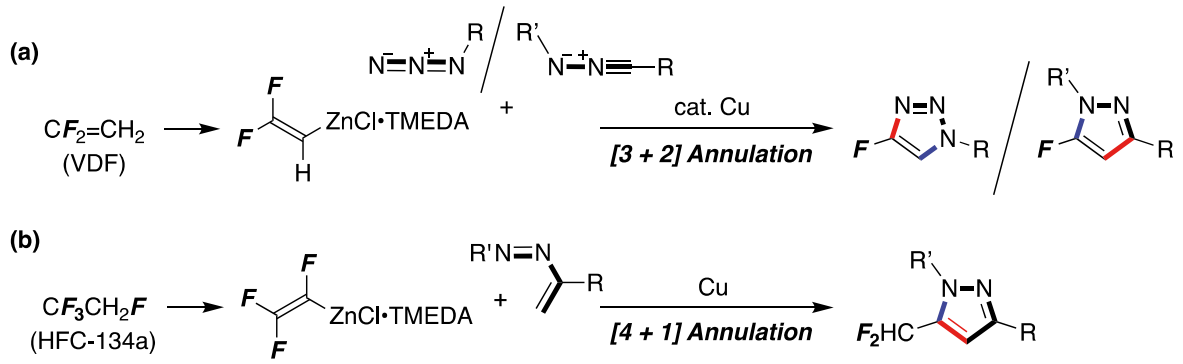
Sagami Chemical Research Institute, 2743-1, Hayakawa, Ayase, Kanagawa 252-1193, JAPAN

E-mail: jichikawa@sagami.or.jp

Fluorine-containing heterocyclic compounds have been applied to a wide range of pharmaceuticals and agrochemicals because their bioactivities are often improved compared with the corresponding fluorine-free compounds. In synthesizing such compounds, strategies of constructing heterocyclic rings at the last step would allow for the regioselective introduction of a fluorine or fluorine-containing substituent on the rings. Among them, ring construction by forming two bonds (annulation) is more efficient because commercially available fluorinated small molecules can be used as building blocks.

We herein demonstrate defluorinative (a) [3 + 2] or (b) [4 + 1] annulations between three- or four-atom units and fluorovinylzinc reagents, generated from VDF or HFC-134a [1,2], respectively (Scheme 1). In each case, copper-mediated β-fluorine elimination [3,4] was involved as a key step for cleavage of carbon–fluorine bonds at room temperature. Good yields of fluorine-containing five-membered heterocycles such as triazoles [5] and pyrazoles were readily obtained. By forming two bonds, we also succeeded in the construction of (i) ring-fluorinated thiophenes and thiazoles via [4 + 1] annulation with difluorocarbene [6,7] and (ii) CF_3- or CHF_2- substituted indoles from HFO-1224yd or 1233yd [8] via Suzuki–Miyaura coupling followed by nucleophilic 5-*endo*-*trig* cyclization [9].

Thus, we have developed methods for constructing five-membered heterocycles by forming two bonds (via annulation) involving vinylic C–F bond activation. Ring-fluorinated, -trifluoromethylated, and -difluoro-methylated triazoles, pyrazoles, indoles, thiophenes, and thiazoles obtained here are expected to serve as parts of promising candidates for pharmaceuticals and agrochemicals.



Scheme 1: Defluorinative [3 + 2] and [4 + 1] annulations of fluorovinylzinc reagents.

References

[1] T. Fujita, T. Ichitsuka, K. Fuchibe, J. Ichikawa, *Chem. Lett.* **2011**, *40*, 986–988.
[2] T. Ichitsuka, T. Takanohashi, T. Fujita, J. Ichikawa, *J. Fluorine Chem.* **2015**, *170*, 29–37.
[3] T. Fujita, K. Fuchibe, J. Ichikawa, *Angew. Chem. Int. Ed.* **2019**, *58*, 390–402.
[4] T. Fujita, Y. Kobayashi, R. Morioka, I. Takahashi, T. Ichitsuka, J. Ichikawa, *Chem. Eur. J.* **2022**, *28*, e202103643.
[5] T. Fujita, M. Takeishi, J. Ichikawa, *Org. Lett.* **2020**, *22*, 9253–9257.
[6] K. Fuchibe, I. Mukohara, A. Yamada, D. Miyazaki, R. Takayama, J. Ichikawa, *Org. Lett.* **2022**, *24*, 169–174.
[7] K. Fuchibe, Y. Morota, T. Miura, J. Ichikawa, *Chem. Lett.* **2022**, *51*, 778–780.
[8] Y. Ishibashi, T. Fujita, J. Ichikawa, *Org. Lett.* **2022**, *24*, 9306–9310.
[9] R. Morioka, T. Fujita, J. Ichikawa, *Helv. Chim. Acta* **2020**, *103*, e2000159.

Synthesis and Reactivity of Fluorinated β-Lactams

Tomasz Cytlak[1], Monika Skibińska[1,2], Henryk Koroniak[1], Benoît Crousse[2]

[1]*Faculty of Chemistry, Adam Mickiewicz University, Uniwersytetu Poznańskiego 8, 61-614 Poznań, Poland,*
[2]*BioCIS UMR 8076 CNRS-Université Paris Saclay, Bâtiment Henri MOISSAN, 17, Avenue des Sciences 91400 ORSAY*

E-mail: tomasz.cytlak@amu.edu.pl

gem-Difluoroalkenes are valuable fluorinated moieties which are characterized by unique features such as electronegative nature of the included fluorine atoms, the metabolic stability and the chemical reactivity as electrophiles. Moreover, the ability of *gem*-difluoroalkenes to mimic the carbonyl and amide group has attracted more attention to modifying biologically active compounds and served as irreversible electrophilic targets for inhibiting various enzymes. [1] The synthetic and biological importance of β-lactams and their combination with difluoromethylene group may give access to the new series of fluorinated small molecules as potential building blocks that could be important in the organic synthesis of biologically active compounds. [2] Therefore, the incorporation of the phosphonate group into the small heterocycles can provide new possibilities in medicinal chemistry as a potential bioactive compounds or intermediates involved in the synthesis of complex phosphonated aza-compounds. [3]

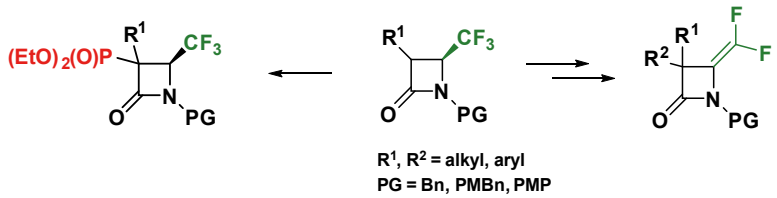


Figure 1: Synthesis of the new series of *gem*-difluoroalkenes and C-3 phosphonated 4-CF_3-β-lactams

References

[1] (a) B. Malo-Forest, G. Landelle, J.-A. Roy, J. Lacroix, R.C. Gaudreault, J.-F. Paquin, *Bioorg. Med. Chem. Lett.*, **2013**, *23*, 1712; (b) G. Chelucci, *Chem. Rev.*, **2012**, *112*, 1344; (c) H. Amii, K. Uneyama, *Chem. Rev.*, **2009**, *109*, 2119

[2] L. Kuznetsova, L. Sun, J. Chen, X. Zhao, J. Seitz, M. Das, Y. Li, J. M. Veith, P. Pera, R. J. Bernacki, S. Xia, S. B. Horwitz, I. Ojima, *J. Fluor. Chem.*, **2012**, *143*, 177

[3] (a) C. Agami, F. Couty, N. Rabasso, *Tetrahedron Lett*., **2002**, *43*, 4633; (b) M. Shevchuk, Q. Wang, R. Pajkert, J. Xu, H. Mei, G.-V. Röschenthaler, J. Han, *Adv. Synth. Catal.*, **2021**, 363, 2912; (c) L. Chen, X.-Y. Liu, Y.-X. Zou, *Adv. Synth. Catal.*, **2020**, 362, 1724; (d) P. Le Noc, *Monocyclic β-lactams*, in: *Antimicrobial Agents: Antibacterials andAntifungals*, Ed. A. Bryskier, ASM Press, 2005, Washington DC; pages: 336–347

Fluorinated Aryl Boronates as Building Blocks in Organic Synthesis

Udo Radius

Institute for Inorganic Chemistry, Julius-Maximilians University Würzburg, Am Hubland, 97074 Würzburg, Germany

E-mail: u.radius@uni-wuerzburg.de

Organoboron compounds are well known building blocks for many organic reactions. In this presentation our efforts to synthesize fluorinated aryl boronic acid derivatives from polyfluoroarenes and their application in homo- and cross-coupling reactions will be summarized.[1] Fluorinated arylboronic acid pinacol esters were synthesized *via* the thermal and photochemical defluoroborylation of fluoroarenes using the [Ni(IMes)$_2$]-catalyzed (IMes = 1,3-dimesitylimidazolin-2-ylidene) C-F bond activation and transmetalation with bis(pinacolato)diboron (B_2pin_2). Thus, [Ni(IMes)$_2$] is a valuable catalyst for the synthesis of various boronate esters of fluorinated arenes. These fluorinated aryl boronic acid derivatives have been applied in homo- and cross-coupling reactions, which will be discussed in some detail. For example, C–C reductive elimination from [PdL$_2$(C$_6$F$_5$)$_2$] to form polyfluorinated biaryls has been a challenge for over 50 years. Thus, palladium-catalyzed homocoupling of arylboronates (Ar$_F$–Bpin) containing two *ortho*-fluorine substituents is very difficult to achieve as the reaction typically stops at the [PdL$_2$(Ar$_F$)$_2$] stage after two transmetalation steps. However, catalytic homocoupling proceeds smoothly in a "weakly coordinating" arene solvent as long as no ancillary ligands or coordination solvents are present. DFT computations performed reveal that the active catalyst formed by arene solvent coordination leads to an overall reduced barrier for the reductive elimination step compared to the formation of stable [PdL$_2$(Ar$_F$)$_2$] complexes in the presence of a donor ligand or solvent L.

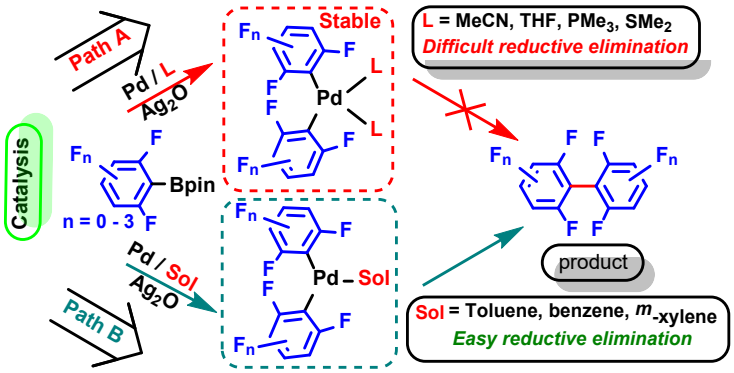


Figure 1: The Palladium-catalyzed homocoupling of highly fluorinated arylboronates: The influence of strongly vs. weakly coordinating solvents on the reductive elimination process.

References

[1] a) J. Zhou, M. Kuntze-Fechner, R. Bertermann, U. S. D. Paul, J. H. J. Berthel, A. Friedrich, Z. Du, T. B. Marder, U. Radius, *J. Am. Chem. Soc.* **2016**, *138*, 5250-5253; b) Y.-M. Tian, X.-N. Guo, M. Kuntze-Fechner, I. Krummenacher, H. Braunschweig, U. Radius, A. Steffen, T. B. Marder; *J. Am. Chem. Soc.* **2018**, *140*, 17612-17623; c) Y. P. Budiman, A. Friedrich, U. Radius, T. B. Marder; *ChemCatChem* **2019**, *11*, 5387-5396; d) Y. P. Budiman, A. Jayaraman, A. Friedrich, F. Kerner, U. Radius, T. B. Marder, *J. Am. Chem. Soc.* **2020**, *142*, 6036-6050; e) Y.-M. Tian, X.-N. Guo, H. Braunschweig, U. Radius, T. B. Marder; Chem. Rev. **2021**, *121*, 3561-3597; f) Y. P. Budiman, S. A. Westcott, U. Radius, T. B. Marder; *Adv. Synth. Catal.* **2021**, *363*, 2224-2255; g) Z. Liu, G. K. Kole, Y. P. Budiman, Y.-M. Tian, A. Friedrich, X. Luo, S. A. Westcott, U. Radius, T. B. Marder; *Angew. Chem. Int. Ed.* **2021**, *60*, 16529-16538.

Fluorinated Polymer Systems for the Transport of Active Substances

Anna Szwajca

Faculty of Chemistry, Adam Mickiewicz Uniwersity in Poznań, Uniwersytetu Poznańskiego 8, 61-614 Poznań, Poland

E-mail: anna.szwajca@amu.edu.pl

Fluorine is an important element in organic compounds of hybrid biomaterials due to its chemical stability, hydrophobicity, biocompatibility, imaging capabilities and drug delivery potential. The presented research combines knowledge in the field of chemistry and physics, and their implementation is one of many nanotechnology problems. The project presents the synthesis of fluorinated polymer nanoparticles as a carrier of active substances. The use of a polymer as a carrier in delivery systems significantly affects the change in the distribution of active compounds, and thus their accumulation. An innovative approach to drug delivery systems is increasingly used in the pharmaceutical market. This is evidenced by the high rotation of chemical biotechnology products compared to conventional small molecule drugs on the market. The presented research includes the preparation and physicochemical analysis of nanoparticle carriers with a size of 70-100 nm, penetrating the three-dimensional structure of the polymer, e.g. a layer of hydrogel. Such systems are the answer to the challenges faced by modern delivery systems, i.e. the efficiency of the delivery process and great variety.

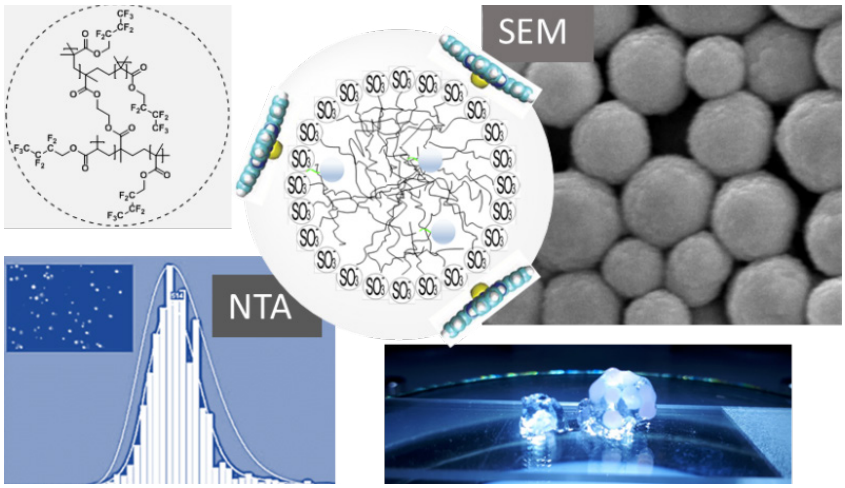


Figure 1: Proposed structure of nanoparticles.

References

[1] R. Koguchi, K. Jankova, M. Tanaka, *Acta Biomaterialia* **2022**, *138*, 34-56.
[2] S. Tingting, G. Yuemei, S. Mingjie, Q. Jia, Z. Huaqing, Z. Jianping, D. Yang,, *Medicine in Drug Discovery* **2022**, *14*, 100123.
[3] L. Xie,W. Jin, X. Zuo, S. Ji, W. Nan, H. Chen, S. Gao, Q. Zhang, *Biomater. Sci.* **2020**, *8*, 1431–1441.

Synthesis of Pentacoordinated Organofluorosilicate and Germanate Salts

Jan Gnidovec[1,2], Evelin Gruden[1], Melita Tramšek[1], Jernej Iskra[3], Jaroslav Kvíčala[4], Gašper Tavčar[1,2]

[1]*Department of Inorganic Chemistry and Technology, Jožef Stefan Institute, Jamova 39, Ljubljana, Slovenia.*
[2]*Jožef Stefan International Postgraduate School, Jamova 39, Ljubljana, Slovenia.*
[3]*Department of Chemistry and Biochemistry, University of Ljubljana, Faculty of Chemistry and Chemical Technology, Večna pot 113, 1000 Ljubljana, Slovenia.*
[4]*Department of Organic Chemistry, University of Chemistry and Technology, Prague, Technická 5, 166 28 Prague 6, Czech Republic.*

E-mail: jan.gnidovec@ijs.si

Fluorine plays an important role in organic compounds due to its small size and high electronegativity. It promotes many desirable properties of compounds, such as bioavailability, lipophilicity and metabolic stability. It is therefore no surprise that many recently produced pharmaceuticals and agrochemicals contain fluorine.[1] Due to the lack of natural organic materials containing fluorine, it remains a challenge to incorporate fluorine into organic scaffolds in a cost-effective manner. Therefore, research into new fluorination reagents continues. Pentavalent silicon and germanium fluorides are one group of chemicals that could be considered as fluorination reagents. In this area of research, pentacoordinated organofluorosilicates have been far more explored than their germanium counterparts, which have been limited to strongly electron-withdrawing alkyl groups.[2]

In our recently published work [3], we used the readily available 1,3-bis(2,6-diisopropylphenyl)imidazolium fluoride and potassium fluoride for the synthesis of a new triphenyl difluorogermanate [IPrH][Ph_3GeF_2] and pentacoordinated organofluorosilicates [IPrH][Ph_3SiF_2], [IPrH][Ph_2SiF_3], [IPrH][$PhSiF_4$], [IPrH][Et_2SiF_3] and [IPrH][$EtSiF_4$]. In addition, we have synthesised and structurally characterised imidazolium-based organofluorogermanate [IPrH][Ph_2GeF_3] and its alkali metal analogue [K][Ph_2GeF_3]. Although many organofluorosilicate salts with alkali metal cations containing crown ethers or cryptands are structurally characterised, organofluorogermanates are quite rare.

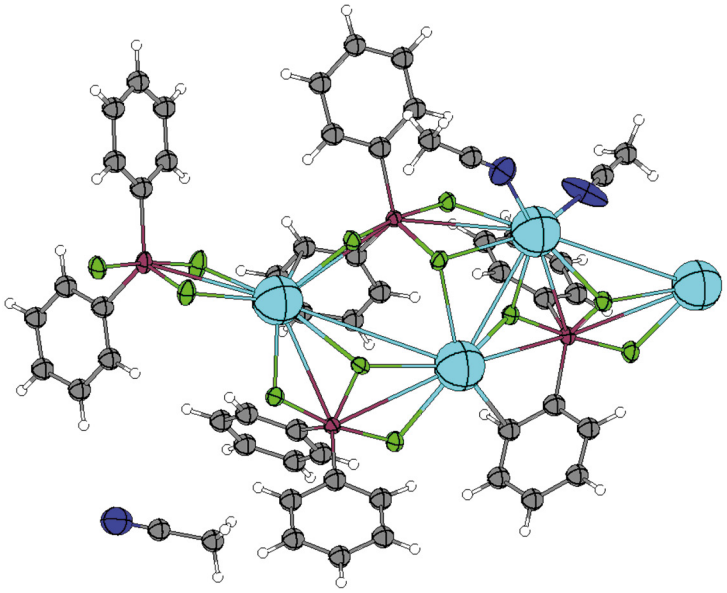


Figure 1: The asymmetric unit of [K][Ph_2GeF_3] · 0.75 MeCN. The compound forms a polymeric "channel-like" structure formed by potassium cations and $[Ph_2GeF_3]^-$ anions.

References

[1] X. T. Furuya, A. S. Kamlet, T. Ritter, *Nature*, **2011**, *473*, 470-477.
[2] D. J. Brauer, H. Burger, R. Eujen, *Angew. Chem., Int. Ed.*, **1980**, *19*, 836-837.
[3] J. Gnidovec, E. Gruden, M. Tramšek, J. Iskra, J. Kvíčala, G. Tavčar, *Dalton Trans.*, **2023**, Advance Article.
[4] R. Pietschnig, K. Merz, *Chem. Commun*., **2001**, *1*, 1210–1211.

Fluorine-sensitized Molecular Probes for Substituent Effects

Tomasz Siodła, Klaudia Anastaziak, Henryk Koroniak, Adam Sokół, Marcin Hoffmann

Faculty of Chemistry, Adam Mickiewicz University, Uniwersytetu Poznańskiego 8, 61-614 Poznań, Poland

E-mail: tsiodla@amu.edu.pl

Substituent effects have been known for a long time as very efficient concepts in organic chemistry. In the last decades, interpretations of substituent effects based on reactivity and physicochemical properties have been replaced by quantum-chemical modelling. In our studies on the substituent effect, we have decided to estimate the effect of many various substituents on fluorine (-F) and trifluoromethyl (-CF_3) groups attached to benzene [1] and naphthalene [2]. Thus, we can observe how the properties of -F and -CF_3 groups are influenced by intramolecular interactions coming from various substituents with well-known Hammett-type constants (σ_p, σ_m, R, and F).

The unique combination of properties of fluorine makes it a remarkable substituent. Fluorine is inductively electron-withdrawing but electron-donating by resonance, while perfluoroalkyl groups (like -CF_3) are purely electron-withdrawing. These two faces of fluorine (σ acceptor/π donor) provided an opportunity in our studies to distinguish σ- and π-electron influences resulting from interactions with various substituents. On the other hand, we have also studied how the -CF_3 group, as one of the most efficient electron-withdrawing groups, can reflect the strength of interactions with other substituents.

The application of DFT computational methods to X-substituted derivatives of polyfluoro and poly(trifluoromethyl) benzene (and naphthalene) allows to study changes in the electronic properties of these compounds under the influence of various substituents. The obtained dependencies of theoretically calculated SESE (substituent effect stabilization energy) values on the empirically determined substituent constants are, so far, the most sensitive SESE probes for the substituent effects in the aromatic system. The presence of more than one so-called probing substituent (-F or -CF_3) significantly increases the response of the SESE values to changes caused by another substitution. Further, the more -CF_3 groups are attached to the molecule, the more sensitive the probe is. The obtained increase in the signal-to-noise ratio is proportional to the number of probing substituents. As such sensitivity increases, the uncertainty in the estimation of the substituent constants decreases. It can be a step forward towards the more sensitive molecular probes for the substituent effects.

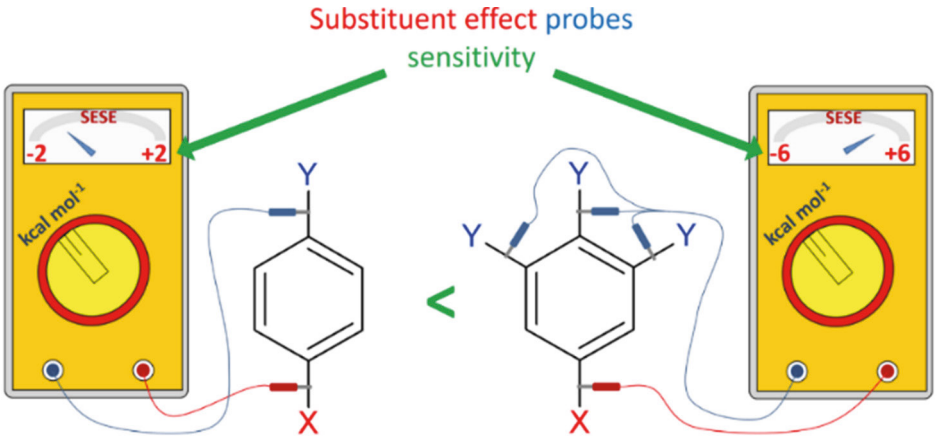


Figure 1: The concept of increasing the sensitivity of the molecular probes for the substituent effect.

References

[1] T. Siodła, K. Anastaziak, H. Koroniak, *J. Mol. Struct.* **2021**, *1246*, 131186.
[2] A. Sokół, H. Koroniak, M. Hoffmann, T. Siodła, *Molecules* **2022**, *27*, 4173.

Diaminomethylation of Fluorine-containing Compounds

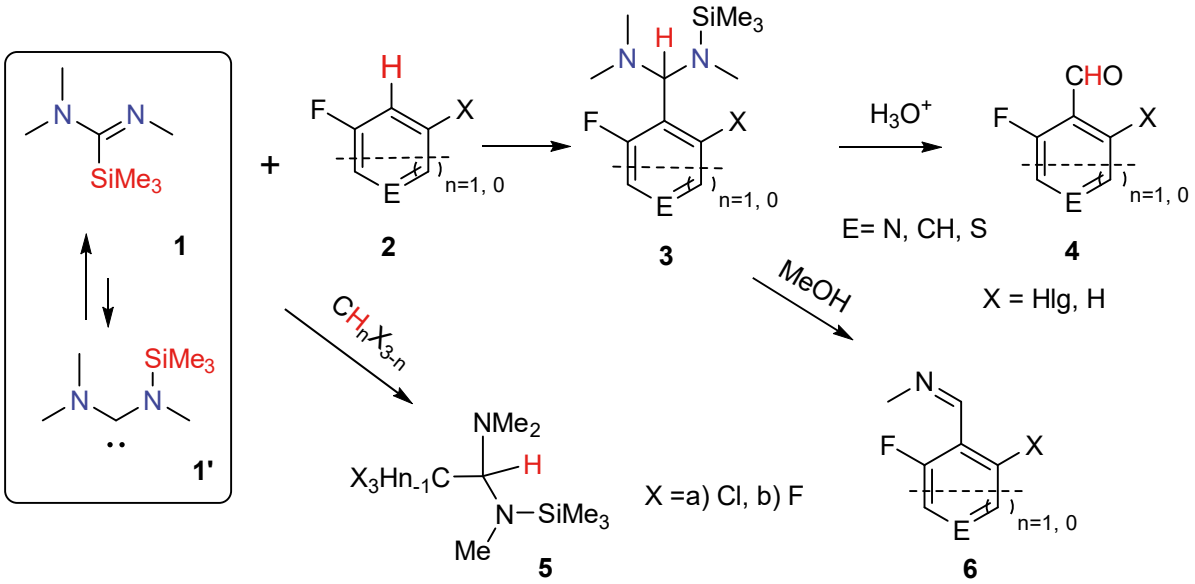
Aleksandr Kostyuk, Anastasiia N. Hurieva, Serhii Zahorulko, Tetiana Shvydenko, Georgyi Koidan

Institute of Organic Chemistry, National Academy of Sciences of Ukraine, Academician Kukhar str. 5, 02094 Kyiv, Ukraine

E-mail: a.kostyuk@yahoo.com

Diaminomethylation of organic substrates is a convenient and easy way to modify organic compounds. It can be achieved by insertion of diaminocarbenes into various types of C-H bonds. The main obstacle is relatively short half-life of reactive diaminocarbenes. Thus, Alder's carbene (tetraisopropyldiaminocarbene) was isolated and can stay intact for a prolong time in solution. At the same time, an analogous less sterically congested tetramethyldiaminocarbene stays in solution for a short period and various methods are employed to stabilize it. We have found that silylformamidine **1** is easily rearranged into the corresponding carbene **1'**, with DFT calculations predicting a low activation barrier for carbene–silylformamidine rearrangement 16.3 kcal/mol (Scheme 1). We were not able to detect carbene form **1'** by spectroscopic methods, but silylformamidine **1** behaves like a carbene in numerous reactions. Thus, it undergoes insertion into sp, sp^2 and sp^3 C-H bonds.

The reactivity of substituted aromatic and heteroaromatic compounds in the reaction with silylformamidine was roughly assessed by calculated pKa values for the C-H hydrogens. Fluorine substituents enhance its reactivity as the fluorine is a powerful acceptor substituent. Numerous fluorine containing compounds were subjected to the reaction with silylformamidine **1**. At first, the reaction provides aminals **3**, which can be easily converted to the corresponding aldehydes **4** by acidic hydrolysis. Since silylformamidine **1** is tolerant to many functional groups, the reaction can be applied to numerous fluoro-containing derivatives. It presents a reliable strategy for application in organic synthesis.



Scheme 1: Silylformamidine in the reaction with fluoroaromatic and heteroaromatic substrates.

References

[1] A. Marchenko, G. Koidan, A. Hurieva, K. Shvydenko, A. B. Rozhenko, E. B. Rusanov, A. A. Kyrylchuk, A. Kostyuk, *J. Org. Chem.* **2022**, 87 (1), 373–385.

[2] G. Koidan, A. Hurieva, S. Zahorulko, A. Zadorozhny, V. Lysenko, T. Shvydenko, E. B. Rusanov, A. Kostyuk, *European J. Org. Chem.* **2022**, (40), e202201048.

Metal-catalyzed Fluoroalkylation for Construction of Fluorinated Heterocycle Library and Application for Drug Discovery

Hong Liu

Shanghai Institute of Materia Medica,555 Zu Chong Zhi Road, Shanghai, China

E-mail: hliu@simm.ac.cn

Fluorine has become a crucial element in the field of drug development due to its unique properties.[1,2] The selective introduction of fluorine or fluorinated substituents into molecules can dramatically improve the pharmacokinetic profiles and drug-like property, which provides flexibility for the drug design. Over the past few decades, extensive efforts have been made in the fluorination and fluoroalkylation reactions. We developed a highly efficient and practical approach for the synthesis of difluoroalkylated pyrrolobenzodiazepines via a Pd-catalyzed C–H difluoroalkylation/cyclization cascade reaction.[3] Meanwhile, we also developed Pd(II)-catalyzed and Rh(III)-catalyzed C–H fluoroalkylation of arenes and heteroarenes by directing group strategy.[4] These methods enable the rapid synthesis of a series of fluorinated heterocycles in high efficiency, and features a broad substrate scope, excellent functional group tolerance under mild conditions. Through the screening of the constructed fluorinated heterocycle compound library and rational drug design by fluorine incorporation to block oxidative metabolism, we discovered LH-1802 as a novel LSD1 inhibitor for the treatment of acute myeloid leukemia. LH-1802 exhibits good anti-cancer activity both *in vitro* and *in vivo*, and it was confirmed in three tumor animal models, with low effective dose and potent anti-cancer activity. LH-1802 received clinical approval as an anti-cancer drug candidate in 2021 by NMPA, and is currently in phase 1 clinical development.[5]

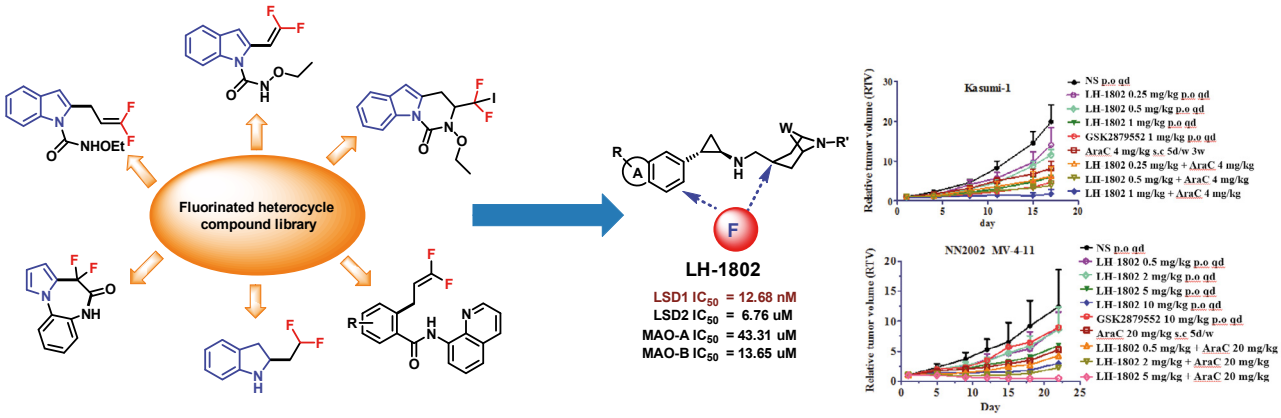


Figure 1. Construction of the fluorinated heterocycle library and discovery novel anti-cancer drug candidate.

References

[1] Jiang Wang, María Sánchez-Roselló, José Luis Aceña, Carlos del Pozo, Alexander E. Sorochinsky, Santos Fustero*, Vadim A. Soloshonok*, and Hong Liu*, *Chem. Rev.* **2014,** *114*, 2432-2506

[2] Yu Zhou, Jiang Wang, Zhanni Gu, Shuni Wang, Wei Zhu, José Luis Aceña*, Vadim A. Soloshonok*, Kunisuke Izawa*, and Hong Liu*, *Chem. Rev.* **2016,** *116*, 422-518.

[3] Yang Gao, Chunpu Li*, Bin Xu, and Hong Liu*, *Org. Chem. Front.* **2019**, *6*, 410-414.

[4] Chunpu Li#, Dengyou Zhang#, Wei Zhu, Penghui Wan, and Hong Liu*, *Org. Chem. Front.* **2016**, *3*, 1080-1083.

[5] Chunpu Li#, Mingbo Su#, Wei Zhu#, Weijuan Kan, Tianpeng Ge, Gaoya Xu, Shuni Wang, Li Sheng, Feng Gao, Yunfei Ye, Jiang Wang, Yubo Zhou*, Jia Li*, and Hong Liu*, *J. Med. Chem.* **2022**, *65*, 4335–4349.

On the Click Reaction as an Efficient Method for Preparing Amphiphilic Aromatic Fluorinated Polymers

Justyna Walkowiak-Kulikowska, Katarzyna Żymańczyk, Anna Szwajca, Joanna Wolska

Faculty of Chemistry, Adam Mickiewicz University, Poznań, Poland

E-mail: Justyna.A.Walkowiak@amu.edu.pl

Polymers containing perfluorinated alkyl groups are classified as PerFluoroAlkyl Substances PFASs, that are currently attracting much attention and care. Unlike non-polymeric PFAS representatives, fluorinated polymers are considered to be of low concern for the environment, humans, and biota, since they have negligible monomer and oligomer content and low or no leachables, are not bioavailable or bioaccumulative, have no chronic toxicity or carcinogenicity, and have no reproductive, developmental or endocrine toxicity [1]. Since non-polymeric amphiphilic PFASs have found application, for example, in manufacturing protective coatings for packaging, as they prevent the absorption of water, grease, or dirt, the aim is to replace long-chain PFASs with short-chain and alternative fluorinated and non-fluorinated compounds. Fluorinated amphiphilic polymers can provide an affordable alternative to non-polymeric substances, as the desired properties can be achieved by introducing the relevant modification, avoiding the risk of bioaccumulation and toxicity [2].

The objective of the presented work was to synthesize amphiphilic aromatic polymers using "click" reactions of suitable building blocks in the form of azido-functionalized derivatives of fluorinated aromatic polymers and propargyl derivatives of monosaccharides (Figure 1). Telechelic α,ω-diazido-functionalized fluorinated polymers were obtained by azidation reaction of α,ω-diiodo-functionalized macromolecules that were previously obtained by iodine transfer copolymerization (ITcoP), while propargyl derivatives of the monosaccharides glucose and glucosamine were obtained by literature-known, two-step syntheses [3,4]. Equally important was to fully characterize structural, thermal, and surface properties.

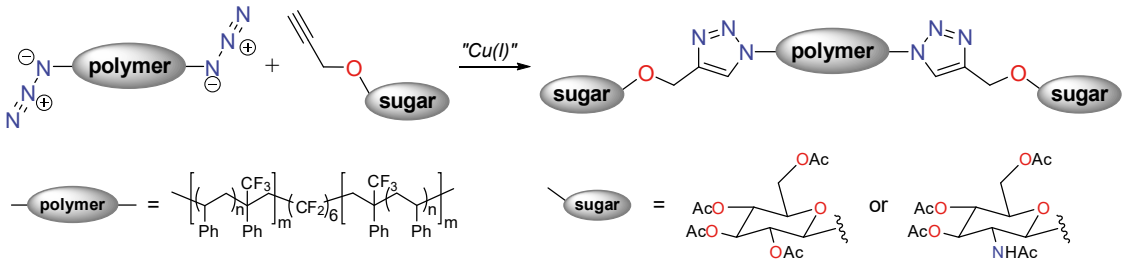


Figure 1: Click chemistry as an efficient tool toward telechelic amphiphilic polymers.

References

[1] J. Walkowiak-Kulikowska, *Poly/Perfluorinated Alkyl Substances (PFASs) – Synthetic Methods, Properties and Applications* in. *Perfluoroalkyl Substances: Synthesis, Applications, Challenges and Regulations*, Eds. B. Améduri, Royal Society of Chemistry, **2022**, 22-65.
[2] Trier, D.X.; Taxvig, C.; Rosenmai, A.K.; Pedersen, G.A. *PFAS in Paper and Board for Food Contact*; Nordic Council of Ministers: Copenhagen, Denmark, **2017**.
[3] J. Walkowiak-Kulikowska, A. Szwajca, F. Boschet, V. Gouverneur, and B. Ameduri, *Macromolecules*, **2014**, *47(24)*, 8634-8644.
[4] J. Walkowiak-Kulikowska, A. Szwajca, V. Gouverneur, and B. Ameduri, *Polym. Chem.*, **2017**, *8(42)*, 6558-6569.

New Perspectives on the Coordination Chemistry of the Pentafluoroorthotellurate Ligand: The Case of Cobalt and Manganese

Alberto Pérez-Bitrián[1], Sebastian Riedel[2]

[1]*Institut für Chemie und Biochemie, Freie Universität Berlin, Fabeckstraße 34/36, 14195 Berlin, Germany.*

E-mail: a.perez.bitrian@fu-berlin.de

The pentafluoroorthotellurate group (teflate, $OTeF_5$) is considered as a bulky analogue of fluoride due to their similar electron-withdrawing properties.[1] Although a handful of complexes are known,[2] the behavior of this ligand in coordination chemistry of transition metals has remained far less investigated than that of main-group elements. In the particular case of first-row transition metals, prototypical homoleptic species are rare, which has hindered the understanding of some fundamental magnetic and structural properties associated to this unique ligand. In fact, only recently, and enabled by the synthesis and characterization of the $[Ni(OTeF_5)_4]^{2-}$ anion, it has been classified as a weak/medium-field ligand, behaving also as an analogue of fluoride in ligand-field terms.[3]

Following up our research on nickel teflate complexes, we present here the synthetic access to different homoleptic cobalt and manganese teflate species, as well as the investigation of their magnetic, structural and chemical properties. The $[Co(OTeF_5)_4]^{2-}$ anion represents the first reported group 9 metal teflate complex (Figure 1, left). The electronic structure of this complex was investigated experimentally and theoretically, as well as the nature of the Co–$OTeF_5$ bond. Manganese species in oxidation states +II and +III were prepared and their spin states and structures analyzed (Figure 1, right). These are unprecedented examples of homolpetic monomeric Mn–O single-bonded compounds, which are formed thanks to the low tendency of the teflate ligand to bridge metal centers.

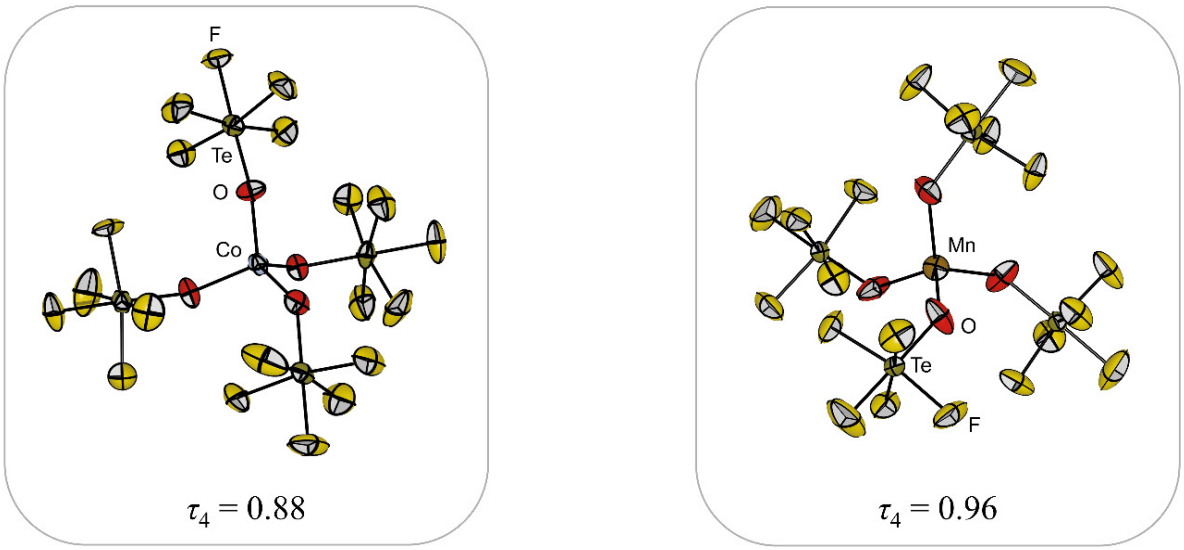


Figure 1: Molecular structure of the $[Co(OTeF_5)_4]^{2-}$ (left) and $[Mn(OTeF_5)_4]^{2-}$ (right) anions in the solid state (thermal ellipsoids set at 50% probability). Geometry indexes indicating the distortion from a perfect tetrahedral geometry are shown.

References

[1] K. Seppelt, *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 877-888.

[2] M. Gerken, H. P. A. Mercier, G. J. Schrobilgen, *Syntheses and Structures of the Oxide Fluorides of the Main-Group and Transition Metal Elements*, in: *Advanced Inorganic Fluorides: Synthesis, Characterization and Applications*, Eds. T. Nakajima, B. Zemva and A. Tressaud, Elsevier, 2000, Lausanne; pages: 117-174.

[3] A. Pérez-Bitrián, K. F. Hoffmann, K. B. Krause, G. Thiele, C. Limberg, S. Riedel, *Chem. Eur. J.* **2022**, *28*, e202202016.

The Synergistic Cytotoxic Effect of Aluminum and Fluoride on Macrophage Cell Line THP-1

Anja Pavlovič[1,2], Larisa Janžič[3], Lucija Levstek[3], Andreja Nataša Kopitar[3], Maja Ponikvar-Svet[1]

[1]*Department of Inorganic Chemistry and Technology, Jožef Stefan Institute, Jamova 39, Ljubljana, Slovenia*
[2]*Jožef Stefan International Postgraduate School, Jamova 39, Ljubljana, Slovenia*
[3]*Institute for Microbiology and Immunology, Medical Faculty Ljubljana, Vrazov trg 2, Ljubljana, Slovenia*

E-mail: anja.pavlovic@ijs.si

Fluoride toxicity is a major concern, especially in areas where water is naturally enriched or deliberately fluoridated [1]. Fluoride is known to cause cytotoxicity in various cell types, including macrophages. Previous studies have shown that high fluoride exposure can induce programmed cell death or apoptosis in macrophages, which can impair immunological function and lead to persistent inflammation [2,3]. In addition, fluoride exposure has also been linked to changes in the signaling pathways controlling macrophage apoptosis, which may enhance the cytotoxic effects of fluoride [4]. In addition to fluoride, water can also contain other elements, including aluminum, which occurs naturally or is added artificially during water treatment [5]. Thus, potentially toxic aluminum fluoride complexes can form [6]. Despite numerous studies examining the effects of fluoride consumption on human health, the potential effects of aluminum and aluminum fluoride complexes on the THP-1 macrophage cell line of the human immune system have not been thoroughly investigated.

The aim of this study was to investigate the effects of fluoride, aluminum and aluminum fluoride complexes on apoptosis and necrosis in THP-1 macrophages at a wide range of concentrations. Standards of fluoride, aluminum, and their combination in a 1:1 molar ratio were administered to the cells, with concentrations ranging from those in blood to those still soluble in water. After flow cytometric analysis of the cells, the early and late stages of apoptosis/necrosis were determined using annexin V/propidium iodide. The results showed that both fluoride and aluminum reduced cell viability in a dose-dependent manner, with aluminum being significantly more effective than fluoride. However, the strongest toxic effects were observed in cells treated with aluminum fluoride complexes, with a significant decrease in the viability curve at millimolar concentrations, suggesting that the complexes have a synergistic effect of toxicity of both elements. Although the annexin V and propidium iodide assays showed no significant difference between apoptosis and necrosis, the study suggests that further investigation of apoptotic signaling pathways is needed. However, when compared to the negative control, significant differences can be seen in all species even at micromolar concentrations. Although low concentrations do not always cause substantial changes in cell metabolism, long-term exposure to fluoride and aluminum and their cumulative effects may pose a potential health risk.

References

[1] J. Han. L. Kiss, H. Mei, A.M. Remete, M. Ponikvar-Svet, D.M. Sedgwick, R. Roman, S. Fustero, H. Moriwaki, V.A. Soloshonok, *Chemical Reviews* **2021**, *121(8)*, 4678–4742.
[2] I. Gutowska, I. Baranowska-Bosiacka, M. Baśkiewicz, B. Milo, A. Siennicka, M. Marchlewicz, B. Wiszniewska, B. Machaliński, E. Stachowska, *Toxicology Letters* **2010**, *196(2)*, 74–79.
[3] S. Hirano, M. Ando, *Archives of Toxicology* **1996**, *70(3–4)*, 249–251.
[4] E. Stachowska, M. Baśkiewicz-Masiuk, B. Machaliński, M. Rybicka, I. Gutowska, J. Bober, K. Grymula, V. Dziedziejko, D. Chlubek, *Fluoride* **2005**, *38(4)*, 297-306.
[5] World Health Organization (WHO), "Aluminium in Drinking-water", Background document for development of WHO Guidelines for Drinking-water Quality [Online], **2003**. Available: https://apps.who.int/iris/bitstream/handle/10665/75362/WHO_SDE_WSH_03.04_53_eng.pdf
[6] T. C. Russ, L. O. J. Killin, J. Hannah, G. D. Batty, I. J. Deary, *The British journal of psychiatry: the journal of mental science* **2020**, *216(1)*, 29–34.

Synthesis and Application of Modified BODIPY Derivatives to Study Interaction with c-*MYC* DNA

Magdalena Rapp, Jakub Żubertowski, Anna Dembska

Faculty of Chemistry, Adam Mickiewicz University, Uniwersytetu Poznanskiego 8, 61-614 Poznan, Poland

E-mail: magdrapp@amu.edu.pl

The fluorescent dyes are promising tools in studying the interactions and visualization of important biomolecules (cellular components). Among them, the important class is origin 4,4-difluoro-4-bora-3a,4a-diaza-s-indacene, known as BODIPY. Due to their attractive properties, such as an intense absorption peak with a high molar absorption coefficient in visible region and a high fluorescence quantum yield these dyes have been useful in bio-imaging, bio-labeling, and photodynamic therapy [1]. Additionally, some fluorinated BODIPY probes as pH sensors [2], as well as tools for surface analysis [3] were described. Moreover, the BODIPY functionalized with a PEG tail as well as polar analogs containing sulfonate moieties or quaternary ammonium groups as sensors for imaging microviscosimetry in an appropriate compartment of living cells [4] were applied. Moreover, BODIPY-based dyes have been used particularly for specific DNA or RNA detection [5]. So far, only a few reports have been published studying the binding ability of BODIPY derivatives towards G4 DNA [6]. Therefore, we decide to examine the potential of polar and hydrophobic BODIPY derivatives such as those containing in *meso*-position phenyl-, pentafluorophenyl-, or phenyl ring modified with PEG tail, quaternary ammonium groups, or sulfonate moieties (compounds **1-5**, Figure 1) as G4 ligands. The development of research on ligands stabilizing DNA G-quadruplexes in the context of the design of anticancer drugs and those involved in the regulation of gene expression is a very important and widely studied topic. For our studies, we selected the parallel G-quadruplex formed by the 23-mer DNA sequence derived from the nuclease hypersensitive region of the c-*MYC* promoter (c-*MYC*) [7]. We tested the ability of the obtained BODIPY derivatives to recognize, stabilize, or induce G-quadruplex formation, as well as the i-motif for comparison.

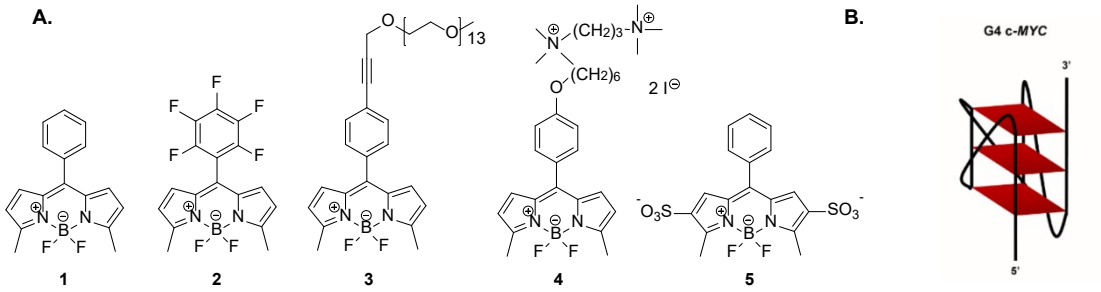


Figure 1: A. Structures of BODIPY ligands (**1-5**); B. schematic representation of parallel G-quadruplex, used in this study.

We believe that our results will contribute to the development research upon the investigation of interactions between BODIPY-derived compounds and tetraplexes and should raise awareness among researchers that these ligands may affect various cellular processes involving G-quadruplexes located at gene promoter sites.

References

[1] a) A. Loudet, K. Burgess, *Chem. Rev.* **2007**, *107*, 4891–4932; b) N. Boens, V. Leen, W. Dehaen, *Chem. Soc. Rev.* **2012**, *41*, 1130–1172.
[2] O. Galangau, C. Dumas-Verdes, R. Méallet-Renault, G. Clavier, *Org. Biomol. Chem.* **2010**, *8*, 4546–4553.
[3] M. Hecht, T. Fischer, P. Dietrich, W. Kraus, A.B. Descalzo, W.E.S. Unger, K. Rurack, *ChemistryOpen* **2013**, *2*, 25–38.
[4] L. Michels, V. Gorelova, Y. Harnvanichvech, J.W. Borst, B. Albada, D. Weijers, J. Sprakel, *Proc. Natl. Acad. Sci. U. S. A.* **2020**, *117*, 18110–18118.
[5] S. Kurata, T. Kanagawa, K. Yamada, M. Torimura, T. Yokomaku, Y. Kamagata, R. Kurane *Nucleic Acids Res.* **2001**, *29*, 6, e34.
[6] a) M.-Q. Wang, J.-J. Gao, Q.-Q. Yu, H.-B. Liu, *New J. Chem* **2020**, *44*, 13557–13564; b) L. Zhang, J.C. Er, K.K. Ghosh, W.J. Chung, J. Yoo, W. Xu, W. Zhao, A.T. Phan, Y.-T. Chang, *Sci. Rep.* **2014**, *4*, 3776-3782.
[7] J. Dai, M. Carver, L.H. Hurley, D. Yang, *J. Am. Chem. Soc.* **2011**, *133*, 17673–17680.

Reactivity of Organoaluminium Compounds with Imidazolium-based Fluorinating Reagents

Evelin Gruden, Melita Tramšek, Gašper Tavčar

Department of Inorganic Chemistry and Technology, "Jožef Stefan" Institute, Jamova cesta 39, Ljubljana, Slovenia

E-mail: evelin.gruden@ijs.si

In 2016, three imidazolium-based fluorinating reagents were prepared in our laboratory. The reagents [IPrH][F], [IPrH][HF_2] and [IPrH][H_2F_3] can be easily obtained from IPr: carbene by adding the appropriate amount of HF using HF-based reagents [1]. All three were tested as nucleophilic fluorinating reagents on organic and inorganic substances and proved to be very useful. The [IPrH][H_2F_3] is suitable for organic transformations due to its solubility in polar organic solvents and stability on air [2], while the [IPrH][F] is more suitable for fluorination of inorganic and organometallic compounds due to its free fluoride nature and the stabilising ability of the bulky cation. Its usefulness has been demonstrated in the synthesis of discrete anionic species such as $[GeF_5]^-$, $[Ph_3GeF_2]^-$, $[SiF_5]^-$, a number of organofluorosilicates and many more [3,4].

In this contribution we would like to present the utility of the above reagents in the chemistry of organoaluminium compounds (AlR_3). Aluminium compounds are in general known for their Lewis acidic nature and the tendency to react with Lewis based. In the presence of fluoride anions, they can form tetrahedrally coordinated fluoroaluminate species [5]. However, the high electronegativity of fluorine atoms usually leads to the formation of bridging bonds with neighbouring centres and the formation of oligomeric or polymeric species [5].

In our work we tested the reactivity of the three imidazolium-based fluorinating reagents with alky- and arylaluminium compounds (Figure 1). As a result, a number of salts with discrete organofluoroaluminate anions were prepared. A crucial role in the selective synthesis was played by the fluorinating reagents with the appropriate HF content, which allowed the fluorination of the AlR_3 species to the desired products. Another advantage of using imidazolium-based reagents was attributed to the stabilising properties of the sterically demanding cation, which enabled the isolation of discrete fluoroaluminate anions by preventing the interactions with neighbouring species.

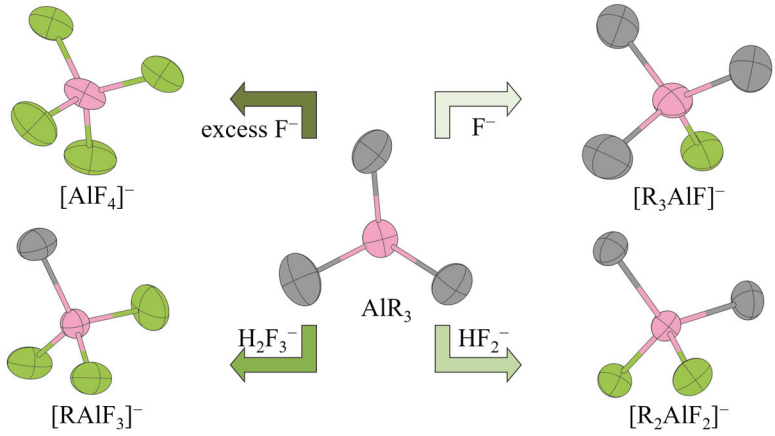


Figure 1: Synthesis of discrete organofluoroaluminate anions.

References

[1] B. Ališ, G. Tavčar, *Journal of Fluorine Chemistry* **2016**, *192*, 141-146.
[2] B. Ališ, J. Petrovčič, J. Jelen, G. Tavčar, J. Iskra, *The Journal of Organic Chemistry* **2022**, *87*, 5987-5993.
[3] B. Ališ, M. Tramšek, A. Kokalj, G. Tavčar, *Inorganic Chemistry* **2017**, *56*, 10070-10077.
[4] J. Gnidovec, E. Gruden, M. Tramšek, J. Iskra, J. Kvíčala, G. Tavčar, *Dalton Transactions* **2023**.
[5] J. Pinkas, H.W. Roesky, *Journal of Fluorine Chemistry* **2003**, *122*, 125-150.

Efficient Ca(II)-catalyzed Hydrosilylation of Olefins through Inverse Piers-Oestreich Mechanism

Przemysław J. Malinowski

Centre of New Technologies, University of Warsaw, Banacha 2c, Warsaw, Poland

E-mail: malin@cent.uw.edu.pl

Hydrosilylation is among key reactions in organic chemistry as an important source of silicon-containing compounds, also those of industrial importance.[1] The most commonly used catalysts are based on precius metals, most commonly platinum and catalyze the reaction according to Chalk-Harrod mechanism. However, high cost of platinum and the fact that it induces also side reactions and often gives poor yields justifies the search and development of novel hydrosilylation catalysts.

It is known that also highly Lewis-acidic species can catalyze hydrosilylation reaction. Generally, this is realized according to Piers-Oestreich mechanism (see Fig 1, left) in which silane is activated by coordination to acidic center through Si-H.[2] Cationic character of silicon in such complex allows the attack on double bond. However, this mechanism has limitations as it does not work well for sterically demanding silanes.

In this contribution we show how simple Ca(II) salt: $Ca[Al(OR^F)_4]_2$ ($R^F = C(CF_3)_3$) efficiently catalyzes Hydrosilylation of olefins at ambient conditions. It turns out that it acts according to inverse Piers-Oestreich mechanism (see Fig 1, right), which to date has been mentioned mostly in a speculative manner.[3] This has practical implications as the catalyst is effective also for sterically demanding silanes like $HSi(iPr)_3$, which are rarely reported to undergo hydrosilylations in decent yields. We present also the first confirmation of the mechanism on the basis of reactivity trends, NMR spectra and DFT calculations.

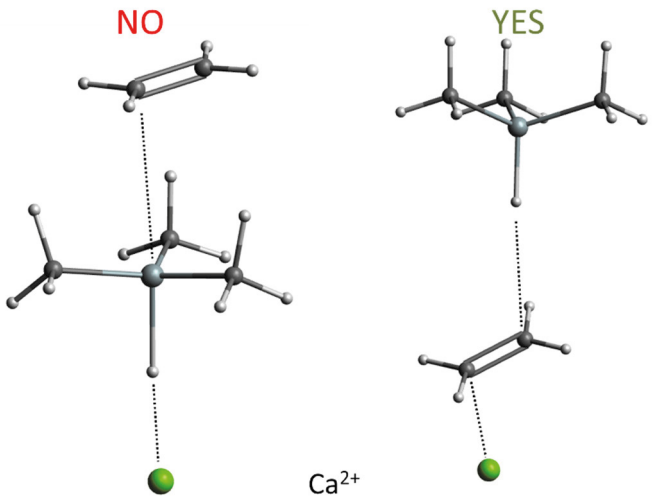


Figure 1: Arrangement of Lewis acid (here Ca^{2+}), silane and olefin according to Piers-Oestreich mechanism (left) and inverse Piers-Oestreich mechanism.

References

[1] B. Marciniec, *Hydrosilylation. A Comprehensive Review on Recent Advances*, Springer, 2009.
[2] S. Rendler and M. Oestreich, *Angew. Chem., Int. Ed.*, **2008**, *47*, 5997−6000.
[3] N. Asao , T. Sudo and Y. Yamamoto, *J. Org. Chem.*, **1996**, *61*, 7654−7655.

Perfluoroalkyl and Perfluoroalkylsulfonyl Nitrogen Compounds: Electrochemical Fluorination as Key Process

Maik Finze

Institute of Inorganic Chemistry, Institute for Sustainable Chemistry & Catalysis with Boron (ICB), University of Würzburg, Am Hubland, 97074, Würzburg, Germany

E-mail: maik.finze@uni-wuerzburg.de

Per- and polyfluorinated groups are key substituents for new materials, pharmaceuticals, and agrochemicals as they decisively influence properties and materials performance.[1] Examples are perfluoroalkylnitrogen derivatives, e.g. compounds that contain the bis(trifluoromethyl)amino group $–N(CF_3)_2$,[2,3] and perfluoroalkylimides such as salts of the cyclic perfluoroalkylsulfonylimide anions[4] [*cyclo*-{$(CF_2)_n(SO_2)_2N$}]$^-$ (n = 1–3). The electrochemical fluorination (ECF, Simons process) is one key method for the synthesis of these fluorinated compounds and materials.[5]

The bis(trifluoromethyl)amide anion $[N(CF_3)_2]^-$ is accessible via ECF to yield $SO_2\{N(CF_3)_2\}_2$ or $CF_3SO_2N(CF_3)_2$ followed by the reaction with a fluoride ion source.[3,5] The $[N(CF_3)_2]^-$ anion, which is the prototype perfluoroalkylamide anion, has been used for the introduction of this group into organic molecules,[5–7] it serves as ligand in coinage metal coordination chemistry,[7] and we have studied selected organic salts and ionic liquids. In addition, partially fluorinated derivatives are being currently investigated.

Perfluoroalkylsulfonylimides are a further, important class of nitrogen-based compounds and materials that are accessible via ECF as key synthetic step.[4,5] Recently, we have studied the three related cyclic perfluoroalkylsulfonylimide anions [*cyclo*-{$(CF_2)_n(SO_2)_2N$}]$^-$ (n = 1–3) in ionic liquid (IL) and transition metal chemistry.[8] The properties of ILs with the anions [*cyclo*-{$(CF_2)_n(SO_2)_2N$}]$^-$ (n = 1–3) have been compared to those of ILs with the related acyclic bis(trifluoromethylsulfonyl)imide (TFSI) anion.

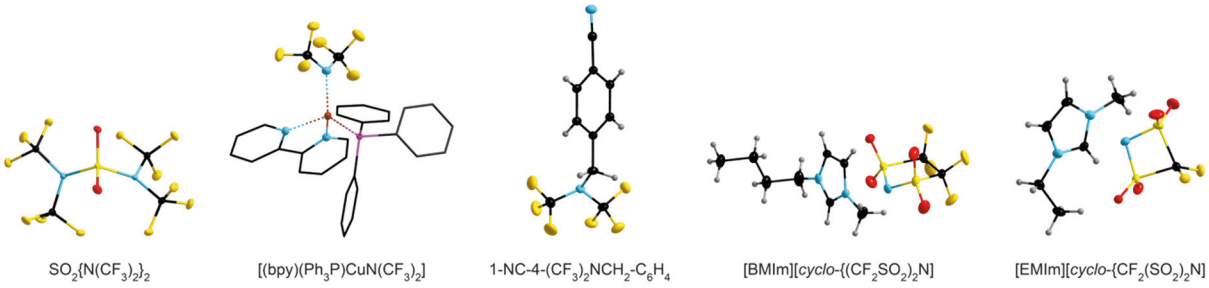
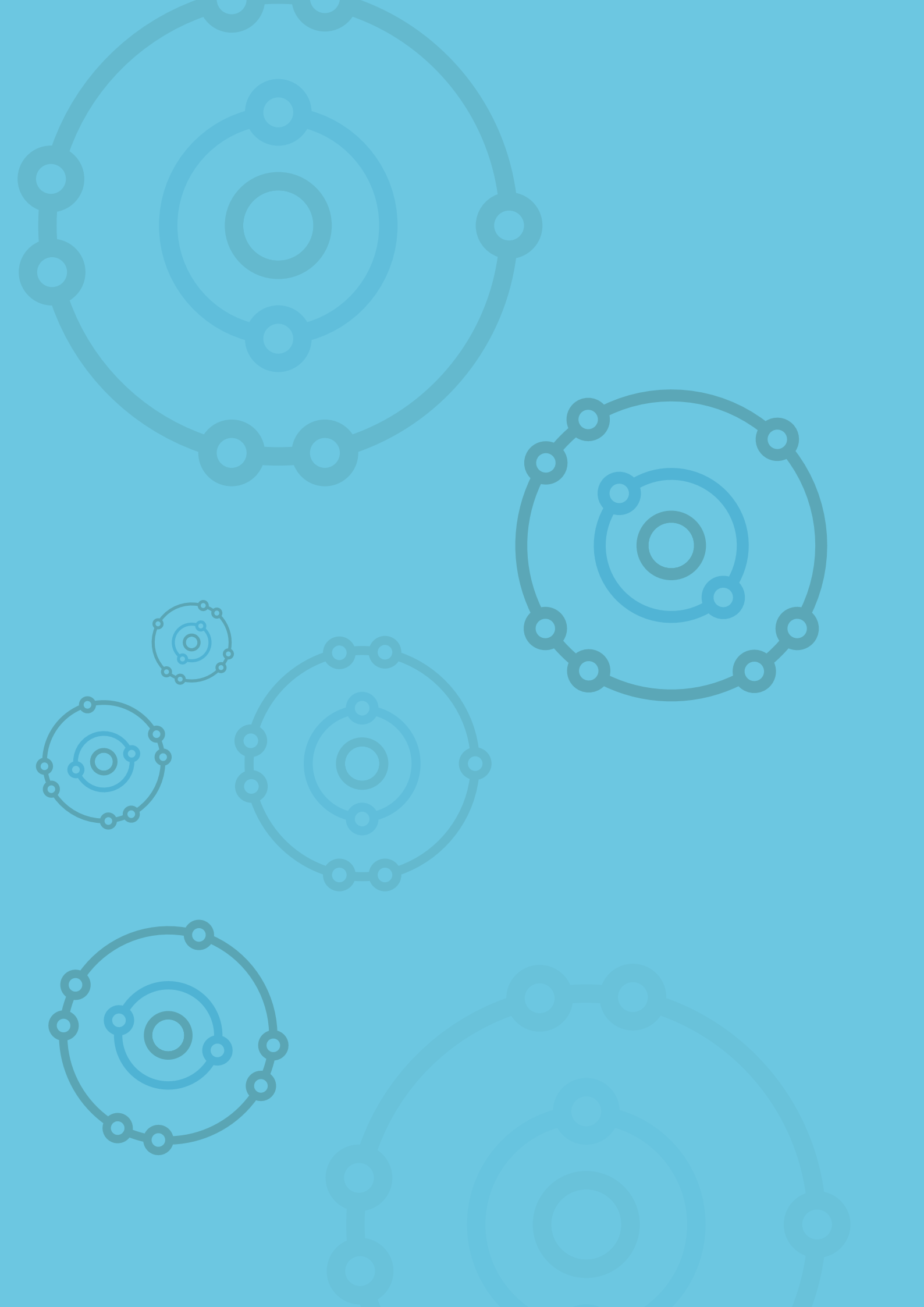


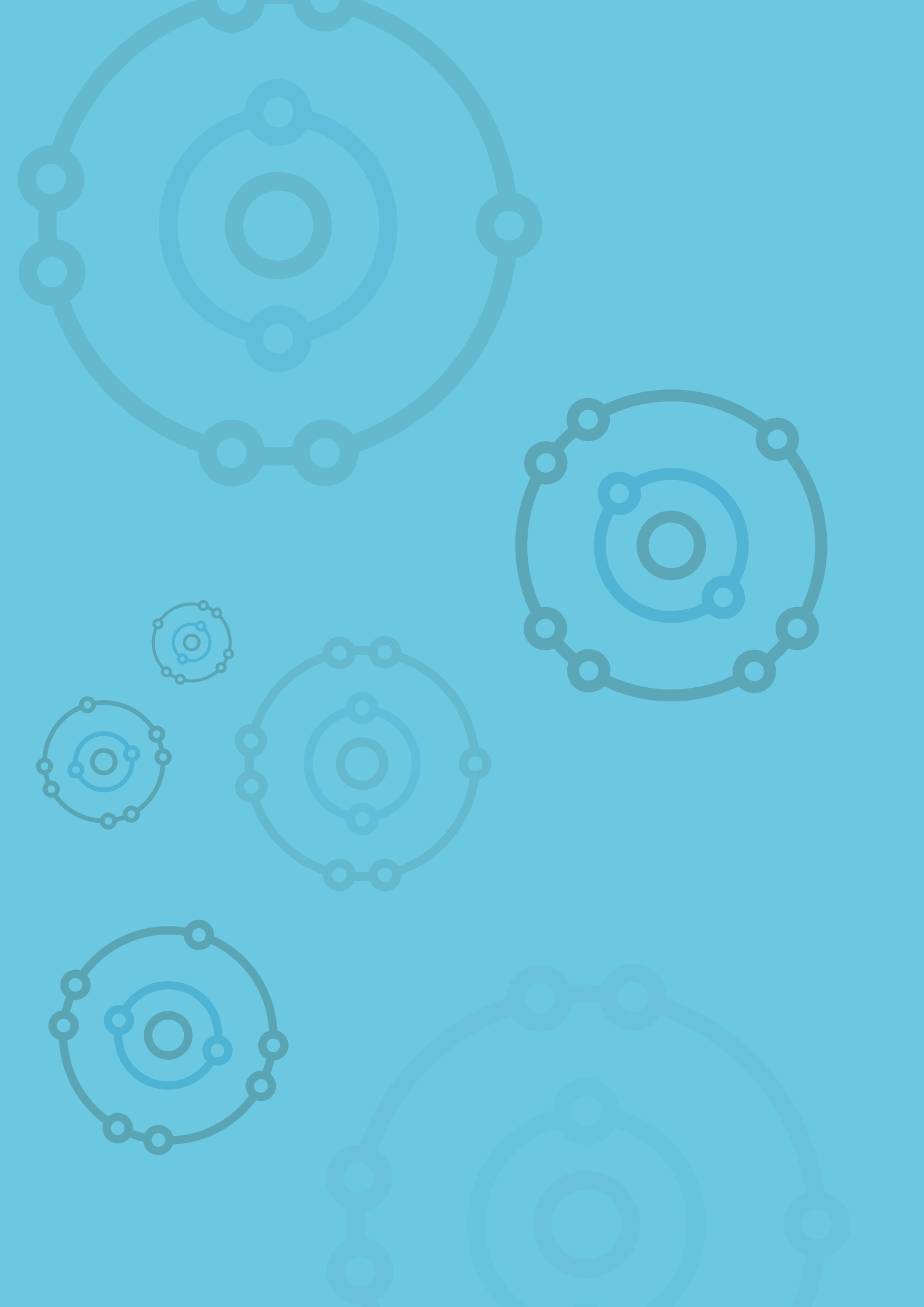
Figure 1: Crystal structures of derivatives of the anions $[N(CF_3)_2]^-$ and [*cyclo*-{$(CF_2)_n(SO_2)_2N$}]$^-$ (n = 1, 2).

References

[1] P. Kirsch, Modern Fluororganic Chemistry, 2 ed., Wiley-VCH Verlag GmbH, Weinheim, Germany, **2013**.
[2] H. G. Ang, Y. C. Syn, *Adv. Inorg. Chem. Radiochem.* **1974**, *16*, 1–64.
[3] P. Sartori, N. Ignat´ev, S. Datsenko, *J. Fluorine Chem.* **1995**, *75*, 157–161.
[4] R. Jüschke, D. Velayutham, P. Sartori, *J. Fluorine Chem.* **1997**, *83*, 145–149.
[5] N. V. Ignat'ev, *Electrochemical Fluorination: A Powerful Tool for the Preparation of Organofluorine Compounds* in *Modern Synthesis Processes and Reactivity of Fluorinated Compounds* (Eds.: H. Groult, F. Leroux, A. Tressaud), Elsevier Inc., London, UK, **2016**.
[6] C. Breitenstein, N. Ignat´ev, W. Frank, *J. Fluor. Chem.* **2018**, *210*, 166–177.
[7] L. N. Schneider, E.-M. Tanzer Krauel, C. Deutsch, K. Urbahns, T. Bischof, K. A. M. Maibom, J. Landmann, F. Keppner, C. Kerpen, M. Hailmann, L. Zapf, T. Knuplez, R. Bertermann, N. V. Ignat´ev, M. Finze, *Chem. Eur. J.* **2021**, *27*, 10973–10978.
[8] Y. K. J. Bejaoui, F. Philippi, H.-G. Stammler, K. Radacki, L. Zapf, N. Schopper, K. Goloviznina, K. A. M. Maibom, R. Graf, J. A. P. Sprenger, R. Bertermann, H. Braunschweig, T. Welton, N. V. Ignat'ev, M. Finze, *Chem. Sci.* **2023**, *14*, 2200–2214.



POSTER SESSION



Stereoselective Synthesis of Fluorinated Alkenylphosphonates Derived from Carbohydrates via the Horner-Wadsworth-Emmons Reaction

Monika Bilska-Markowska[1], Marcin Kaźmierczak[1,2], Wojciech Jankowski[1], Marcin Hoffmann[1]

[1]*Faculty of Chemistry, Adam Mickiewicz University, Uniwersytetu Poznańskiego 8, 61-614 Poznań, Poland*
[2]*Centre for Advanced Technologies, Adam Mickiewicz University, Uniwersytetu Poznańskiego 10, 61-614 Poznań, Poland*

E-mail: mbilska@amu.edu.pl

The synthesis of biologically significant compounds is based mainly on the ability to introduce an appropriate group of atoms into a target molecule. An interesting approach relevant to this case may be introduction of fluorine containing groups into organic molecules [1]. There are many examples of biological activities of phosphonic acid derivatives containing a fluorine atom in α position to the phosphonate group [2]. These compounds are isosteric analogues of natural products and act as the enzyme inhibitors [3]. There are also examples of phosphonate derivatives having a fluorine atom in a β position to a phosphorus atom and fluorinated or nonfluorinated unsaturated phosphonates [4].

A good route to obtain fluorinated alkenylphosphonates may be the Horner-Wadsworth-Emmons olefination [5]. Stereoselective synthesis of fluorinated unsaturated phosphonates derived from carbohydrates applying this reaction is a subject of the poster presentation. Due to the chiral nature and the possibility of functionalization, sugars were used as starting materials in this study [6,7].

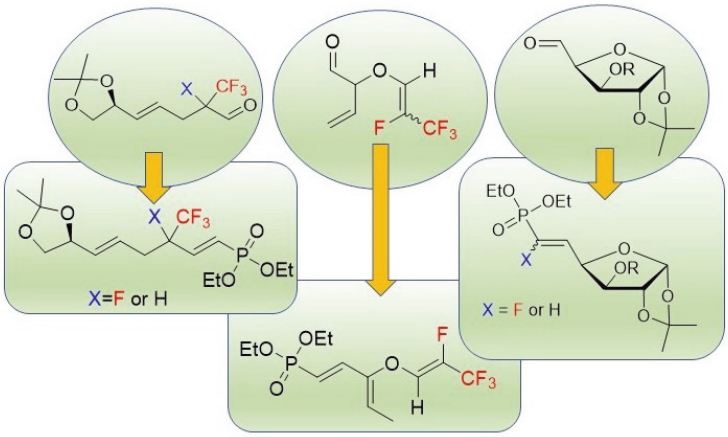


Figure 1: The goal of our research.

References

[1] N.A. Meanwell, *J. Med. Chem.* **2018**, *61*, 5822–5880.
[2] V.D. Romanenko, V.P. Kukhar, *Chem. Rev.* **2006**, *106*, 3868–3935.
[3] T.S. Elliott, A. Slowey, Y. Ye, S.J. Conway, *MedChemComm* **2012**, *3*, 735–751.
[4] M. Kaźmierczak, H. Koroniak, *J. Fluorine Chem*. **2012**, *139*, 23–27.
[5] M. Bilska-Markowska, M. Kaźmierczak, *Org. Biomol. Chem*. **2023**, *21*, 1095-1120.
[6] M. Bilska-Markowska, E. Patyk-Kaźmierczak, A. Lusina, *Eur. J. Org. Chem*. **2022**, *2022*, e202101378.
[7] M. Bilska-Markowska, W. Jankowski, M. Hoffmann, M. Kaźmierczak, *Molecules* **2022**, *27*, 5404.

Novel Deoxyfluorination Reagents

Šárka Bouzková, Markéta Rybáčková, Jaroslav Kvíčala

University of Chemistry and Technology, Prague, Technická 5, 166 28, Prague 6

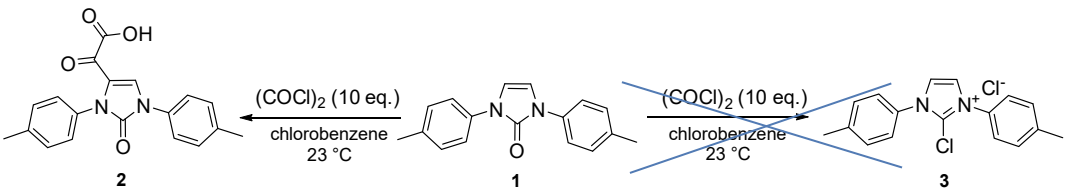
E-mail: bouzkovs@vscht.cz

Approximately 20% of the drugs available in the market contain at least one fluorine atom. However, the methods for safe and selective fluorination remain limited [1].

The introduction of commercially available *N*-heterocyclic reagents PhenoFluor™ and AlkylFluor™ have paved the way for the safe and selective insertion of fluorine into various aromatic and aliphatic compounds by replacing the hydroxyl group with a fluorine atom [2,3]. The biggest advantage of this method is its ability to deoxyfluorinate electron deficient substrates [2]. The main drawback is their high price.

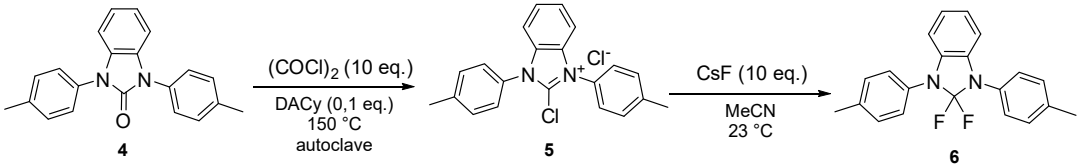
The published pathway to AlkylFluor™ and PhenoFluor™ involves carbene as the intermediate [2], but insufficient stability of the intermediary carbenes limits the strategy to the substrates bearing sterically demanding aromatic substituents. We hence developed a versatile route towards diarylated 1,3-dihydroimidazol-2*H*-ones and 1,3-dihydro-2*H*-benzimidazol-2-ones via Cu-catalyzed coupling of aryl iodides with the respective diamines.

Under chlorination conditions with oxalyl chloride, imidazolone **1** exhibited unexpected reactivity, as the enamine bond was more reactive than the intended carbonyl group. The reaction provided 2-oxocarboxylic acid **2** as the only product instead of the chloroimidazolium chloride **3** (Scheme 1).



Scheme 1: Chlorination of imidazolone **1**

On the contrary, chlorination of benzimidazolone **4** was successful. Following that, we were able to transform the key intermediate **5** into a novel type of the deoxyfluorinating reagent **6** (Scheme 2). The same reaction pathway was applied to synthesize derivate **7** (Figure 1).



Scheme 2: Synthesis of novel deoxyfluorinating reagent **6**

This work discusses the synthesis, reactivity, and efficacy of the new fluorinating reagents **6** and **7** towards variously substituted phenols.

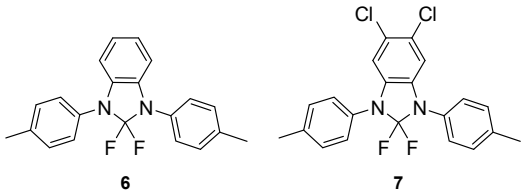


Figure 1: New deoxyfluorinating reagents **6** and **7**

References

[1] M.G. Campbell, T. Ritter, *J. Am. Chem. Soc.* **2014**, *18*, 474-480.
[2] P. Tang, W. Wang, T. Ritter, *J. Am. Chem. Soc.* **2011**, *133*, 11482-11484.
[3] N. W. Goldberg, X. Shen, J. Li, T. Ritter *Org. Lett.* **2016**, 18, 6102-6104.

TBAT Analogues: Syntheses, Structures, Fluorinations, Role of Substrates, Solvents and Additives

Adam Hroch, Michal Trojan, Jaroslav Kvíčala, Markéta Rybáčková

Department of Organic Chemistry, University of Chemistry and Technology, Prague, Technická 5, 166 28 Prague 6, Czech Republic

E-mail: hrocha@vscht.cz

Tetrabutylammonium difluorotriphenylsilicate (TBAT) is a nonhygroscopic salt well soluble in organic solvents, which serves as a cheap and ecological nucleophilic fluorination reagent. Compared to TBAF, it does not decompose in THF [1] and its basicity is lower, making it an ideal candidate for fluorination of substrates prone to elimination as secondary sulfonates or halides. However, high excess of the reagent has been reported to be essential for good yields of the fluorinated products [2]. With the idea to improve reactivity and chemoselectivity of the TBAT reagent, we synthesized several analogues modified in the aryl group by either electron-donating or electron-withdrawing substituents. For synthesized silicates **1a-1c**, single crystals were obtained (Figure 1).

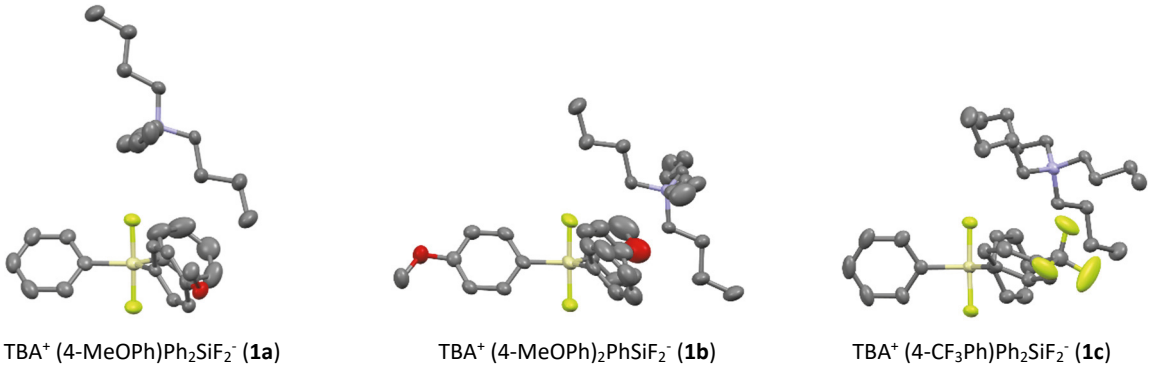
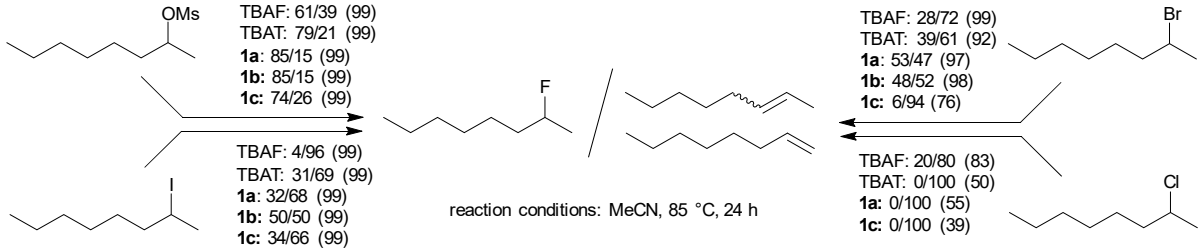


Figure 1: X-ray structures of synthesized TBAT analogues

Reactivity and chemoselectivity of new synthesized difluorosilicates **1a-1c** were compared with TBAT and TBAF in fluorinations of a series of primary and secondary sulfonates and halides, using only 2-fold excess of the reagents. As an example, the yields of fluorinations of 2-octyl substrates decreased in the following order:
R-OMs > R-Br > R-I > R-Cl (Scheme 1)



Scheme 1: NMR yields (in parentheses) and selectivities (fluorination/elimination) of the reactions of 2-octyl substrates

Difluorosilicates **1a** and **1b** bearing electron-donating groups provided comparable or better results than TBAT with almost all examined substrates, while **1c** gave inferior yields. For low temperature studies, EtCN was more suitable due to lower melting point, while *t*-BuCN could be used without the risk of solvent deprotonation. The role of other reaction conditions (solvents, temperature, additives etc.) will be further discussed.

This work was supported by the Czech Science Foundation (reg. No. 21-29531K).

References

[1] H. Sun, S.G. DiMagno, *J. Am. Chem. Soc.* **2005**, *127*, 2050-2051.
[2] A.S. Pilcher, H.L. Ammon, P. DeShong, *J. Am. Chem. Soc.* **1995**, *117*, 5166-5167.

A Novel Approach for Formylation of Halopyridines

Anastasiia N. Hurieva, Aleksandr N. Kostyuk, Serhii Zahorulko[1], Tetiana A. Shvydenko, Georgyi N. Koidan

Organophosphorus Department, Institute of Organic Chemistry, National Academy of Sciences of Ukraine, Akademika Kukharia Str. 5, 02094 Kyiv, Ukraine,

E-mail: stasyachem@ukr.net

Along with the broad catalytic utility of transition metal NHC complexes, C-H activation promoted by such species is also known. The use of diaminocarbenes as reagents themselves is generally diminished, since they differ in a relatively short half-life. We have experimentally observed formation of the latent diaminocarbene through a formal 1,2-silyl shift of isolable trimethylsilyl-substituted formamidine **1**. Its chemistry has been studied to some extent. Specifically, C-H bond insertion of this particular carbene into aromatics provided successful direct diamino methylation of benzene and thiophene derivatives[1,2]. The mechanism investigated by DFT methods showed that deprotonation of the electron-deficient arene by the basic carbene and subsequent collapse of the formed ion pair are the crucial steps of the C-H insertion reaction.

Pyridines $C_5NF_nH_{5-n}$ that arise when n varies from 1 to 4 with all possible regioisomers and a set of 3,5-disubstituted pyridines with various combination of halogen atoms were considered in this study. The reaction proceeded regiospecific depending on the structure of parent pyridine to give aminals **3**. Acidic hydrolysis of aminals **3** resulted in the corresponding aldehydes **4** presenting a novel formylation strategy for electron-deficient substrates (Scheme 1). Though methanolysis of derivatives **3** to methylimines was at times accompanied with nucleophilic substitution of one fluorine atom.

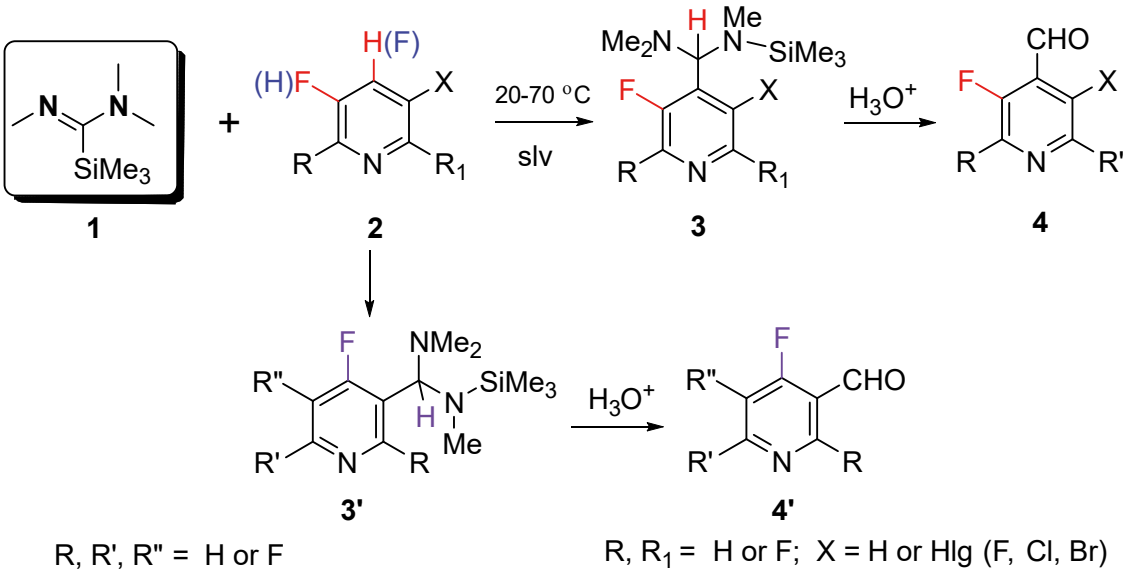


Figure 1: Silylformamidine **1** in the reaction with polyhalogenated pyridines.

References

[1] G. Koidan, A. Hurieva, S. Zahorulko, A. Zadorozhny, V. Lysenko, T. Shvydenko, E. B. Rusanov, A. Kostyuk, European *J. Org. Chem*. **2022**, (40), e202201048.

[2] G. Koidan, A. Hurieva, A. Rozhenko, U. Manthe, T. Spengler, S. Zahorulko, T. Shvydenko, A. Kostyuk, *J. Org. Chem*. **2023**, jo-2023-00470z under publication.

One-pot Synthesis of 1-Aryl-3-CF_3-pyrazoles Using Nitrile Imines and Mercaptoacetaldehyde as a Surrogate of Acetylene

Marcin Jasiński, Kamil Świątek, Greta Utecht-Jarzyńska

Department of Organic and Applied Chemistry, Faculty of Chemistry, University of Lodz, Tamka 12, 91403 Lodz, Poland

E-mail: mjasinski@uni.lodz.pl

1-Aryl-3-trifluoromethylpyrazole has been identified as privileged structural motif for a number of bioactive compounds applied either as pharmaceutics, crop protection materials or advanced organic materials.[1] For this reason, development of new synthetic methods to access fluorinated pyrazoles is of general interest. In this context, recently we have reported on several new protocols for preparation of multi-functionalized 3-CF_3-pyrazoles, including fused analogues, using readily available trifluoroacetonitrile imines as key fluorinated building blocks.[2-4] Here, synthetically useful approach for *one-pot* preparation of 1-aryl-3-trifluoromethylpyrazoles using the latter 1,3-dipoles and mercaptoacetaldehyde as an equivalent of acetylene will be presented. This protocol comprises (3+3)-annulation of the mentioned reagents to form 5,6-dihydro-5-hydroxy-4*H*-1,3,4-thiadiazine, followed by *p*TsCl-mediated dehydration and spontaneous or thermally induced Eschenmoser sulfide contraction.

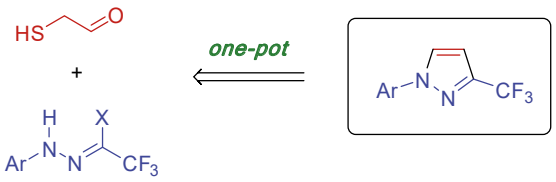


Figure 1: Structures of target 1-aryl-3-trifluoromethylpyrazoles and key reagents *i.e.* CF_3-nitrile imines and α-mercaptoacetaldehyde.

References

[1] P.K. Mykhailiuk, *Chem. Rev.* **2021**, *121*, 1670.
[2] G. Utecht, A. Fruziński, M. Jasiński, *Org. Biomol. Chem.* **2018**, *16*, 1252.
[3] A. Kowalczyk, G. Utecht-Jarzyńska, G. Mlostoń, M. Jasiński, *J. Fluorine Chem.* **2021**, *241*, 109691.
[4] A. Kowalczyk, G. Utecht-Jarzyńska, G. Mlostoń, M. Jasiński, *Org. Lett.* **2022**, *24*, 2499.

Synthesis and Cytotoxic Activity of Fluorinated Analogues of Lepidiline Alkaloids

Marcin Jasiński, Wiktor Poper, Mateusz Kowalczyk, Grzegorz Mlostoń

Department of Organic and Applied Chemistry, Faculty of Chemistry, University of Lodz, Tamka 12, 91403 Lodz, Poland

E-mail: mjasinski@uni.lodz.pl

Aqueous extracts of *Lepidium meyenii* (so-called *Maca*) have been applied for centuries in traditional folk medicine of the South American region. Nowadays, *Maca* is commercially available in Europe, and it is offered as food additive and dietary supplement. Some time ago, a series of imidazolium alkaloids, named as lepidilines, has been identified in *Maca*, and their promising cytotoxicity was reported (Fig 1).[1,2] Here we report on development of new methodology to access lepidilines, their fluorinated derivatives as well as non-ionic structural analogues, starting with readily available imidazole *N*-oxides. [3,4] Remarkable cytotoxicity of new F-containing derivatives against selected cell lines will also be presented.

natural alkaloids:

lepidiline A (X = H, Y = Cl),
lepidiline C (X = OMe, Y = Cl)

synthetic fluorinated analogues:

X = F, CF_3, OCF_3
Y = Cl, Br, PF_6

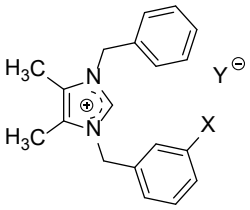


Figure 1. Structures of natural lepidilines and theirsynthetic fluorinated analogues

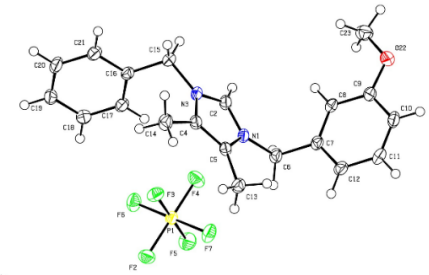


Figure 2. X ray structure of *lepidiline C hexafluorophosphate*.

Remarkably, the exchange of Cl to hexafluorophosphate (PF_6) resulted in substantial enhancement of native oily material (X = OMe) to form crystalline product, which enabled the ever first X-ray analysis of imidazolium salt considered as a lepidiline representative (Fig 2). [3]

The Authors gratefully thank the University of Lodz for financial support (W.P., grant no. 5/ODW/DGB/2022; G.M., project IDUB 2023).

References

[1] B. Cui, B. L. Zheng, K. He, Q. Y. Zheng, *J. Nat. Prod.* **2003**, *66*, 1101.
[2] W. Jin, X. chen, P. Dai, L. Lu, *Phytochem. Lett.* **2016**, *17*, 158
[3] G. Mlostoń, M. Kowalczyk, M. Celeda, K. Gach-Janczak, A. Janecka, M. Jasiński, *J. Nat. Prod.* **2021**, *64*, 3071.
[4] G. Mlostoń, M. Kowalczyk, M. Celeda, M. Jasiński, M. Denel-Bobrowska, A. B. Olejniczak, *Molecules* **2022**, *27*, 3524.

Chiral 5-Alkyl[2.2]paracyclophane-4-amines as Fluorination Reagent Precursors

Vít Jeníček, Jaroslav Kvíčala, Markéta Rybáčková

Department of Organic Chemistry, University of Chemistry and Technology, Prague, Technická 5, 166 28 Prague, Czech Republic

E-mail: jenicekv@vscht.cz

2-Fluoroimidazolium salt bearing two 2,6-diisopropylphenyl groups, known as AlkylFluor, is a powerful and stable reagent used for deoxyfluorination of alcohols.[1] The use of [2.2]paracyclophane units instead of diisopropylphenyl groups provides chiral compounds, which could be applied in enantioselective fluorination (Figure 1).

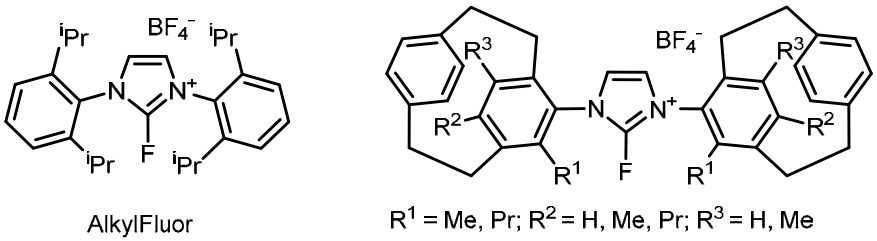
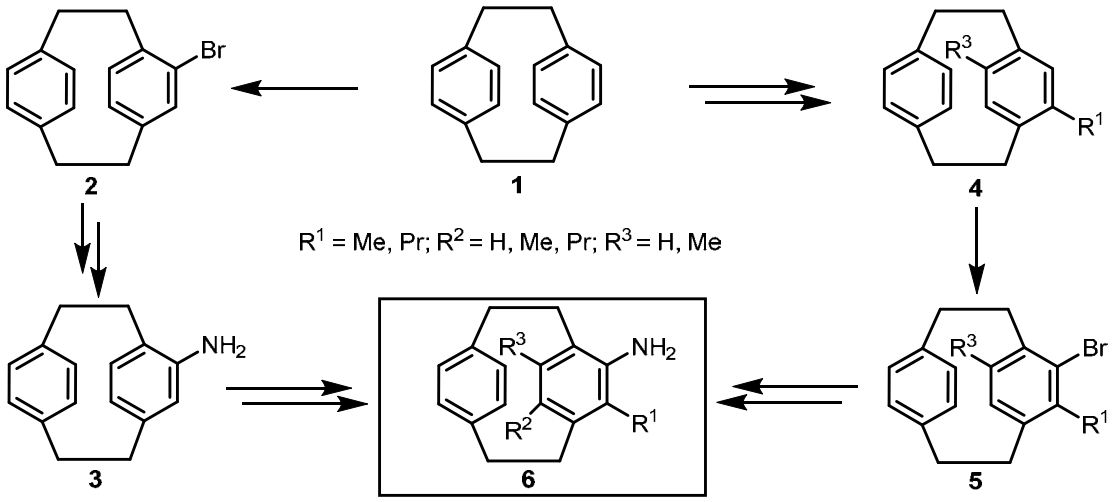


Figure 1: AlkylFluor and its [2.2]paracyclophane based analogue

We focused on synthesis of *ortho*-alkylated paracyclophanylamines. The steric effect of the *ortho*-alkyl substituents is important, as it is expected to increase thermodynamic stability of the intermediary carbene species.

Substituted [2.2]paracyclophane-4-amines **6** were prepared from commercially available [2.2]paracyclophane (**1**) either *via* intermediary 4-bromo-[2.2]paracyclophane (**2**) and [2.2]paracyclophane-4-amine (**3**), which was then alkylated, or *via* 4-alkyl[2.2]paracyclophane intermediate **4**,[2,3] which was brominated and subsequently transformed to the target amine.



Scheme 1: Synthesis of *ortho*-alkylated paracyclophanylamines

References

[1] N.W. Goldberg, X. Shen, J. Li, T. Ritter, *Org. Lett.* **2016**, *18*, 6102–6104.
[2] C.J. Friedmann, S. Ay, S. Bräse, *J. Org. Chem.* **2010,** *75*, 4612-4614.
[3] J.E. Gready, T.W. Hambley, K. Kakiuchi, K. Kobiro, S. Sternhell, C.W. Tansey, Y. Tobe, *J. Am. Chem. Soc.* **1990,** *112*, 7537-7540.

Synthesis of Bis(α,α-difluoro)ethers *via* Halo-perfluoroalkoxylation of *gem*-Difluoroalkenes

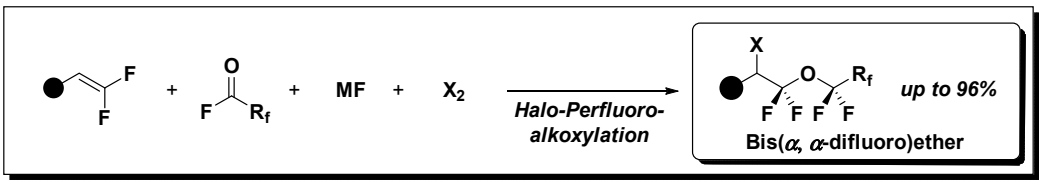
Koki Kawai[1], Naoyuki Hoshiya[2], Yoshimitsu Kato[1], Taichi Araki[1], Sota Ikawa[1], Yosuke Kishikawa[2], and Norio Shibata[1]

[1]*Department of Nanopharmaceutical Sciences, Nagoya Institute of Technology, Nagoya, Japan.*
[2]*DAIKIN Industies, LTD. Osaka, Japan*

E-mail: nozshiba@nitech.ac.jp

Organofluorine compounds are characterized by their high lipophilicity and metabolic stability, making them widely used in pharmaceuticals[1] and agrochemicals.[2] Among the organofluorine compounds, fluoroalkyl ethers, in which oxygen atoms link fluoroalkyl groups, have garnered significant attention in recent years. These compounds are not only useful in pharmaceutical and agrochemical applications but also in industrial applications such as battery electrolytes and semiconductor etching agents. Perfluoroalkyl ethers can be synthesized using various strategies, including the perfluorination of ethers and perfluoroalkylation of alcohols.[3] Nucleophilic perfluoroalkoxylation reactions are attractive methods for the preparation of perfluoroalkyl ethers.[4-7] However, one limitation of nucleophilic perfluoroalkoxylation is the instability of perfluoroalkoxides. They quickly decompose into perfluoroacyl fluorides by the elimination of fluoride through fluorine-induced negative hyperconjugation, making the reaction challenging.[3] Thus, highly electrophilic reactants such as alkyl triflates, benzyl bromides,[4] benzynes,[5] alkyl iodides,[6] and activated alkenes[7] should be used as reactants to perfluoroalkoxides, although the yields and substrate scope still need to be improved.

Previously, Evans et al. reported that fluorinated ethers were prepared in a three-component reaction involving olefins, halogens, and perfluorinated alkoxides.[7] However, the conversions were unsatisfactory. Building on this report, we investigated the halo-perfluoroalkoxylation of *gem*-difluoroalkenes using an improved reagent addition method (Scheme 1). High yields of the desired products were obtained under mild conditions at room temperature. Additionally, this reaction exhibited broad substrate applicability, enabling the synthesis of new bis(*α*,*α*-difluoro)ethers from bioactive substance derivatives. Notably, halo-substituted bis(*α*,*α*-difluoro)ethers produced in this reaction can undergo various conversion reactions, resulting in the synthesis of novel bis(*α*,*α*-difluoro)ethers.



Scheme 1: Halo-perfluoroalkoxylation of *gem*-difluoroalkenes

References

[1] Inoue, M., Sumii, Y., Shibata, N. *ACS Omega*, **2020**, *5*, 10633-10640.
[2] Ogawa, Y., Tokunaga, E., Kobayashi, O., Hirai, K., Shibata, N. *iScience* **2020**, *23*, 101467.
[3] Kirsch, P. *Modern Fluoroorganic chemistry*, Wiley-VCH, **2013**.
[4] Jelier, B. J., Howell, J. L., Montgomery, C. D., Leznoff, D. B., Friesen, C. M. *Angew. Chem. Int. Ed.* **2015**, *54*, 2945 –2949.
[5] Zhou, M., Ni, C., Zeng, Y., Hu, J. *J. Am. Chem. Soc.* **2018**, *140*, 6801-6805.
[6] Tong, C.-L., Xu, X.-H., Qing, F.-L. *Angew. Chem. Int. Ed.* **2021**, *60*, 22915-22924.
[7] Evans, F. W., Litt, M. H., Weidler-Kubanek, A-M., Avonda, F. P., *J. Org. Chem.* **1968**, *33*, 1839.

Difluoromethylation of Alkenes with Difluoroacetic Anhydride: Structure and Reactivity of Fluorinated Diacyl Peroxides and Radicals

Shintaro Kawamura[1,2], Takuma Tagami[1], Yusuke Mitani[2], Mikiko Sodeoka[1,2]

[1]*Catalysis and Integrated Research Group, RIKEN Center for Sustainable Resource Science, 2-1 Hirosawa, Wako, Saitama 351-0198, Japan*
[2]*Synthetic Organic Chemistry Laboratory, RIKEN Cluster for Pioneering Research, 2-1 Hirosawa, Wako, Saitama 351-0198, Japan*

E-mail: skawamura@riken.jp

Recently, difluoromethyl compounds have emerged as one of the most promising classes of molecules for the development of new pharmaceuticals and agrochemicals. This is due to their improved membrane permeability, metabolic stability, and pharmacokinetics resulting from the presence of fluorine, as well as their ability to induce unique intermolecular interactions, such as hydrogen bonding, due to the C–H bond. Therefore, practical and versatile synthetic methods for difluoromethyl compounds are highly desirable. Catalytic difluoromethylation reactions of alkenes mediated by CF_2H radicals are useful for the efficient construction of valuable skeletons bearing a CF_2H group. However, the catalytic reactions under thermal conditions are quite limited compared to the photocatalytic reactions, although the thermal ones can be performed by simple procedure without any special apparatus.

Our recent interest has focused on radical fluoroalkylation reactions using fluorinated carboxylic anhydrides as an inexpensive and readily available fluoroalkyl source.[1] We here developed a novel difluoromethylation reaction of alkenes using difluoroacetic anhydride (DFAA) (Figure 1).[2] We employed diacyl peroxide (BDFAP), which was in-situ prepared from DFAA and hydrogen peroxide, in the reactions of various alkenes in the presence of a copper catalysts. This method showed good generality in difunctionalizing difluoromethylations and could be applied to amino-, allylic, oxy-difluoromethylations, affording a wide variety of difluoromethyl molecules. In addition, alkenes bearing a pendant aromatic ring could provide benzofused molecules bearing a difluoromethyl group without the need for a copper catalyst. In addition to developing the reaction, we investigated the structures and reactivities of BDFAP and CF_2H radical in detail using theoretical calculations including NBO analysis, and discussed their behavior in the catalytic difluoromethylation.

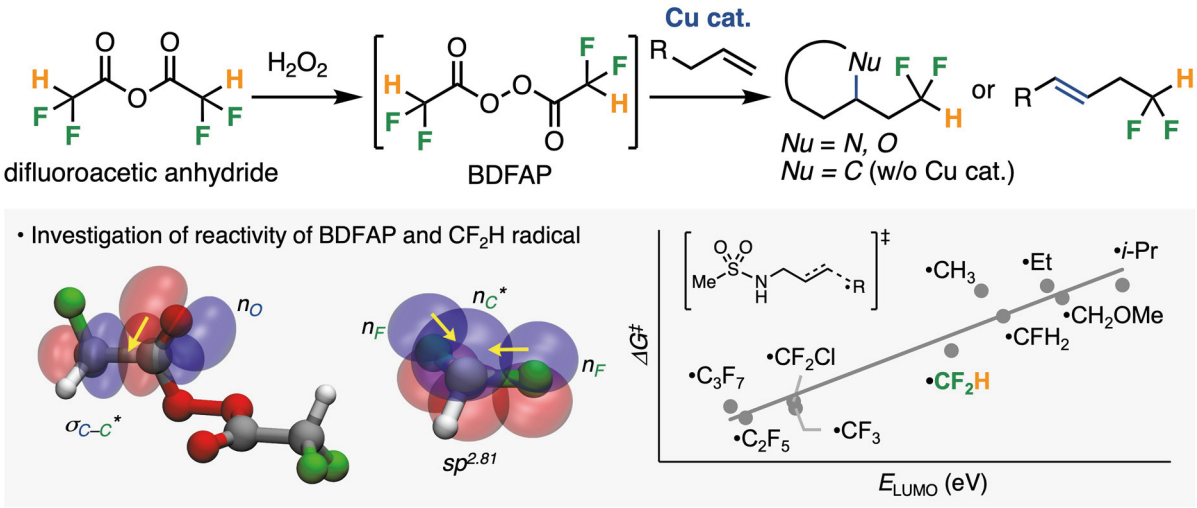


Figure 1: Difluoromethylation of alkenes: Structure and reactivity of BDFAP and fluoroalkyl radicals.

References

[1] Reviews: a) S. Kawamura, S. Mukherjee, M. Sodeoka, *Org. Biomol. Chem.* **2021**, *19*, 2096–2109; b) B. Fu, J. Escorihuela, J. Han, S. Fustero, P. Barrio, M. Sodeoka, S. Kawamura, A. Sorochinsky, V. Soloshonok, *Molecules* **2021**, *26*, 7221; c) S. Kawamura, P. Barrio, S. Fustero, J. Escorihuela, J. Han, V. A. Soloshonok, M. Sodeoka, *Adv. Synth. Catal.* **2023**, *365*, 398–462.
[2] T. Tagami, Y. Mitani, S. Kawamura, M. Sodeoka, *submitted*.

Synthesis and Potential Applications of Fluorinated Analogues of Aminophosphonic Acids

Marcin Kaźmierczak[1,3], Małgorzata Pawełczak[2], Henryk Koroniak[1]

[1]*Faculty of Chemistry, Adam Mickiewicz University in Poznań, Uniwersytetu Poznańskiego 8, 61-614 Poznań, Poland*
[2]*Institute of Chemistry, Opole University, 45-052 Opole, Poland*
[3]*Centre for Advanced Technologies, Adam Mickiewicz University in Poznań, Uniwersytetu Poznańskiego 10, 61-614 Poznań, Poland*

E-mail: marcin.kazmierczak@amu.edu.pl

Fluorinated aminophosphonates and phosphonic acids play a crucial role in the investigation of biochemical processes. They have wide-ranging applications in fields such as biological and medicinal chemistry, serving as enzyme inhibitors, agrochemicals, and pharmaceuticals.[1] One method for synthesizing fluorinated aminophosphonates involves the direct reaction between α-hydroxyphosphonates and nucleophilic fluorinating reagents. However, it is important to note that fluorination of molecules with diverse functional groups is challenging, and often requires creative synthetic approaches.[2]

We will present our synthesis efforts and explore the potential applications of dipeptide analogues of fluorinated aminophosphonic acid sodium salts (Figure 1).[3]

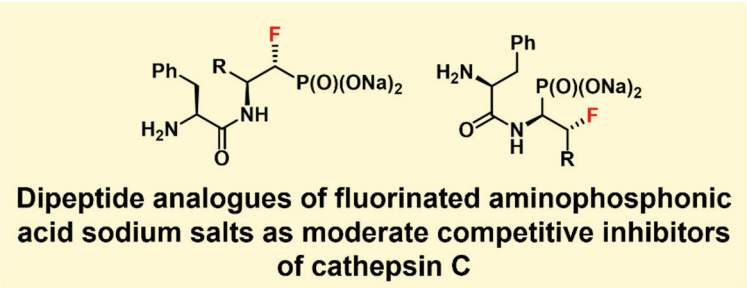


Figure 1: Structures of dipeptide analogues of fluorinated aminophosphonic acid sodium salts.

Acknowledgements:
We thank the National Science Centre (grant no. MINIATURA 2018/02/X/ST5/02867, HARMONIA 2017/26/M/ST5/00437) for the financial support

References

[1] (a) V. D. Romanenko, V. P. Kukhar, *Chem. Rev.* **2006**, *106*, 3868-3935; (b) K.V. Turcheniuk, V. P. Kukhar, G.-V. Röschenthaler, J. L.Aceña, V. A. Soloshonok, A. E. Sorochinsky *RSC Adv.* **2013**, *3*, 6693–6716; (c) T. Cytlak, M. Kaźmierczak, M. Skibińska, H. Koroniak, *Phosphorus Sulfur Silicon Relat Elem* **2017**, *192*, 602-620.
[2] M. Kaźmierczak, M. Bilska-Markowska, *Eur. J. Org. Chem*. **2021**, *2021*, 5585-5604.
[3] (a) M. Kaźmierczak, G. Dutkiewicz, T. Cytlak, *Synthesis*, **2020**, *52,* 2364-2372; (b) M. Kaźmierczak, H. Koroniak, *Beilstein J. Org. Chem*. **2020**, *16*, 756–762; (c) K. Wątroba, M. Pawełczak, M. Kaźmierczak, *Beilstein J. Org. Chem.* **2023**, *19*, 434–439.

Stereocontrolled Route to Fluorine-containing Functionalized Azaheterocycles and Amino Acid Derivatives

Melinda Nonn[1], Tamás Novák[2], Loránd Kiss[2]

[1]*MTA TTK Lendület Artificial Transporter Research Group, Institute of Materials and Environmental Chemistry, Research Center for Natural Sciences, Hungarian Academy of Sciences, Magyar Tudósok krt. 2, H-1117 Budapest, Hungary*
[2] *Stereochemistry Research Group, Institute of Organic Chemistry, Research Center for Natural Sciences, Magyar Tudósok krt. 2, H-1117 Budapest, Hungary*

E-mail: kiss.lorand@ttk.hu

Fluorine-containing azaheterocycles exhibit interesting biological properties and represent a valuable class of compounds in pharmaceutical research. Several fluorinated piperidine derivatives possess antiviral, antifungal and antibacterial properties [1-3 and cited references herein].

A simple, efficient synthetic methodology for the construction of fluorine-containing functionalized azaheterocycles and beta-amino acid derivatives has been developed. The synthetic concept was based on oxidative ring opening of substituted cycloalkenes through the ring olefinic bond through ozonolysis, followed by double reductive amination of the diformyl intermediates performed in the presence of various fluorinated alkylamines. The method has been extended for the preparation of alkylated and perfluoroalkylated derivatives. The transformations proceeded with stereocontrol: the configuration of the stereocenters in the products were predetermined by the configuration of the chiral centers of the starting substituted cycloalkanes [4,5].

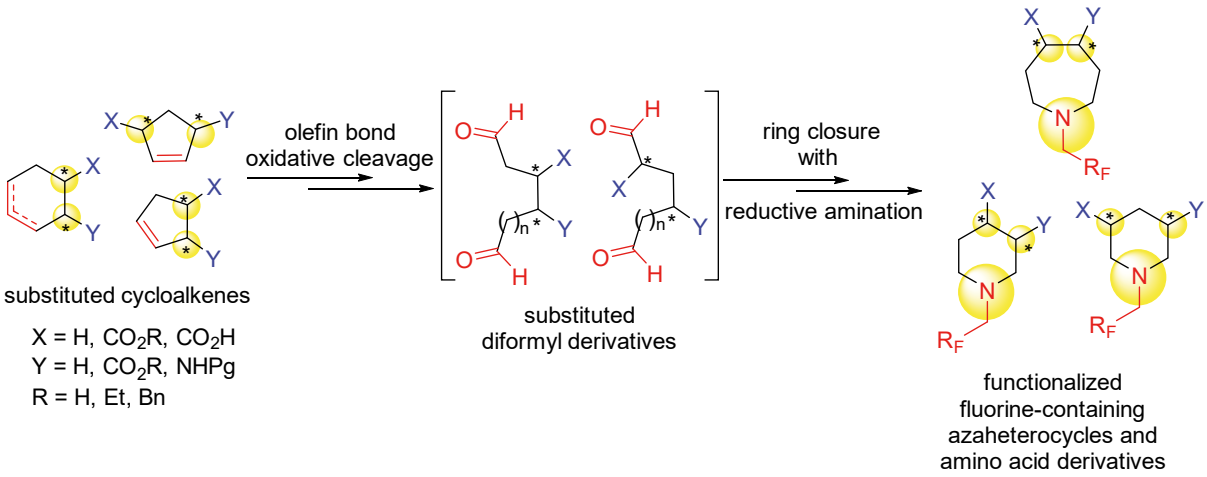


Figure 1: Synthesis of some functionalized, fluorine-containing azaheterocycles.

References

[1] L. Ouchakour, M. Nonn, A.M. Remete, L. Kiss, *Eur. J. Org. Chem.* **2021**, 3874-3885
[2] M. Nonn, D. Kara, L. Ouchakour, E. Forró, M. Haukka, L. Kiss, *Synthesis* **2021**, *53*, 1163-1173
[3] L. Kiss, L. Ouchakour, R.A. Ábrahámi, M. Nonn, *Chem. Rec*. **2020**, *20*, 120-141.
[4] L. Ouchakour, R.A. Ábrahámi, E. Forró, M. Haukka, F. Fülöp, L. Kiss, *Eur. J. Org. Chem.* **2019**, 2202-2211.
[5] L. Kiss, L. Ouchakour, M. Nonn, A.M. Remete, *Synlett* **2022**, *33*, 307-328

Synthesis and Reactivity of 2-Fluorinated Aziridine 2-Phosphonates from α,α-Halofluorinated ß-Iminophosphonates

Mateusz Klarek[1], Tomasz Siodła[1], Jean-Luc Pirat[2], David Virieux[2], Magdalena Rapp[1]

[1]*Department of Synthesis and Structure of Organic Compounds, Adam Mickiewicz University, Uniwersytetu Poznanskiego 8, 61-614 Poznan, Poland*
[2]*UMR 5253 - ICG Montpellier, Equipe AM2N, ENSCM, 8, rue de l'Ecole, Normale, 34296, Montpellier Cedex 5, France*

E-mail: matkla@amu.edu.pl

Aziridines represent one of the most valuable groups of heterocyclic intermediates in modern synthetic chemistry. The high attractiveness of title compounds, results from the possibility of ring opening, which can lead to many highly functionalized amino derivatives.[1] In addition, a strongly strained three membered ring plays an important role as a key building block in the synthesis of biologically important molecules, including natural products such as aza-sugars and alkaloids.[2, 3] A particular group of azaheterocyclic compounds are aziridine-2-phosphonates, which could be used as starting material in the synthesis of aminophosphonates.[4] Due to their structural similarities to amino acids, aminoalkylphosphonic acids and their esters can be recognized by enzymes or receptors as substrate counterparts and, in this way, may show inhibiting properties. Such structural features cause a unique enzyme response which led to the discovery of antifungal, antibacterial, and antihypertensive agents, inhibitors of proteases, including HIV-protease.[5] Moreover, the incorporation of fluorine into *β*-imino or *β*-aminophosphonate moiety may cause dramatic changes in their physical and biological properties. A very important consequence of the incorporation of fluorine atoms is the increased stability against proteolytic degradation derived from the high bond dissociation energy.[6]

Here, we disclose the first example of the synthesis of *N*-inactivated aziridines substituted by a fluorine and phosphonate moiety at the same carbon atom. We propose a convenient strategy starting from the condensation of the *β*-ketophosphonate (**1**, Fig.1) with primary amines (PG-NH_2), followed by a one-pot halofluorination reaction producing *α,α*-halofluorinated *β*-iminophosphonates (**2**, Fig.1). Reduction of the imine bond allows for intramolecular cyclization and the formation of three-membered fluorinated heterocycles (**3,** Fig.1). The synthesized products are air-stable and don't undergo spontaneous degradation. Based on the spectroscopic and theoretical studies as well as literature reports, we determined the *cis*/*trans* geometry of the obtained aziridines. We also present the intriguing influence of fluorine atom on the reactivity of aziridine-2-phosphonates *via* an acid-catalyzed ring opening reaction.

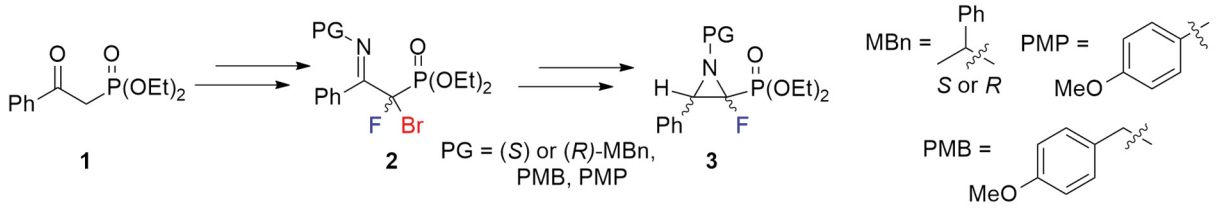


Figure 1: Synthesis of 2-fluorinated aziridine-2-phosphonates.

References

[1] T. Qadir, A. Amin, D. Sarkar, P. K. Sharma, *Current Organic Chemistry* **2021**, *25(16)*, 1868-1893.
[2] G.S. Singh, *Mini Reviews in Medicinal Chemistry* **2016**, *16(11)*, 892-904.
[3] G.S. Singh, M. D'hooghe, N. De Kimpe, *Chemical Reviews* **2007**, *107(5)*, 2080-2135.
[4] S. Polat-Cakir, N. Beksultanova, Ö. Dogan, *Phosphorus, Sulfur, and Silicon and the Related Elements* **2018**, *193(12),* 858-864.
[5] J. Wang, M.F. Ansari, J.M. Lin, C.H. Zhou, *Chinese Journal of Chemistry* **2021**, *39(8),* 2251-2263.
[6] W. R. Dolbier Jr, *Journal of Fluorine Chemistry* **2005**, *126(2),* 157-163.

Trapping of In Situ-Generated Trifluoroacetonitrile Imines with Electron-rich Dipolarophiles

Anna Kowalczyk[1,2], Greta Utecht-Jarzyńska[1], Marcin Jasiński[1*]

[1]*Department of Organic and Applied Chemistry, University of Lodz, Tamka 12, 91403 Łódź, Poland*
[2]*The University of Lodz Doctoral School of Exact and Natural Sciences, Banacha 12/16, 90237 Łódź, Poland*

E-mail: anna.kowalczyk@edu.uni.lodz.pl

Fluorinated pyrazoles, including fused analogues, have been recognized as privileged structural motif for a number of biologically active compounds applied either as pharmaceutics or as crop protection materials. A number of fluoroalkylated pyrazole-derived drugs exhibit a variety of activities such as anticancer, antiviral, antifungal, anti-inflammatory, and antibacterial, among the others. In this context, there is steadily increasing interest in development of synthetic methods towards fluorinated and non-fluorinated indazoles as platform for drug design.[1-4] Here, we report on our recent results in applications of nitrile imines of type **A** and arynes selected as electron-rich reaction partners for preparation of trifluoromethylated indazoles.

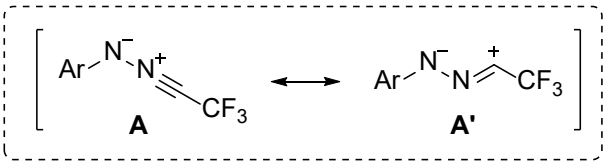


Figure 1: Structure of *in situ*-generated trifluoroacetonitrile imines **A**.

Financial support by the University of Lodz (grant no. 9/DGB/2022) is acknowledged

References

[1] J. Teichert *et al.*, *New J. Chem.* **2007**, *31*, 936.
[2] G.N. Lipunova, E.V. Nosova, V.N. Charushin, O.N. Chupakhin, *J. Fluorine Chem.* **2016**, *192*, 1.
[3] S.-G. Zhang, C-G. Liang, W-H. Zhang, *Molecules*, **2018**, *23*, 2783.
[4] S. Mal, U. Malik, M. Mahapatra, A. Mishra, D. Pal, S.K. Paidesetty, *Drug Dev. Res.* **2022**, *83*, 1469.

The Bis(trifluoromethyl)amino Group $N(CF_3)_2$ Synthesis and Building Blocks

Kristina A. M. Maibom[1], Leon N. Schneider[1], N.V. Ignat'ev,[1] Min Shan[2], Jean Wakim[2], Klaus Urbahns[2] ,M. Finze[1]

[1]*Institute of Inorganic Chemistry, Institute for Sustainable Chemistry & Catalysis with Boron (ICB), University of Würzburg, Am Hubland, 97074, Würzburg, Germany*
[2]*Merck Healthcare KGaA, Frankfurter Str. 250, Darmstadt, Germany*

E-mail: kristina.maibom@uni-wuerzburg.de

Per- and polyfluorinated groups are key substituents for new materials, pharmaceuticals, and agrochemicals as they decisively influence properties and materials performance.[1] The bis(trifluoromethyl)amino group $-N(CF_3)_2$ is an example for a perfluorinated group that offers high thermal and chemical stability, in general and provides lipophilicity and hydrophobicity. Due to the strongly electron-withdrawing trifluoromethyl groups, the amine is very weakly basic, only.[2–4]

The bis(trifluoromethyl)amino group $N(CF_3)_2$ is accessible via electrochemical fluorination (ECF, Simons process) in anhydrous HF (aHF) as key step.[3,4] The bis(trifluoromethyl)nitrogen derivatives $CF_3SO_2N(CF_3)_2$ and $SO_2\{N(CF_3)_2\}_2$, which are obtained via ECF of $CF_3SO_2N(CH_3)_2$ and $SO_2\{N(CH_3)_2\}_2$,[3,4] can be reacted with a fluoride source to give the $N(CF_3)_2^-$ anion.[4,5] Alkali metal salts of the $N(CF_3)_2^-$ anion can be generated and handled in solution, only, whereas salts with organic cations[4] and coinage metal complexes such as $[(bpy)AgN(CF_3)_2]$[6] can be isolated and stored. The bis(trifluoromethyl)amide anion can be introduced into organic molecules providing access to organic building blocks that contain a $N(CF_3)_2$ group. The nitrile $(CF_3)_2NCH_2CN$ and $(CF_3)_2NCH_2C(O)OH$ that are depicted in Figure 1[6,7] are examples for small organic building blocks, which have been used as versatile building blocks for the preparation of $N(CF_3)_2$-functionalized molecules.

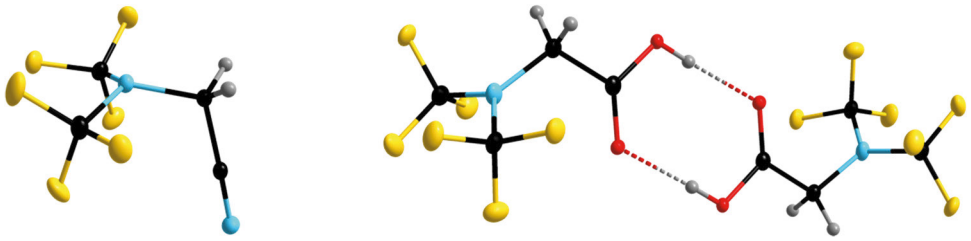


Figure 1: Crystal structures of $(CF_3)_2NCH_2CN$ (left) and a H-bonded dimer of $(CF_3)_2NCH_2C(O)OH$ (right).

References

[1] P. Kirsch, Modern Fluororganic Chemistry, 2 ed., Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, Germany, **2013**.
[2] H. G. Ang, Y. C. Syn, *Adv. Inorg. Chem. Radiochem.* **1974**, *16*, 1–64.
[3] P. Sartori, N. Ignat´ev, S. Datsenko, *J. Fluor. Chem.* **1995**, *75*, 157-161.
[4] Ignat'ev, in Modern Synthesis Processes and Reactivity of Fluorinated Compounds (Eds.: H. Groult, F. Leroux, A. Tressaud), Elsevier Inc., London, UK, **2016**.
[5] V. Hilarius, H. Buchholz, P. Sartori, N. Ignatiev, A. Kucherina, S. Datsenko, Merck Patent GmbH, WO2000046180, **2000**.
[6] L. N. Schneider, E.-M. Tanzer Krauel, C. Deutsch, K. Urbahns, T. Bischof, K. A. M. Maibom, J. Landmann, F. Keppner, C. Kerpen, M. Hailmann, L. Zapf, T. Knuplez, R. Bertermann, N. V. Ignat´ev, M. Finze, *Chem. Eur. J.* **2021**, *27*, 10973-10978.
[7] C. Breitenstein, N. Ignat´ev, W. Frank, *J. Fluor. Chem.* **2018**, *210*, 166-177.

Synthesis and Reactivity of Selected 2-Diazo-1,1-Difluoroalkyl Phosphonates: Masked Carbenes

Romana Pajkert,[1] Ita Hajdin,[1] Haibo Mei,[2] Jianlin Han,[2] Gerd-Volker Roeschenthaler[1]

[1]*School of Science, Constructor University Bremen, Bremen, Germany*
[2]*College of Chemical Engineering, Nanjing Forestry University, Nanjing, China*

E-mail: groeschenthaler@constructor.university

The phosphonate moiety is a common structural fragment present in a wide range of biologically active compounds. In addition, α,α-difluoromethylenphosphonates are very important analogues of natural phosphates[1] and have been found to be, for example, valuable enzyme inhibitors. To exploit one aspect of the rich chemistry we used the diazo group as a versatile building block and succeeded to synthesize 2-diazo-1,1,3,3,3-pentafluoropropyl phosphonate, a masked carbene, for the first time from 2-amino-1,1,3,3,3-pentafluoropropyl phosphonate and tert-butyl nitrite. Subsequently we applied the diazo derivative in different reaction routes, namely in insertion, cyclopropanation, and [3+2] cycloaddition reactions. As a result, diethyl (*Z*)-(2-ethoxy-1,3,3,3-tetrafluoroprop-1-en-1-yl) phosphonate, diethyl {difluoro[2-phenyl-1-(trifluoromethyl)cyclopropyl]methyl} phosphonate and ethyl 3-[(diethoxyphosphoryl) difluoromethyl]-3-(trifluoromethyl)-3H-pyrazole-5-carboxylate were obtained.[2,3] There are ongoing investigations, on synthesising further divers 2-diazo-1,1-difluoroalkyl phosphonate derivates as valuable building blocks.[2-9]

References

[1] M. Shevchuk, Q. Wang, R. Pajkert, J. Xu, H. Mei, G.-V. Röschenthaler, J. Han, *Adv. Synth. & Cat*., *Adv. Synth. & Cat*., **2021**, *363*, 2912–2968.
[2] H. Mei, J. Liu, R. Pajkert, L. Wang, G.-V. Röschenthaler, J. Han, *Org. Chem. Frontiers* **2021**, 8(4), 767-772.
[3] H. Mei, L. Wang, R. Pajkert, Q. Wang, J. Xu, J. Liu, G.-V. Röschenthaler, J. Han, *Org. Lett.,* **2021**, *23*, 1130−1134.
[4] J. Liu, J. Xu, R. Pajkert, H. Mei, G.-V. Röschenthaler, J. Han, *Acta Chim. Sinica* 化 学 学 报 **2021**, *79*, 747-750.
[5] Q. Wang, L. Wang, R. Pajkert, I. Hajdin, J. Liu, H. Mei, G.-V. Röschenthaler, J. Han, *J. Fluorine Chem.* **2021**, *251*, 109899.
[6] J. Liu, R. Pajkert, L. Wang, H. Mei, G.-V. Röschenthaler, J. Han, *Chinese Chem. Lett*., **2022,** *33*, 2429–2432.
[7] Haibo Mei, Qian Wang, R. Pajkert, Jiang Liu, G.-V. Röschenthaler, Jianlin Han, *Adv. Synth. & Cat*., **2022**, 364(12), 1969-1974.
[8] Qian Wang, Nana Wang, Jiang Liu, Haibo Mei, R. Pajkert, M. Kessler, G.-V. Röschenthaler, Jianlin Han, *Org. Lett.* **2022**, *24*(43), 8036-8040.
[9] I. Hajdin, R. Pajkert, M. Keßler, Jianlin Han, Haibo Mei, G.-V. Röschenthaler, Beilstein *J. Org. Chem*. **2023**, *19*, 541–549.

Acylation of Electron-rich Arenes with Unprotected Amino Acids

Michał Piotrowicz[1], Natasza Masłowska[1], Róża Jastrzębska[2], Anna Makal[2], Bogna Rudolf[1]

[1]*Department of Organic Chemistry, Faculty of Chemistry, University of Łódź, Tamka 12, 91-403 Łódź, Poland*
[2]*Biological and Chemical Research Center, University of Warsaw, Żwirki i Wigury 101, 02-089 Warsaw, Poland*

E-mail: michal.piotrowicz@chemia.uni.lodz.pl

Aminoketones are an important class of organic compounds. They play an important role as a high-value synthons in synthetic and medicinal chemistry. The most notable examples are Bupropion, Amfepramone, Tolperisone and Oxyfedrine [1,2]

Herein we reported the synthesis of the *N*-trifluoroacetyl amidoketones by direct acylation of electron-rich arenes (ferrocene and pyrene) with unprotected amino acids. The acylation is achieved with the use of trifluoroacetic anhydride/ triflic acid system, previously used for functionalization of ferrocene and pyrene with carboxylic acids.[3, 4]

We postulate mechanism that includes *in situ* conversion of unprotected amino acids to reactive *N*-trifluoroacetamides mixed anhydride species. Protonated by triflic acid they generate appropriate carbocations which attacks the electron-rich arenes to form *N*-trifluoroacetic amidoketones.

The obtained *N*-trifluoroacetyl amidoketones can be easily deprotected and converted to corresponding aminoketones. Both ferrocenyl and pyrenyl amidoketones can be used as versatile building blocks for syntheses of more complex compounds, like molecular probes or optoelectronic materials.

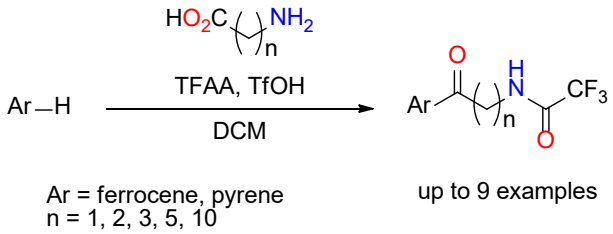


Figure 1: Acylation of electron-rich arenes with unprotected amino acids.

References

[1] L. A. T. Allen, R.-C. Raclea, P. Natho, P. J. Parsons, *Org. Biomol. Chem.* **2021**, *19*, 498.
[2] M. M. Hammouda, K. M. Elattar, *RSC Adv.* **2022**, *12*, 24681.
[3] D. Plażuk, J. Zakrzewski, *Synth. Commun.* **2004**, *34*, 99-107.
[4] R. Flamholc, D. Plażuk, J. Zakrzewski, R. Metivier, K. Nakatani, A. Makal, K. Woźniak, *RSC Adv*. **2014**, *4*, 31594-31601.

Amino Acids with Fluorovinyl Moiety: Synthesis and Mechanistic Studies

Katarzyna Salamon-Krokosz[1], Katarzyna Koroniak-Szejn[2], Henryk Koroniak[1]

[1]*Synthesis and Structure of Organic Compounds department, Faculty of Chemistry, Adam Mickiewicz University, Uniwersytetu Poznańskiego 8, Poznań, Poland*
[2]*Coordination Chemistry department, Faculty of Chemistry, Adam Mickiewicz University, Uniwersytetu Poznańskiego 8, Poznań, Poland*

E-mail: katarzyna.salamon@amu.edu.pl

Fluorination has become recently an increasingly popular strategy in protein biochemistry [1]. Fluorination has been shown as being well tolerated by a variety of proteins without introducing steric perturbation to the parent structure. The employment of ^{19}F-labeled amino acids appeared an attractive approach due to the signal sensitivity of fluorine and lack of background signals [2]. Replacement of peptide bonds with non-hydrolyzable mimetic is one of the most promising approaches toward overcoming the major drawbacks of peptides, including poor bioavailability and rapid proteolysis. One of the possible mimetic approaches is replacing the peptide bond with fluorovinyl group. In fluorvinyl moiety, the fluorine atom in *Z*-fluoroalkene mimics the carbonyl oxygen atom of peptide bond. It allows improving bioavailability and reducing susceptibility to rapid proteolysis [3].

Herein, we present the synthesis of fluorovinyl amino acid derivatives based on a typical modification of *L*,α-amino acids with the use of the Horner-Wadsworth-Emmons reaction which allowed the incorporation of the monofluorovinyl moiety into molecule. The unexpected formation of fluorinated lactams by the self-driving cyclization of the linear derivative of *N*-Boc-protected fluorovinyl amino acids is also reported. We also present the DFT calculations which have shown the most probable mechanism of cyclization [4].

The authors acknowledge the financial support from the HARMONIA 9 Grant UMO-2017/26/M/ST5/00437 and High-Chem Project POWR.03.02.00-00-I020/17 co-financed by European Union resources.

References

[1] A. Choudhary, R.T. Raines, *ChemBioChem* **2011**, 12, 1801-1807.
[2] C. Dalvit, S.Y. Ko, A. Vulpetti, *J. Fluorine Chem*. **2013**, 152, 129-135.
[3] P.A. Champagne, J. Desroches, J.F. Paquin, *Synthesis* **2015**, 47, 306.
[4] K. Salamon-Krokosz, M. Gołdyn, T. Siodła, E. Bartoszak-Adamska, H. Koroniak, K. Koroniak-Szejn, *Synthesis* **2022**, 54, 3785-3792.

Copper-mediated 1,2-Bis-perfluoroalkylations of Alkenes and Alkynes with Perfluorocarboxylic Anhydrides

Takuma Tagami[1], Yuma Aoki,[1] Shintaro Kawamura,[1,2] Mikiko Sodeoka[1,2]

[1]*Catalysis and Integrated Research Group, RIKEN Center for Sustainable Resource Science, 2-1 Hirosawa, Wako, Saitama 351-0198, Japan*
[2]*Synthetic Organic Chemistry Laboratory, RIKEN Cluster for Pioneering Research, 2-1 Hirosawa, Wako, Saitama 351-0198, Japan*

E-mail: takuma.tagami@riken.jp

Perfluoroalkyl-containing organic molecules are highly valued in the field of pharmaceuticals and organic functional materials, because the perfluoroalkyl group can improve their physical, chemical, and biological properties. Among perfluoroalkyl compounds, alkanes and alkenes bearing two perfluoroalkyl groups on their vicinal carbons are expected to exhibit unprecedent functions due to their unique structures. Thus, methods for the 1,2-bis-perfluoroalkyaltion of alkenes and alkynes have been actively studied for nearly 50 years. However, accessible 1,2-bis-perfluoroalkylated compounds remain limited maybe due to a scarcity of perfluoroalkylating reagents that can introduce long perfluoroalkyl chains, in contrast to various 1,2-bis-trifluoromethylated compounds that can be synthesized with sophisticated trifluoromethylating reagents.

Our group successfully utilized perfluorocarboxylic anhydrides as an inexpensive and readily available perfluoroalkyl radical source so far. Under our conditions, diacyl peroxides were prepared in situ from the anhydrides and hydrogen peroxide and used for radical perfluoroalkylation reactions.[1] Here, we report a novel copper-mediated protocol for the 1,2-bis-perfluoroalkyaltion of alkenes/alkynes with perfluorocarboxylic anhydrides, which can introduce not only CF_3 group but also C_2F_5 and C_3F_7 groups (Figure 1).[2] The reaction allows for the synthesis of various 1,2-bis-perfluoroalkylated compounds, including unique tetrasubstituted alkenes. The addition of bipyridyl ligand (bpy) together with a copper(I) salt was essential for the successful transformation. Our mechanistic studies suggested that the key step in this reaction is the formation of a stable perfluoroalkylcopper intermediate $[(bpy)_2Cu^{II}R_f]^+$, which promotes the introduction of the second perfluoroalkyl group to the alkyl- or viny-radical generated by the reaction of the substrate alkene or alkyne with perfluoroalkyl radical, respectively.

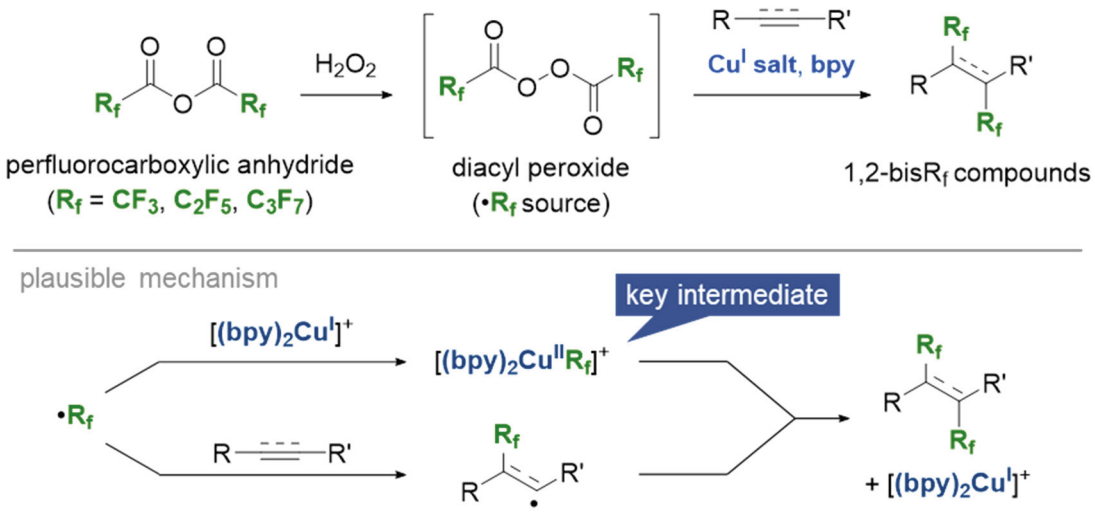


Figure 1: 1,2-Bis-perfluoroalkylations of alkenes and alkynes with perfluorocarboxylic anhydrides.

References

[1] Recent reviews: (a) S. Kawamura, P. Barrio, S. Fustero, J. Escorihuela, J. Han, V. A. Soloshonok, M. Sodeoka, *Adv. Synth. Catal.* **2023**, *365*, 398–462. (b) S. Kawamura, S. Mukherjee, M. Sodeoka, *Org. Biomol. Chem.* **2021**, *19*, 2096–2109. (c) S. Kawamura, M. Sodeoka, *Bull. Chem. Soc. Jpn.* **2019**, *92*, 1245–1262.

[2] T. Tagami, Y. Aoki, S. Kawamura, M. Sodeoka, *Org. Biomol. Chem.* **2021**, *19*, 9148–9153.

S_NAr Reactions of Phenol Derivatives with Fluorobenzenes

Feng Wang, Frederik Diness

Department of Science and Environment, Roskilde University, Universitetsvej 1, Roskilde, Denmark

E-mail: Fengw@ruc.dk

Diphenyl ether is an important molecular substructure due to its widespread occurrence in natural compounds and diverse applications e.g. as pharmaceuticals or polymers. [1] As a general concept we have explored S_NAr reactions for N-, O- or S-arylations. [2, 3, 4, 5] In this communication we present the synthesis of diphenyl ether from phenols and fluorobenzene derivatives via S_NAr reactions. A range of phenol derivatives was reacted with selected fluorobenzenes in order to optimize reaction conditions, examining the influence of the phenol pKa, and asses the steric effects. This approach enables the development of efficient and convenient protocols for the synthesis of diphenyl ether. The methodology was successfully applied to complex phenol-containing natural products, highlighting the potential for application in late-stage modifications of bioactive compounds.

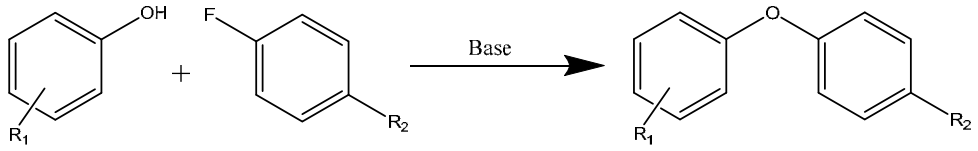


Figure 1: S_NAr reaction of phenol derivatives with fluorobenzenes.

References

[1] Hou, J.; Zhao W.; Huang, Z. N.; et al. *Chemical Biology & Drug Design*, **2015**. *86*(2): p. 223-231.
[2] Nikitin, S.; Lie, Y.; Diness, F. *Macromolecular Chemistry and Physics* **2022**, 2100484
[3] Embaby, A. M.; Schoffelen, S.: Kofoed, C.; Meldal, M.; Diness, F. *Angewandte Chemie International Edition*, **2018**, *57*, 8022-8026
[4] Jacobsen, C. B.; Meldal, M.; Diness, F. *Chemistry - A European Journal*, **2017**, *23*, 846-851
[5] Diness, F.; Fairlie, D. P. *Angewandte Chemie International Edition*, **2012**, *51*, 012-8016.

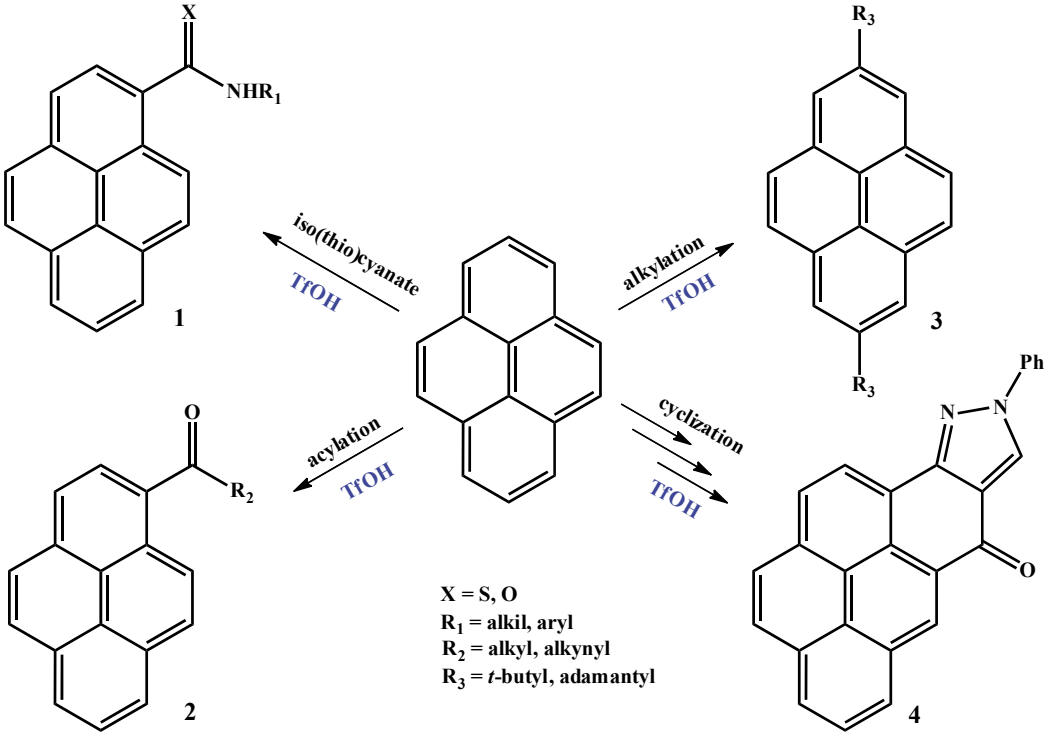
The Use of Triflic Acid in the Synthesis of New Pyrene Fluorophores

Anna Wrona-Piotrowicz[1], Anna Makal[2], Janusz Zakrzewski[1]

[1]*Department of Organic Chemistry, Faculty of Chemistry, University of Lodz, Tamka 12, 91-403 Lodz, Poland,*
[2]*Biological and Chemical Research Center, University of Warsaw, Żwirki i Wigury 101, 02-089 Warsaw, Poland*

E-mail: anna.wrona@chemia.uni.lodz.pl

Pyrene and its derivatives have found application in many areas of science, technology and life. This is influenced by the unique properties of these compounds, including: long fluorescence lifetimes or high fluorescence quantum efficiency, as well as the ability to control the color of the emitted light. Due to the high application potential, methods of modification the pyrene system which leads to new derivatives are still being sought [1]. In recent years, we have proposed several solutions to obtain new pyrene fluorophores with interesting photophysical properties, both in solutions and in solid state. Trifluoromethanesulfonic acid (CF_3SO_3H, triflic acid, TfOH) turned out to be particularly useful for us in the synthesis of these pyrene derivatives (Scheme 1). Triflic acid, due to increased thermal stability and resistance to oxidation and reduction, is particularly useful as a reagent and solvent in organic synthesis. We have shown that the Friedel-Crafts reaction of pyrene or 2,7-di*tert*butylpyrene with alkyl and aryl isocyanates and isothiocyanates, carried out in the presence of trifluoromethanesulfonic acid, allows obtaining the corresponding amides and thioamides **1** in high yields (85-95%) [2, 3].



Scheme 1: Application of triflic acid in the synthesis of pyrene derivatives.

In recent years, we have also demonstrated the great utility of TfOH in the acylation and alkylation of pyrene [4, 5]. In addition, triflic acid was used by us for the cyclization reaction, as a result of which we obtained type **4** fluorophores with a rigid structure and interesting photophysical properties [6].

This research was funded by University of Lodz, grant number 9/GNZPA/2022.

References

[1] T. M. Figueira-Duarte, K. Müllen, *Chem. Rev*. **2011**, *111*, 7260-7314.
[2] A. Wrona-Piotrowicz, J. Zakrzewski, R. Métivier, A. Brosseau, A. Makal, K. Woźniak, *RSC Advances* **2014**, *4*, 56003–56012.
[3] A. Wrona-Piotrowicz, M. Witalewska, J. Zakrzewski, A. Makal, *Beilstein J. Org. Chem* **2017**, *13*, 1032–1038.
[4] Y. Hirai, L. Laize-Générat, A. Wrona-Piotrowicz, J. Zakrzewski, A. Makal, A. Brosseau, L. Michely, D.-L. Versace, C. Allain, R. Métivier, *ChemPhysChem,* **2021**, *22*, 1638–1644.
[5] A. Wrona-Piotrowicz, A. Makal, J. Zakrzewski, *J. Org. Chem.* **2020**, *85*, 11134–11139.
[6] A. Wrona-Piotrowicz, A. Makal, J. Zakrzewski, *Molecules*, **2022**, *27*, 1272.

Dehydrofluorination of Fluoroalkanes Catalyzed by Germylium Ions

Julie Borel, Thomas Braun

Department of Chemistry, Humboldt-Universität zu Berlin, Brook-Taylor-Str. 2, 12489 Berlin, Germany

E-mail: julie.borel@hu-berlin.de

Silylium and germylium cations present both a strong Lewis Acidity and a high fluoride affinity, making them compounds of particular interest for the activation of C–F bonds. Unlike the reactions using silylium ions that lead to hydrodefluorinations, [1,2] *in situ* generated germylium cations $[R_3Ge]^+[WCA]^-$ enable C–F bond activation of monofluoroalkanes and tend - through a catalytic reaction - to give hydrodefluorination but also dehydrofluorination products (Figure 1). During the process, H_2 and fluorogermanes are formed, as well as di- and polynuclear germane species, that may be crucial for the olefin formation to take place. [3,4]

The reactivity of some isolated and *in situ* generated germylium ions was studied as well as their interactions with the reaction system. Generally, germylium ions exhibit different reactivities when compared to these of their silylium analogues, which opens up a range of possibilities for the C–F bond activation and functionalisation of fluoroalkanes.

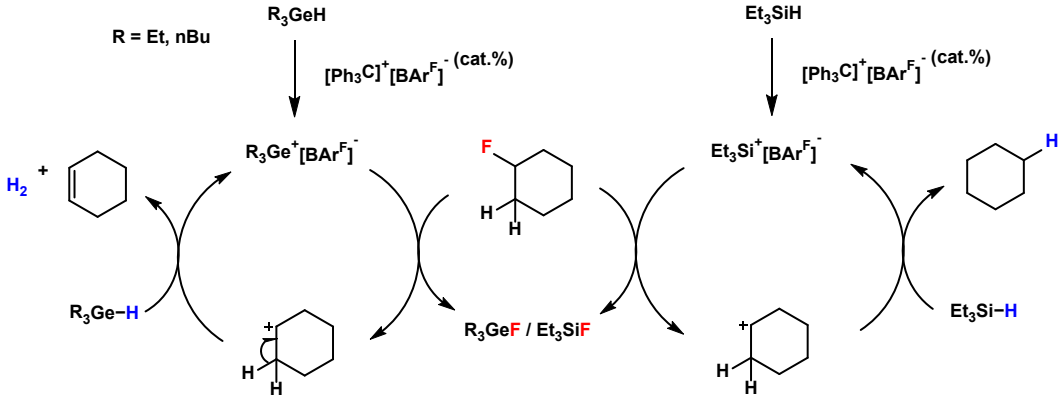


Figure 1: Catalytic cycles of the dehydrofluorination and hydrodefluorination of fluorocyclohexane.

References

[1] V.J. Scott, R. Celenligil-Cetin, O.V. Ozerov, *J. Am. Chem. Soc.* **2005**, *127*, 2852–2853.
[2] R. Panisch, M. Bolte, T. Müller, *J. Am. Chem. Soc*. **2006**, *128*, 9676−9682.
[3] A. Hayatifar, A. Borrego, D. Bosek, M. Czarnecki, G. Derocher, A. Kuplicki, E. Lytle, J. Padilla, C. Paroly, G. Tubay, J. Vyletel, C. S. Weinert, *Chem. Commun.* **2019**, *55*, 10852–10855.
[4] M. Talavera, G. Meißner, S. G. Rachor, T. Braun, *Chem. Commun.* **2020**, *56,* 4452–4455.

Two Candidates as Potential Alternatives for SF_6 in Electric Devices

Holger Pernice, Paul Golz, Gesa H. Dreyhsig, Jan-Hendrik Nissen, Thomas Drews, Tobias Schlöder, Anja Wiesner, Helmut Beckers, Simon Steinhauer, Sebastian Hasenstab-Riedel

Inorganic Chemistry, BCP, Freie Universität Berlin, Fabeckstr. 34-36, D-14195 Berlin, Germany

E-mail: holger.pernice@fu-berlin.de

Sulfur hexafluoride (SF_6) has been used as an insulating gas in medium and high voltage electric devices for decades. Due to its very high Global Warming Potential (GWP) of about 24000, the search for alternatives has been going on for decades too. The European Commission intends to phase out use of SF_6 in all new equipment for electrical transmission by 2031 [1].

Two potential candidates, CF_3OSO_2F [2] and CF_3OSF_5 [3], were identified, synthesized and evaluated in our search for suitable SF_6 alternatives. While both seem promising in some respects, neither completely fulfils all the requirements.

Electric discharge breakdown properties and light arc decomposition products were investigated, the critical points of both molecules were determined and the molecular structures, see figure 1, in solid state were investigated by single-crystal X-ray diffraction after crystals were obtained by *in-situ* crystallization [4].

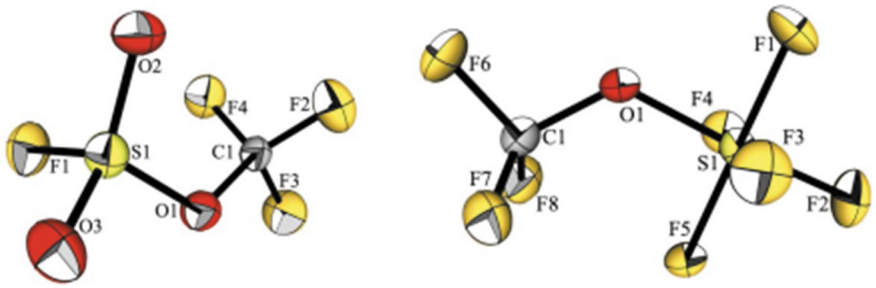


Figure 1: Molecular structures in the solid state of trifluoromethyl fluorosulfonate (CF_3OSO_2F) and of trifluoromethoxy sulfur pentafluoride (CF_3OSF_5). Displacement ellipsoids set at 50% probability.

References

[1] Green Deal: Phasing down fluorinated greenhouse gases and ozone depleting substances, European Commission, Brussels, Belgium, Press release 5. April 2022.

[2] J. Fabre, F. Hardinghaus, H. Pernice, C. Janssen, S. Hasenstab-Riedel, H. Beckers, S. Steinhauer, T. Schlöder, WO2017093503A1, *Methods for Dielectrically Insulating Electrical Active Parts.* EP15198056A·2015-12-04.

[3] J. Fabre, F. Hardinghaus, H. Pernice, C. Janssen, S. Hasenstab-Riedel, H. Beckers, S. Steinhauer, T. Schlöder, EP3384506A1, *Methods for Dielectrically Insulating Electrical Active Parts.* EP15198062A·2015-12-04.

[4] Paul Golz, Gesa H. Dreyhsig et. al. to be published.

A Case Study for $Fe(CO)_5$ as a Ligand to Divalent Species

Vadim Zhuravlev, Przemysław J. Malinowski

Centre of New Technologies, University of Warsaw, Banacha 2c, Warsaw, Poland

E-mail: v.zhuravlev@cent.uw.edu.pl

Iron pentacarbonyl has emerged as an exotic, yet interesting ligand to metal cations. Complexes containing the molecule were possible to isolate and characterize thanks to the use of weakly coordinating anions which allow to provide a weakly basic environment for a metal cation where no species is a better ligand than $Fe(CO)_5$. To date, with the exception of $GaCl_3$ [1], currently there are only complexes where $Fe(CO)_5$ binds to monovalent and closed shell M^+, where M = Cu, Ag, Au.[2,3] Thus, it would be interesting to extend the set of central metal cations to open shell divalent species.

In the current contribution we present DFT results which provide stability assessment of $M(II)L_5$–$Fe(CO)_5$ complexes (Fig. 1), where M = Cr, Mn, Fe. In order to have these systems as close to experimental conditions as possible, the reference state for the calculations were $[ML_6]^{2+}$ complexes, where L are ligands of low basicity which are known to stabilize highly Lewis-acidic complexes of divalent metals. These include SO_2, halogenated acetonitriles and more common nitromethane and acetonitrile. We also performed experiments to obtain and characterize M(II)-$Fe(CO)_5$ complexes in the most promising systems selected in calculations.

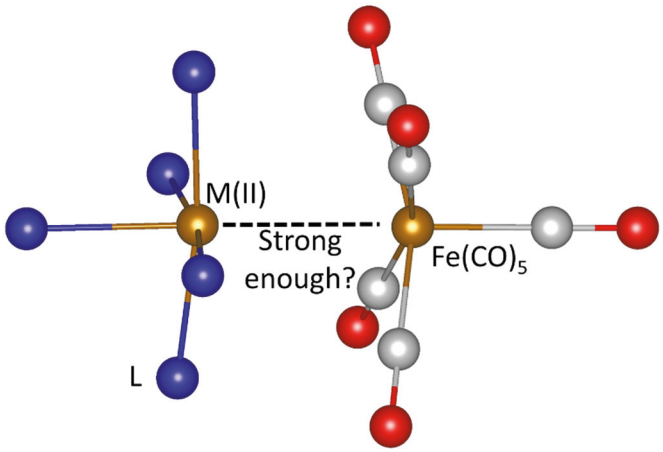


Figure 1: Schematic picture of $M(II)L_5$–$Fe(CO)_5$ complexes considered in the study.

References

[1] H. Braunschweig, R. D. Dewhurst, F. Hupp, C. Kaufmann, A. K. Phukan, C. Schneider, Q. Ye, *Chem. Sci.* **2014**, *5*, 4099–4104.
[2] S. Pan, S. M. N. V. T. Gorantla, D. Parasar, H. V. R. Dias, G. Frenking, *Chem. Eur. J.* **2021**, *27*, 6936–6944.
[3] V. Zhuravlev, P. J. Malinowski, *Eur. J. Inorg. Chem.* **2023**, DOI: 10.1002/ejic.202300177.

New Biologically Active Fluorinated Phosphonate Analogues of Phenylglycine Obtained by Stereoselective Imine Phosphonylation

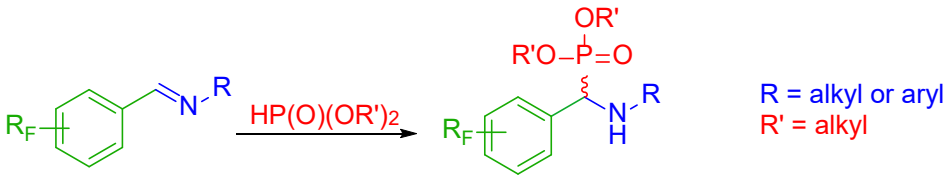
Karolina Ciesielska[1], Donata Pluskota-Karwatka[1], Maciej Kubicki[1], Grzegorz Dutkiewicz[1], Marcin Hoffmann[1], Wojciech Jankowski[1], Dariusz Wawrzyniak[2]

[1]*Faculty of Chemistry, Adam Mickiewicz University, Uniwersytetu Poznańskiego 8, 61-614 Poznań, Poland*
[2]*Institute of Bioorganic Chemistry, Polish Academy of Sciences, Noskowskiego 12/14, 61-704 Poznań, Poland*

E-mail: karcie5@amu.edu.pl

α-Aminophosphonates are an important group of chemical compounds which, due to their structural similarity to natural α-amino acids, exhibit a number of biological activities, such as for example antiviral, antibacterial and anticancer [1-3]. Among the already known α-aminophosphonates, compounds containing fluorine constitute especially important group. The presence of this element in the structure of chemical compounds, can significantly change their chemical, physical and biological properties [4].

The title α-aminophosphonates were synthesized using the Pudovik method by subjecting the previously obtained imines [5] to hydrophosphonylation. Fluorinated benzaldehyde derivatives and enantiomerically pure amines were used for the synthesis of imines. Therefore, the imine hydrophosphonylation resulted in the formation of diastereomeric mixtures of the expected products (Scheme 1). The products were obtained with good yields and satisfactory or very good diastereomeric ratios (Fig. 1), and subjected to structural and biological studies. The preliminary results obtained are very promising.



Scheme 1: Imine hydrophosphonylation reaction.

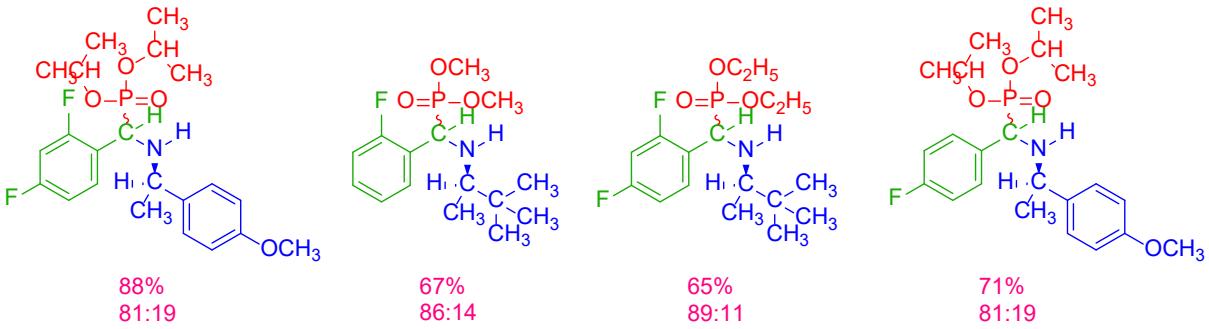


Figure 1: Exemplary structures, yields and diastereomeric ratios of the α-aminophosphonates obtained.

References

[1] G. Mohan, S. Kuma, M. Sudileti, C. Sridevi, P. Venkatesu, C. S. Reddy, *International Journal of Biological Macromolecules* **2020**, *165*, 2010-2021.
[2] N. ali S. Ali, S. Zakir, N. Patel, M. Farooqui, *European Journal of Medicinal Chemistry* **2012**, *50*, 39-43.
[3] B.-A. Song, Y.-L. Wu, S. Yang, D.-Y. Hu, X.-Q. He, L.-H. Jin, *Molecules* **2003**, *8 (1)*, 186–192.
[4] M. Salwiczek, E. K. Nyakatura, U. I. M. Gerling, S. Ye, B. Koksch, *Chem. Soc. Rev.* **2012**, *41*, 2135–2171.
[5] K. Ciesielska, M. Hoffmann, M. Kubicki, D. Pluskota-Karwatka, *Molecules* **2022**, *27*, 4557–1003.

Neural Networks in the Design of Fluoroorganic Molecules with Affinity to RORγ Protein Domains

Damian Nowak[1], Rafał Bachorz[2], Marcin Hoffmann[1]

[1]*Department of Chemistry, Adam Mickiewicz University in Poznan, Uniwersytetu Poznanskiego 8, 61-614 Poznan, Poland*
[2]*Institute of Medical Biology of Polish Academy of Sciences, Lodowa 106, 93-232 Lodz, Poland*

E-mail: mmh@amu.edu.pl

Drug design with machine learning support can speed up new drug discoveries. While current databases of known compounds are smaller in magnitude (approximately 10^8), the number of small drug-like molecules is estimated to be between 10^{23} and 10^{60}. The use of molecular docking algorithms can help in new drug development by sieving out the worst drug-receptor complexes. New chemical spaces can be efficiently searched with the application of artificial intelligence.[1] From that, new structures can be proposed. The research proposed aims to create new chemical structures supported by a deep neural network that will possess an affinity to the selected protein domains. Transferring chemical structures into SELFIES codes helped us pass chemical information to a neural network. On the basis of vectorized SELFIES, new chemical structures can be created. With the use of the created neural network, novel compounds that are chemically sensible can be generated. Newly created chemical structures are sieved by the quantitative estimation of the drug-likeness descriptor, Lipinski's rule of 5, the synthetic Bayesian accessibility classifier score, and the presence of fluorine atom in the molecule. The affinity to selected protein domains was verified with the use of the AutoDock tool.[2] As per the results, we obtained the structures that possess an affinity to the selected protein domains, namely PDB IDs 7NPC, 7NP5, and 7KXD.[3]

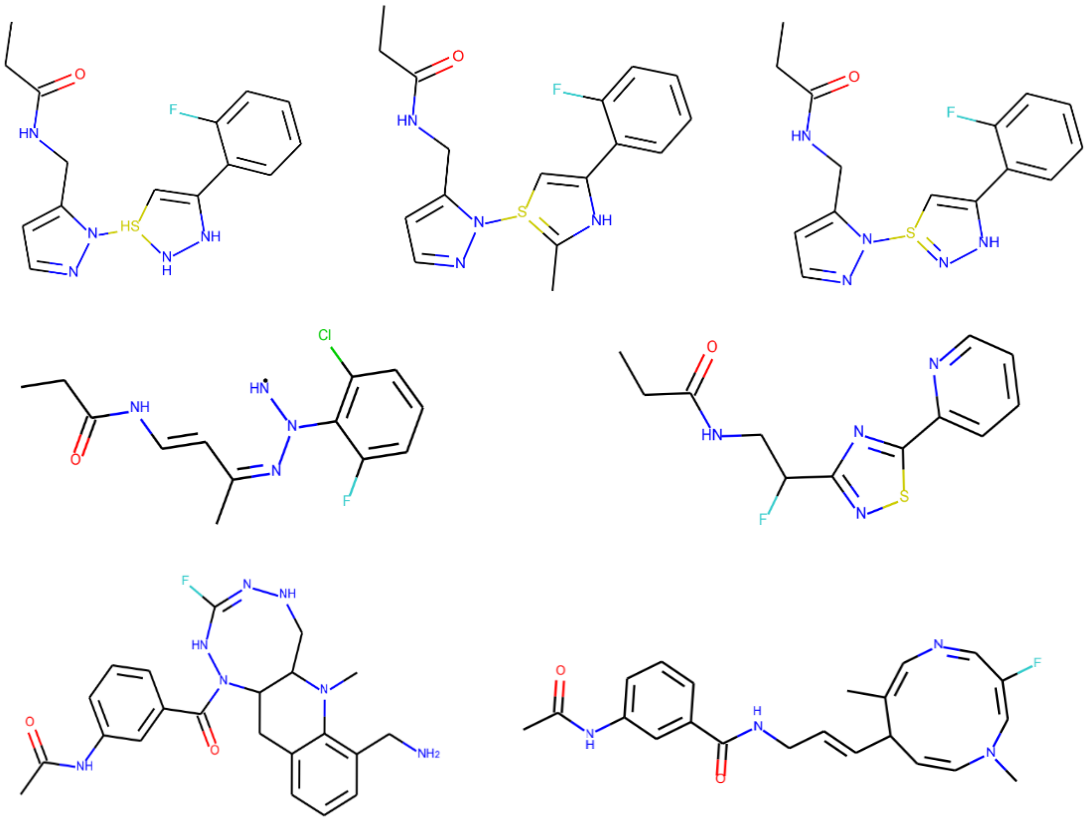


Figure 1: A.I. proposed fluoro organic molecules, likely to bind to RORγ receptors.

References

[1] G. M. Morris, D. S. Goodsell, R. S. Halliday, R. Huey, W. E. Hart, R. K. Belew, A. J. Olson, *J. Comput. Chem.* **1998**, *19*, 1639-1662.
[2] Y. Xu, X. Li, H. Yao, K. Lin, *Future Med. Chem.* **2019**, 11, 1669-1672.
[3] D. Nowak, R.A. Bachorz, M. Hoffmann, *Int. J. Mol. Sci.* **2023**, 24, 1762.

Synthesis of Trifluoromethylated Amino Acids Derivatives as Isosteres of Peptide Building Blocks

Karolina Paszek, Katarzyna Koroniak-Szejn, Henryk Koroniak

Faculty of Chemistry, Adam Mickiewicz University, Uniwersytetu Poznańskiego 8, 61-614 Poznań, Poland

E-mail: karolina.paszek@amu.edu.pl

Fluorinated amino acids play an important role in the field of peptide and protein engineering. [1] Combination of the unique physical and chemical properties of fluorine with proteinogenic amino acids represents a new approach for the design of biologically active peptides with improved pharmacological parameters. Recently, a lot of attention has been focused on the synthesis of analogues of amino acids having different groups that can act as isosteres of the peptide bond. These compounds, generally called peptidomimetics, are commonly used in medicinal chemistry and pharmaceutical research. In medicinal chemistry one of the most popular strategies to improve the activity of pharmaceuticals is to introduce one or more fluorine substituents into the molecule [2]. Replacement of a carbon bound hydrogen by fluorine increases the bond strength and, therefore, the metabolic stability of the resulting compound [3, 4].

Herein, we present the synthesis of modified amino acids with a trifluoromethyl group as building blocks for peptidomimetics. The introduction of this moiety was performed by a nucleophilic trifluoromethylation of carbonyl compounds using the Ruppert-Prakash reagent ($TMSCF_3$). Our main focus is the synthesis of analogues of amino acids bearing trifluorometylated olefinic moiety. The introduction of fluorine into amino acids offers a wide spectrum of options for modifications with regard to number and position of fluorine substituents in the amino acid side chain. Taking into account that many biologically active compounds contain the trifluoromethyl group as the essential motif, the proposed synthetic path may be a convenient solution for the introduction of trifluoromethylated olefinic moiety. These types of compounds may open new possibilities in their application as synthons for developing new therapeutic peptides and pharmaceutics.

We thank National Science Centre Poland (NCN, grant HARMONIA 2017/26/M/ ST5/00437) and The Excellence Initiative – Research University (IDUB UAM, Minigrant doktorancki 054/13/SNŚ/0042) for financial support.

References

[1] V. Prakash Reddy, *Organofluorine Compounds in Biology and Medicine*, Elsevier, Amsterdam, **2015**.
[2] H. J. Böhm, D. Banner, S. Bendels, *ChemBioChem*. **2004**, *5*, 637-643.
[3] B. K. Park, N. R. Kitteringham, P. M. O´Neill, *Annu. Rev. Pharmacol. Toxicol*. **2001**, *41*, 443-470.
[4] B. Bilgicer, K. Kumar, *Tetrahedron,* **2002,** *58*, 4105-4112.

Fluorinated Methacrylate Nano-sized Particles for Biomedical Application

Anna Szwajca[1], Patrycja Wróbel[1], Wiktor Kluba[1], Maciej Jarzębski[2]

[1]*Faculty of Chemistry, Adam Mickiewicz Uniwersity in Poznań, Uniwersytetu Poznańskiego 8, 61-614 Poznań, Poland*
[2]*Faculty of Food Science and Nutrition, Poznan University of Life Sciences, Wojska Polskiego 38/42, 60-637 Poznań, Poland*

E-mail: anna.szwajca@amu.edu.pl

The new materials of different diameters that could lead to drug delivery agents [1–5], contrast agents [2–4], biomaterials [1,3–5] and so on still are sought after by scientists. The therapeutic agent should: work fast without side effects, be delivered directly to the exact place (infected cell, tissue or organ), do not interact with other medicines and be easily excreted.

The purpose of the presented project is to modify the fluorinated polymer nanoparticles with the fluorescent compounds (Fig.1). Proper anchoring of active nanoparticles inside the nanoparticle with low refractive index ensures its proper functioning, i.e. distribution and excitation of the active agent. Synchronization of these two gives the desired effects.

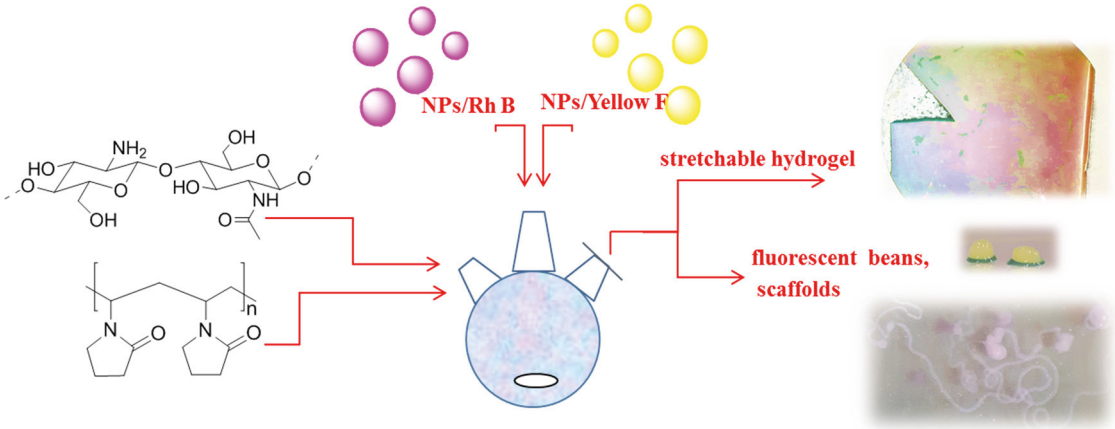


Figure 1: Nanoparticles- synthetic route.

References

[1] A.S. Abreu, J.A. Carvalho, A.C. Trindade, M. Beltrame Junior,A.R. Simioni, *J. Biomater. Sci. Polym. Ed.* **2019**, *30*, 1559–1573.
[2] K. Błaszczak-Świątkiewicz, P. Olszewska, E. Mikiciuk-Olasik, *Nowotwory* **2013**, *63*, 320–330.
[3] L. Xie,W. Jin, X. Zuo, S. Ji, W. Nan, H. Chen, S. Gao, Q. Zhang, *Biomater. Sci.* **2020**, *8*, 1431–1441.
[4] E.M. Kim,H.J. Jeong, *Nucl. Med. Mol. Imaging* **2017**, *51*, 106–117.
[5] S.Y. Baek, K. Na, *J. Porphyr. Phthalocyanines* **2013**, *17*, 125–134.

Synthesis of Modified Monosaccharides with Highly Fluorinated Motifs as a Key Building Block for Hyaluronic Acid Subunits

Joanna Tomaszewska, Katarzyna Koroniak-Szejn, Henryk Koroniak

Faculty of Chemistry, Adam Mickiewicz University, Uniwersytetu Poznańskiego 8, 61-614 Poznań, Poland

E-mail: joanna.tomaszewska@amu.edu.pl

Biological properties of modified hyaluronic acid subunits might offer many benefits in the drug delivery area. [1] Thereby, an emphasis on the synthesis of hyaluronic acid (Fig.1) subunits and their further use for the construction of certain complex structures, which can potentially act as drugs or drug delivery platforms in a modern medicine, is made.

A significant number of experiments has proved that tissue cancer is surrounded by hyaluronic acid (HA) since it has an affinity to CD44 and RHAMM receptors. [2] HA, as a naturally occurring polymer in the human body, can have an important role as drug delivery systems. [3] Its nontoxic and biodegradable properties makes this molecule conjugate with drugs. [4]

The main goal of this work was the synthesis of monosaccharides with fluorinated aliphatic chain of different length which contains 1,2,3-triazole ring or phosphonate moiety. These modifications could allow the molecule to pass the cellular membrane, reach the targeted cells and increase the biocompatibility of the drug delivery system. Subsequently, we plan to use these building blocks for the preparation of dimers and higher oligomers modified hyaluronic acid subunits.

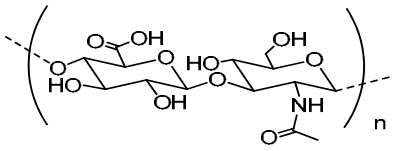


Figure 1: Hyaluronic acid (HA) subunits

References

[1] M.B. Brown, S. A. Jones, *J. Eur. Acad. Dermatol. Venereol.,* **2005***, 19*, 308-318.
[2] M. S. Karbownik, J. Z. Nowak, *J. Oncol*., **2011**, *61*, 380-395.
[3] N.E. Larsen, E.A. Balazs, *Adv. Drug Delivery Rev*., **1991**, *7*, 279-293.
[4] T.C. Laurent, J.R.E. Fraser, *FASEB J.,* **1992**, *6*, 2397-2404.

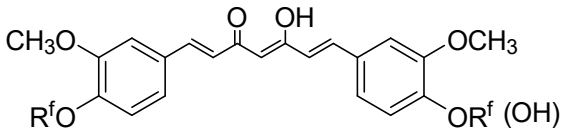
Fluorinated Derivatives of Curcumin

Hanna Wójtowicz-Rajchel, Aleksandra Lar

Faculty of Chemistry, Adam Mickiewicz University, Uniwersytetu Poznańskiego 8, 61-614 Poznań, Poland

E-mail: wojto@amu.edu.pl

Curcumin, a polyphenolic compound derived from the herb *Curcuma longa*, has a wide spectrum of biological and pharmacological activities. Curcumin is safe even at high doses in humans, but exhibit poor bioavailability. Major reasons contributing to the low plasma and tissue levels of curcumin appear to be due to poor absorption, rapid metabolism, and rapid systemic elimination. To improve the bioavailability of curcumin, numerous approaches have been undertaken, mostly application of adjuvants like piperine [1] and the use of structural analogues of curcumin [2]. Despite the lower bioavailability, the therapeutic efficacy of curcumin against various human diseases, including, cardiovascular diseases, arthritis, neurological diseases, and primarily cancer has been documented [3]. Fluorinated derivatives of biologically important compounds have aroused much interest because of their unique properties which are important for medicinal chemistry and biochemistry. In the course of our work on fluorinated derivatives of natural products [4] we would like to report our results on the synthesis of both mono and disubstituted fluorinated curcumin analogues.



The presence of fluorine can significantly change the properties of the molecule, its geometry, lipophilicity and susceptibility to metabolism and enzymatic degradation.

References

[1] G. Shoba, D. Joy, T. Joseph, M. Majeed, R. Rajendran, P.S. Srinivas. *Planta. Med.* **1998**, *64 (4)*, 353-356.
[2] C.A. Mosley, D.C. Liotta, J.P. Snyder, *Ad*V. *Exp. Med. Biol.* **2007**, *595*, 77-103.
[3] M. Tomeh, R. Hadianamrei, X. Zhao, *Int. J. Mol. Sci.* **2019**, *20*, 1-14.
[4] H. Wójtowicz-Rajchel, M. Kaźmierczak, *New J. Chem.* **2020**, 44, 6015-6025.

Synthesis and Biological Activity of Glycoconjugates of Mucochloric Acid

Katarzyna Żurawska[1,2], Daria Burdalska[1], Magdalena Skonieczna[2,3], Anna Byczek-Wyrostek[2], Anahit Dawicka[2,3], Anna Kasprzycka[1,2] and Krzysztof Walczak[1]

[1]*Department of Organic Chemistry, Bioorganic Chemistry and Biotechnology, Faculty of Chemistry, Silesian University of Technology, Krzywoustego Street 4, 44-100 Gliwice, Poland;*
[2]*Centre of Biotechnology, Silesian University of Technology, Krzywoustego Street 8, 44-100 Gliwice, Poland;*
[3]*Department of Systems Biology and Engineering, The Silesian University of Technology, Akademicka Street 16, 44–100 Gliwice, Poland.*

E-mail: katarzyna.zurawska@polsl.pl

The furanone scaffold is present in many natural products and exhibits diverse biological properties, such as antibacterial, anticancer, antifungal, antiviral, anti-inflammatory and antioxidant [1-3]. The pharmacological effects of the presence of a sugar moiety, 1,2,3-triazole ring and silyl groups in the structure of biologically active compounds have been extensively studied in drug design and medicinal chemistry [4,5]. These components can be useful tools to modulating the bioavailability of target molecules. Herein we present the study on the impact of the sugar substituent structure and triisopropylsilyl group presence on the anticancer activity of mucochloric acid (MCA) derivatives containing the furan-2(5*H*)-one or 2*H*-pyrrol-2-one core.

The glycoconjugates of 2(5*H*)-furanone and 2*H*-pyrrol-2-one derivatives were obtained under click-chemistry reaction conditions. The resulted structures differed in the point of attachment of the linker to the sugar unit. The resulted structures differed in the sugar unit, point of attachment of the linker to the sugar unit, type of aglycone (furan-2(5*H*)-one or 2*H*-pyrrol-2-one unit) and presence of silyl group. The cytotoxicity of the compounds was determined by the MTT test, while the effect of derivatives on the cell cycle was determined by flow cytometry and microscopic preparations.

The obtained biochemical results clearly indicated that tested compounds caused a significant decrease in cell viability of HCT116, and MCF-7 cell lines. MCF-7 cells indicate serious resistance toward investigated compounds in comparison with HCT116 cell line, suggesting significantly lower sensitivity of estrogen-dependent breast cancer cells to the tested derivatives.

Depending on the structure of derivatives, the selectivity of the compound towards cancer cells can be modulated. The obtained results may have an impact on the design of new furanone-based anticancer compounds.

Funding: This work partially was financially supported by the National Science Centre (Poland) under the project number 2016/21/B/NZ7/01766 and BK-242/RCh-2/2023.

References

[1] Yan-Cheng Wu, Shi-He Luo, Wen-Jie Mei, L. Cao, Han-Qing Wu, Zhao-Yang Wang, *Eur. J. Med. Chem.* **2017**, *139*, 84-94.
[2] J.M. Calderón-Montaño, E. Burgos-Morón, M.L. Orta, N. Pastor, C.A. Austin, S. Mateos, M. López-Lázaro, *Toxicol. Lett.* **2013**, *222*, 64-71.
[3] E. Lattmann, D. Kinchington, S. Dunn, H. Singh, W.O. Ayuko, M.J. Tisdale, *J. Pharm. Pharmacol.* **2004**, *56*, 1163-1170.
[4] D. Dheer, V. Singh, R. Shankar, *Bioorg. Chem.* **2017**, *71*, 30-54.
[5] R. Kitel, A. Byczek-Wyrostek, K. Hopko, A. Kasprzycka, K. Walczak, *Pharmaceuticals.* **2021**, *14*, 1079-1089.

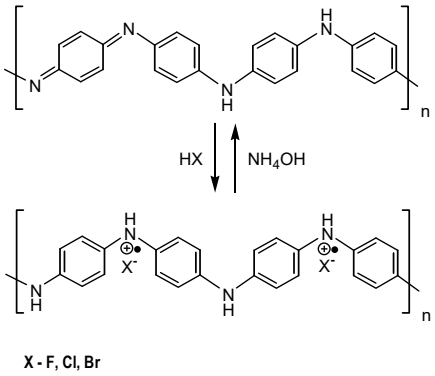
Polyaniline Synthesis Using Hydrofluoric Acid as Doping Agent: Comparative Evaluation with Polyaniline Doped with HCl and HBr

Sebastian Golczak

Faculty of Chemistry, Adam Mickiewicz University, Uniwersytetu Poznańskiego 8, 61-614 Poznań, Poland

E-mail: golczak@amu.edu.pl

Conducting polymers containing conjugated π-electron systems have been the subject of a great deal of attention in the last few decades. Polyaniline (PANI) has emerged as one of the more promising conductive polymers for commercial application [1]. It is electrically conductive with good thermal and environmental stability. The electrical properties of PANI can be changed within a range of factors. It is possible to highlight the effect of synthesis adopted (chemical or electrochemical synthesis), oxidation percentage, pH solution during the synthesis, humidity, operating temperature, the kind of doping agent and the protonation degree. In PANI, the doping process occurs by the protonation of nitrogen atoms (N-type doping), promoting consistency in the number of electrons associated to the polymeric chain. This process happens when polyaniline is in contact with the Brönsted acid HX, and some nitrogen atoms are protonated, creating positive charges that are moved in the conjugated chain. At the end of the process, the resulting polymer is in a salt form (Scheme 1).



Scheme 1: Protonation/deprotonation process of PANI.

This work focuses on the synthesis of PANI using hydrofluoric acid as doping agent and the comparison of electrical, magnetic and morphological characteristics with the PANI doped with hydrochloric acid and hydrobromic acid. PANI has been obtained by the oxidative polymerization of aniline in acidic solution with ammonium persulfate as oxidizing agent [2,3].

References

[1] M. Beygisangchin, S.A. Rashid, S. Shafie, A.R. Sadrolhosseini, H.N. Lim, *Polymers* **2021**, *13*, 2003.
[2] F.Z. Silveira, G.W. Duarte, C.G. Tachinski, R. Piletti, J. Fiori Jr., M. Peterson, H.G. Riella, M.A. Fiori, *J. Appl. Polym. Sci.* **2013**, *128*, 430-435.
[3] J.J. Langer, R. Krzyminiewski, Z. Kruczyński, T. Gibiński, I. Czajkowski, G. Kramski, *Synth. Met.* **2001**, *122*, 359-362.

Rational Design of Polyfluorinated Amphiphilic Peptides: Evaluation of Self-assembly

Maurizio Iannuzzi[1], Suvrat Chowdhary[1], Boris Schade[2], Beate Koksch[1]

[1]*Department of Chemistry and Biochemistry, Freie Universitat Berlin, Arnimallee 20, 14195, Berlin, Germany*
[2]*Department of Physics, Freie Universitat Berlin, Arnimallee 14, 14195 Berlin, Germany*

E-mail: maurizio.iannuzzi@fu-berlin.de

The self-assembly of peptides has attracted considerable attention due to the unique properties of these biomolecules such as biocompatibility, chemical versatility and biological recognition abilities[1]. Through several non-covalent forces, including hydrogen bonding and hydrophobic interactions, a variety of shape-specific architectures have been constructed by spontaneous aggregation. Herein, peptides are particularly appealing to generate efficient nanocarriers for biomedical applications because they can be rationally designed to serve as building blocks for self-assembly into nanoscale structures. The advantages of peptides are based on their diversity, illustrated by the varying properties of the respective side chains.[2] The introduction of the C-F bond influences key properties of amino acids like hydrophobicity, polarity and secondary structure propensity. Thus, fluorinated amino acids can be a powerful tool to fine-tune a broad range of peptide and protein properties such as protein folding, proteolytic and thermal stability, and protein-protein interactions[3].

Here in this work, we designed a pH responsive amphiphilic peptide motif that contains a KKGRGDS hydrophilic/bioactive head, a VVVVVVGYG hydrophobic core,[4] and a tyrosine residue as an analytical tool. Furthermore, the respective fluorinated derivative was prepared, incorporating the fluorinated amino acid (2S)-4,4,4-trifluoroethylglycine (TfeGly) into the hydrophobic component of the molecule (Figure 1); this building block was chosen because its hydrophobicity is comparable to that of valine. This strategy enables the investigation of how fluorination affects the secondary structure formation and the self-assembly properties of peptides in a systematic manner. Our current results demonstrate that the interplay between polarity and hydrophobicity of the sidechains has a substantial impact on peptide selfassembly due to the high degree of fluorination achieved.

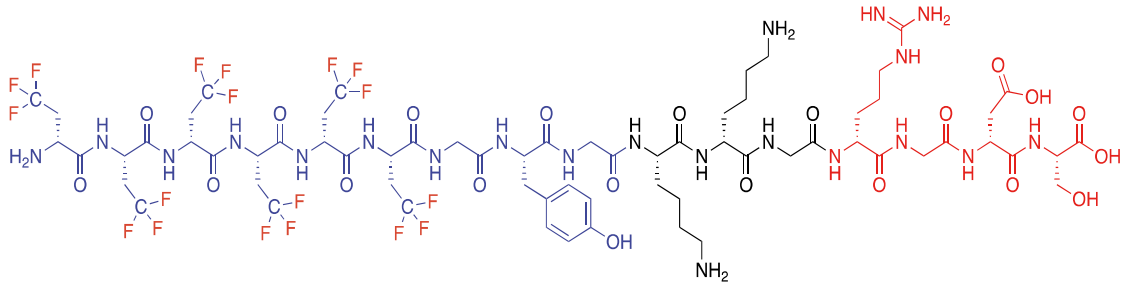


Figure 1: Peptide motif $(TFeGly)_6GYGKKGRGDS$

References

[1] Zhang, S., Fabrication of novel biomaterials through molecular self-assembly. Nat Biotechnol, **2003**. 21(10): p. 1171-8.
[2] Qi, G.B., et al., Self-Assembled Peptide-Based Nanomaterials for Biomedical Imaging and Therapy. Adv Mater, **2018**. 30(22): p. e1703444.
[3] Berger, A.A., et al., Deciphering the Fluorine Code—The Many Hats Fluorine Wears in a Protein Environment. Accounts of Chemical Research, **2017**. 50(9): p. 2093-2103
[4] Liang, J., et al., pH Responsive micelle self-assembled from a new amphiphilic peptide as anti-tumor drug carrier. Colloids and Surfaces B: Biointerfaces, **2014**. 114: p. 398-403

Liquid Crystal Property and Gelation Ability of Cyclotriphosphazenes with Perfluoroakylethylthiophenyl Group

Hiroaki Okamoto[1], Kohei Arai and Yuki Morita[2]

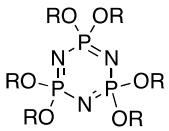
[1]*Graduate School of Sciences and Technology for Innovation, Yamaguchi University, Tokiwadai 2-16-1, Ube, Japan*
[2]*Advanced Technology Institute, Yamaguchi University, Tokiwadai 2-16-1, Ube, Japan*

E-mail: oka-moto@po.cc.yamaguchi-u.ac.jp

A lot of functional cyclotriphosphazenes have been prepared, and their physical properties were investigated [1,2]. Regarding functionality, liquid crystal phase is also very important because it is the intermediate state between liquid and crystal phases for understanding the difference between liquid and crystalline phases. It is also known that fluorination has effect on the thermal property and molecular arrangements of liquid crystal compounds [3]. On the other hand, several kinds of perfluoroalkylated compounds can gelatinize various organic solvents such as ethanol, 1-octanol, acetonitrile, DMF and DMSO [4,5].

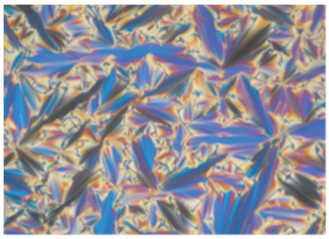
In this work, cyclotriphosphazenes with a perfluoroalkylethylthiophenyl group (compounds **1**-n and **2**-n) were prepared as shown Figure 1, and their liquid crystal property and gelation ability were studied by differential scanning calorimetry (DSC) measurements, polarizing microscope observation, and binary phase diagrams.

As can be seen from Fig. 2(a) and (c), compound **1**-2 and **2**-1 show an enantiotropic smectic A (SmA) phase with a typical focal-conic fan texture under polarized microscope observation. For compound **2**-1, also shows smectic C (SmC) phase in addition, while, compounds **1**-1 and **2**-2 are non-mesogenic. Interestingly, compound **1**-2 can form a gel in perfluorotributylamine, which is a thermally reversible physical gel. These results suggest that the perfluoroalkyl group is indispensable to exhibit smectic phase and gelation ability.

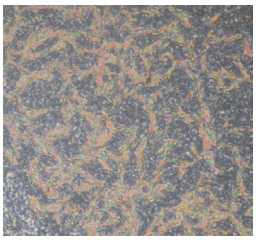


Compound **1**-1; R=$C_6H_4SC_2H_4C_4F_9$
Compound **1**-2; R=$C_6H_4SC_2H_4C_6F_{13}$
Compound **2**-1; R=$C_6H_4C_6H_4SC_2H_4C_4F_9$
Compound **2**-2; R=$C_6H_4C_6H_4SC_2H_4C_6F_{13}$

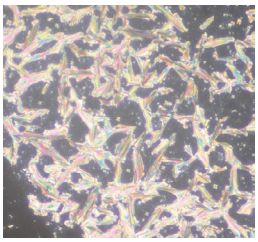
Figure 1: Chemical Structures of Compounds **1**-n and **2**-n



(a) SmA (85°C) for compound **1**-2



(b) SmC (120°C) for compound **2**-1



(c) SmA (180°C) for compound **2**-1

Figure 2: Polarized Microscope Images for SmA and SmC phases

Acknowledgements

This work is financially supported by Kumagai Science and Technology Foundation, Cosmetrogy Research Promotion Foundation, JKA 2020M-143, Amano Institute of Technology and KAKENHI 22H03781.

References

[1] I. Haiduc, The Chemistry of Inorganic Ring Systems Part 2; Wiley-Interscience: New York, 1970; p 624.
[2] K. Moriya, H. Mizusaki, M. Kato, T. Suzuki, S. Yano, M. Kajiwara, and K.Tashiro, *Chem. Mater.* **1997**, *9*, 255-263.
[3] M. Yano, T. Taketsugu, K. Hori, H. Okamoto, and S. Takenaka, *Chemistry-A Eur. J.* **2004**, *10*, 3991-3999.
[4] B. Cao, C. Shen, Y. Xu, Q. Zhou, Y. Morita, H. Okamoto, and Q. Xiao, *J. Fluorine Chem.* **2019**, *226*, 109348-109354.
[5] T. Yoshida, T. Nakamura, Y. Morita, and H. Okamoto, *Chem. Lett.*, **2015**, *44*, 512-514.

The Role of Exposed Crystal Facets in F-doped TiO_2 Photocatalysts Synthesized from $TiOF_2$ for Naproxen Removal and Toxicity Rate

Marta Kowalkińska[1], Karol Sikora[2], Marcin Łapiński[3], Jakub Karczewski[3], Anna Zielińska-Jurek[1]

[1]*Department of Process Engineering and Chemical Technology, Faculty of Chemistry, Gdansk University of Technology, Poland*
[2]*Department of Inorganic Chemistry, Faculty of Pharmacy, Medical University of Gdansk, Poland,*
[3]*Institute of Nanotechnology and Materials Engineering, Faculty of Applied Physics and Mathematics, Gdansk University of Technology, Poland*

E-mail: marta.kowalkinska@pg.edu.pl

In the recent years, fluorinated anatase photocatalysts, including surface fluorination, fluorine doping and stabilization of highly energetic {0 0 1} crystal facets, are of great research interest [1]. However, most of the described F-TiO_2 were synthesized using highly toxic hydrofluoric acid (HF). In the present work, we proposed titanium oxyfluoride ($TiOF_2$) as a promising precursor, which is a metastable phase in a fluorine-based environment and can be easily transformed to anatase under hydrothermal conditions [2,3]. This compound was used for the synthesis of F-doped TiO_2 nanocrystals with {1 0 1}, {0 0 1} and {1 0 0} facets. Furthermore, the obtained photocatalysts were studied toward naproxen (NPX) photocatalytic degradation under simulated solar (UV-vis) and visible light ($\lambda > 420$ nm). The most efficient photocatalyst in the series was octahedral F-TiO_2 exposing {1 0 1} facets, with the highest kinetic constant rate and total organic carbon (TOC) removal. The analysis of by-products using mass spectrometry showed that the photocatalytic NPX degradation was facet-dependent. Toxicity assessment of post-process wastewater using *Vibrio fischeri* bacteria showed that octahedral F-TiO_2 are non-toxic, although F^- ions were the reactants in the synthesis. The overall results showed that crystal-facets-engineered F-TiO_2 photocatalysts have the potential for practical application, thus providing a new idea for the synthesis of highly efficient photocatalytic materials.

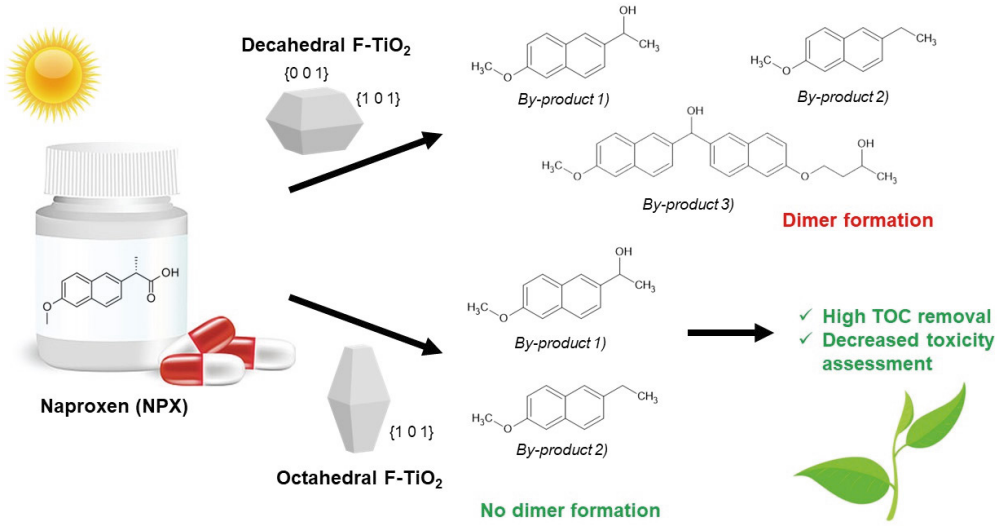


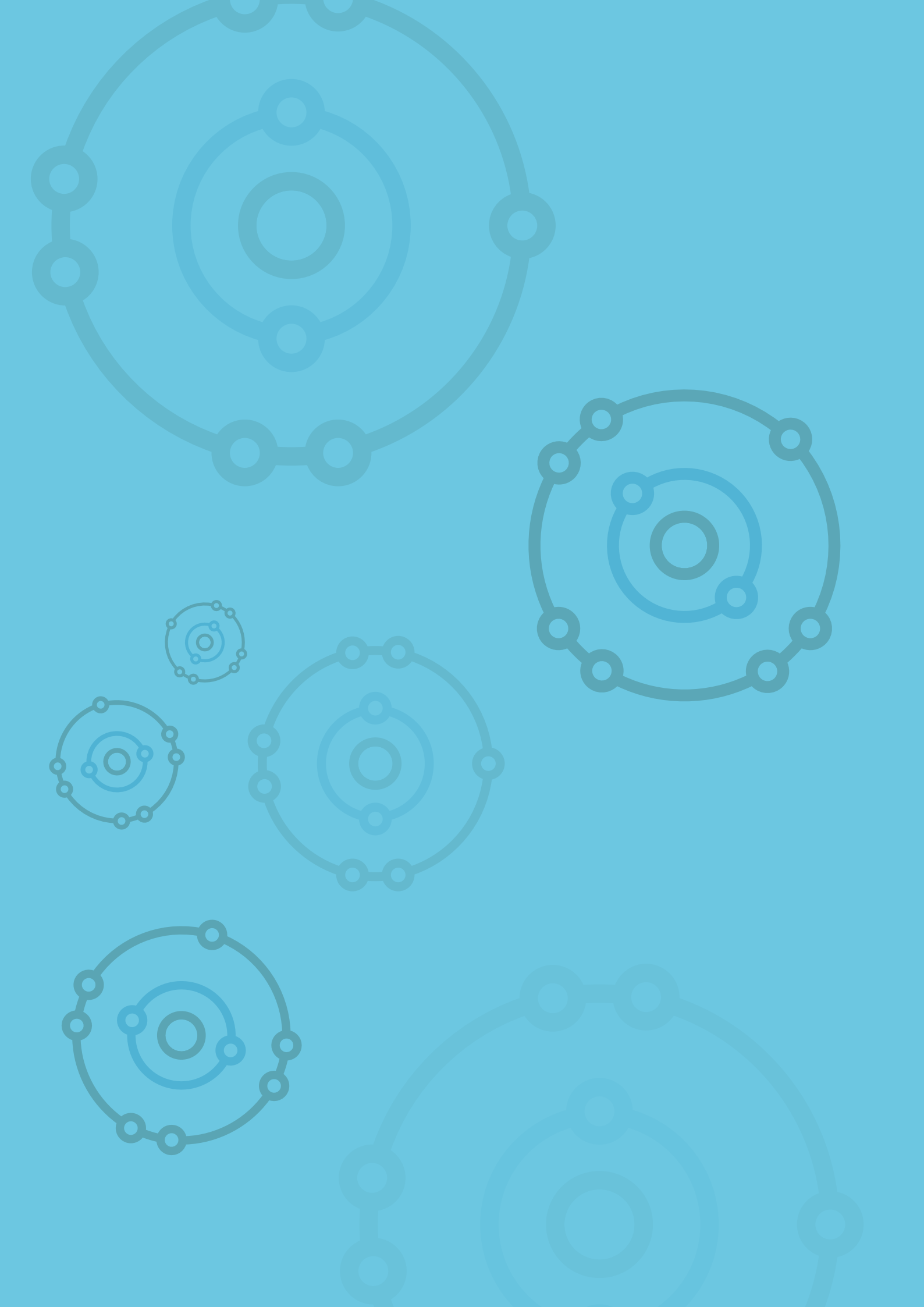
Figure 1: Schematic illustration of emerging contaminant removal in the presence of obtained F-TiO_2 photocatalysts.

Acknowledgement

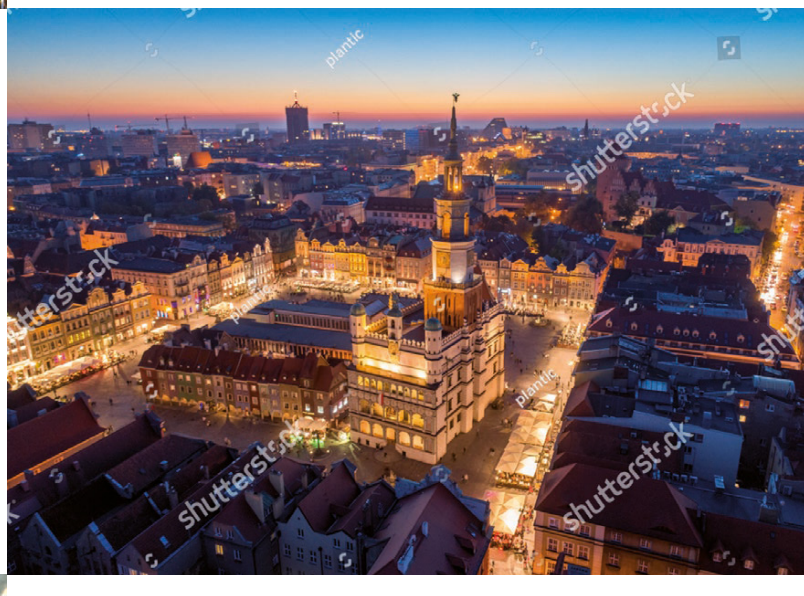
The research was financially supported by Polish National Science Centre grant no. NCN 2018/30/E/ST5/00845 and grant no. NCN 2021/43/B/ST5/02983.

References

[1] T. R. Gordon, M. Cargnello, T. Paik, F. Mangolini, R. T. Weber, P. Fornasiero, C. B. Murray, *Journal of American Chemical Society*, **2012**, 134, 6751-6761.
[2] M. Kowalkińska, K. Sikora, M. Łapiński, J. Karczewski, A. Zielińska-Jurek, *Catalysis Today*, **2023**, 413–415, 113959.
[3] M. Kowalkińska, J. Karczewski, A. Zielińska-Jurek, *Crystals*, **2023**, 13, 356.



ADAM MICKIEWICZ
UNIVERSITY
POZNAŃ



POZnań

Honorary Patronage
of the Mayor of Poznań

POLSKIE TOWARZYSTWO CHEMICZNE

PTCh

PPNT

Poznan Science
and Technology Park