Program & Abstracts

Conference venue:

University of Łódź, Faculty of Chemistry, Tamka-Str. 12,

The Faculty Council Room, #1-020

Organizing committee:

Chairman:	Prof. dr. hab. Grzegorz Mlostoń
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IXth International Mini-Symposium
'Advances in the Chemistry of Fluorinated Organic Compounds'

University of Łódź, Faculty of Chemistry
May 19th, 2016

Program

12:15 **– 13:15**	***Lunch***
13:25	***Opening***
Session 1:	**Chairman: Józef Drabowicz**
	Jan Długosz University in Częstochowa, Poland
Invited Lectures	
13:30 – 14:05	**Constantin Czekelius**
IL-1	University of Düsseldorf, Germany
14:05 – 14:40	**Mieczysław Mąkosza**
IL-2	Institute of Organic Chemistry, Polish Academy of Sciences, Poland
14:40 – 15:15	**Henryk Koroniak**
IL-3	Adam Mickiewicz University in Poznań, Poland
15:15 – 16:00	*Coffee break*
Session 2:	**Chairman: Piotr Kiełbasiński**
	Polish Academy of Sciences, Łódź, Poland
16:00 – 16:35	**Dieter Lentz**
IL-4	Free University of Berlin, Germany
Short Lectures	
16:35 – 17:00	**Michał Michalak**
SL-1	Institute of Organic Chemistry, Polish Academy of Sciences, Poland
17:00 – 17:25	**Rafał Loska**
SL-2	Institute of Organic Chemistry, Polish Academy of Sciences, Poland
17:25 – 17:50	**Emilia Obijalska**
SL-3	University of Łódź, Poland
18:00 – ……	*Garden Grill Party*

IL-1

Synthesis of Fluorinated Aminoacids and Carbohydrates by Conjugate Fluoroalkylation

Constantin Czekelius

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The chemistry of fluorine has evolved dramatically over the past years due to the importance of fluorinated compounds in both fine chemical synthesis and novel materials.[1] The incorporation of fluorine in pharmaceutically active compounds can alter their activity profile as well as their pharmacodynamics and –kinetics. While selective and efficient fluorination and fluoroalkylation protocols have been developed for the functionalization of aromatic compounds, the related transformations of aliphatic starting materials are more challenging, in particular when new stereogenic centers shall be formed selectively. We have developed an auxiliary-based hydrofluoroalkylation of crotonic acid derivatives as well as a catalytic fluoroalkylation of simple alkenes.[2] The optically active fluorinated carboxylic acids can serve as starting materials for the synthesis of fluorinated analogs of natural products such as amino acids or carbohydrates.[3][4] It has shown that peptides incorporating sterically encumbered fluorinated amino acids show very fast refolding from □-helical to □-sheet structures while exhibiting the same polarity profile as the natural analog.[5] The fluorinated carbohydrates allow access to new (desoxy-)ribonucleotide analogs in which ring conformations and receptor binding can be fine-tuned.

Keywords: Fluoroalkylation, Halogenation, Fluorinated Nucleosides

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IL-2

Cocatalysis in Phase-Transfer Catalyzed Fluorination of Alkyl Halides and Sulfonates

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Introduction of fluorine into organic molecules is an important process, because numerous pharmaceuticals, agrochemicals etc. contain fluorine. One of the main way to introduce fluorine is nucleophilic substitution of halogens or sulfonates by fluoride anion in the reaction with KF. The most efficient and general methodology for nucleophilic substitution – phase transfer catalysis is of limited application for introduction of fluorine, because of low lipophilicity of F^- anions. Moreover due to high basicity of F^- the substitution or often accompanied with undesired β-elimination. We have developed an efficient cocatalytic variant of PTC for $S_N2$reaction with F^- anions applicable for replacement of primary and secondary alkyl chlorides, bromides and sulfonates than not only assure high conversion, but also low degree of undesired β-elimination.The cocatalyticcycle consist in continuous reaction of the cocatalysts Ph_3SnF and Q^+X^- with solid KF to form soluble $Ph_3SnF_2^-Q^+$ that acts as F^- donor as shown in scheme 1.

$$Ph_3SnF + Q^+X^- + KF_{solid} \longrightarrow Ph_3SnF_2^-Q^+_{org} + KX_{solid}$$

$$Ph_3SnF_2^-Q^+ + R-F \longrightarrow R-X + Ph_3SnF + Q^+X^-$$

In solvents able to dissolve $Ph_3SnF_2^-K^+$ e.g. sulfolane new type of liquid-solid PTC operates via continuous formation of lipophilic potassium salt of hypervalent anion $Ph_3SnF_2^-$.Scheme 2.

$$Ph_3SnF + KF_{solid} \xrightarrow{\text{sulfolane}} Ph_3SnF_2^-K^+_{org}$$

$$Ph_3SnF_2^-K^+_{org} + R-X_{org} \longrightarrow R-F + Ph_3SnF + KX_{solid}$$

Reference:

J. Fluorine Chem. **2005**, *126*, 209.

IL-3

Fluorinated Aminophosphonates – Steroselective Synthesis and Properties

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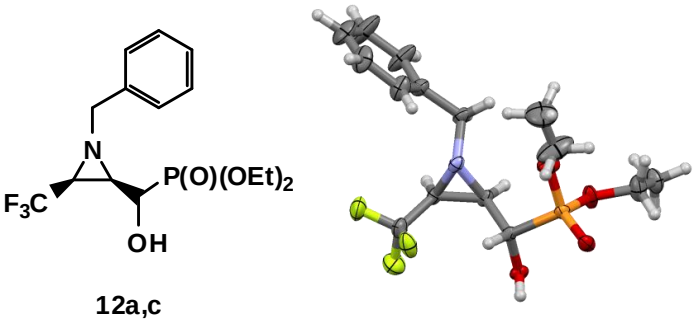
Aminophosphonates are known as a compounds showing interesting biological activity (e.g. potent drugs against osteoporosis). In this work some new strategies of a synthesis of several mono and difluorinatedas well asCF_3 containing aminophosphonates has been presented. As a key strategic step for a stereoselectivesynthesis, aziridine and oxirane derivatives of fluorophosphonates were prepared. Their properties and structure were elucidated (e.g. X-ray analysis, NMR).



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IL-4

Buckybowls Meet Fluorine

Dieter Lentz,Axel Haupt, Blazej Duda, Annika K. Meyer, Bernd M. Schmidt

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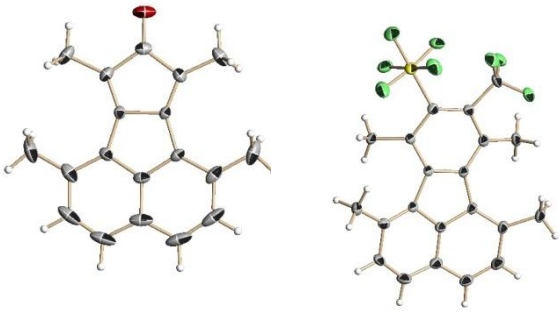
Geodesic polyarenes became the focus of attention not only because they can be considered as substructures of fullerenes with three-dimensional bowl-shape or the polar end-caps of carbon nanotubes, but also because of their own chemical and physical properties. Corannulene ($C_{20}H_{10}$)[1] and sumanene ($C_{21}H_{12}$)[2] are the best-studied buckybowl compounds and various synthetic routes have been published. As demonstrated by us [3] and others [4] introduction of electron withdrawing substituents like fluorine or perfluoroalkyl alters the properties of these compounds drastically.

Herein we report various routes which allow a systematic introduction of perfluoroalkyl groups in specific positions of corannulene.Using appropriate substituted alkynes offers the introduction of specific substitutents in 1,2-position of the corannulene. Carbon-carbon cross-coupling reactions using perfluoroalkyl copper reagents or palladium catalyzed reactions permit the selective synthesis of specific regio isomers.

The electronic and structural properties of new compounds were investigated by UV-vis spectroscopy and cyclic voltammetry. Evaluation of non-covalent interactions in the solid state which generate each structural motif, are supported by single-crystal X-ray diffraction data.



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SL-1

NHC-Copper(I) Halide-Catalyzed Direct Alkynylation of Trifluoromethylketones on Water. Unexpected Synthesis of Dibenzo[1,5]diazocines

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The synthesis of fluorine-containing compounds has attracted much attention in the last decades due to their unique physical and biological properties. In particular, α-trifluoromethylcarbinol moiety is present in many pharmaceuticals, including Efavirenz,[1] a key drug used in the treatment of HIV. This structural motif is also a matter of interest to the synthetic organic chemist due to, inter alia, the *unquestionable* role of Mosher's acid as a chiral shift reagent.

One of the synthetic pathways leading to propargylα-trifluoromethyl alcohols is based on the direct addition of a metal acetylide to trifluoromethylketones (TFMK's). To date, there are only scarce reports devoted to the catalytic alkynylation of trifluoromethylketones. Among metal complexes able to catalyse the addition reaction are Ag/phosphine,[2] Ag–Ti nanoparticles,[3] $ZnMe_2$/RLi,[4]andCuOtBu/Xantphos.[5]

Herein, we present the first NHC–copper(I) halide–catalyzed addition of terminal alkynes to TFMK's on water. A series of addition reactions was performed with as little as 2.0 mol% of the IPrCuCl complex, providing tertiary trifluoromethylpropargyl alcohols in high yields and with excellent chemoselectivity. In addition, the same catalytic system was applied for the synthesis of quinolines, starting from *o*-aminotrifluoromethylketones. The influence of the electronic and steric nature of the NHC–copper(I) complexes and the scope of substrates is discussed. Unexpected base-catalyzed formation of diazocinesis also presented.

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SL-2

1,3-Dipolar Cycloaddition of 1,1-Difluoroalkenes and *N*-Oxides of Azines and Azoles

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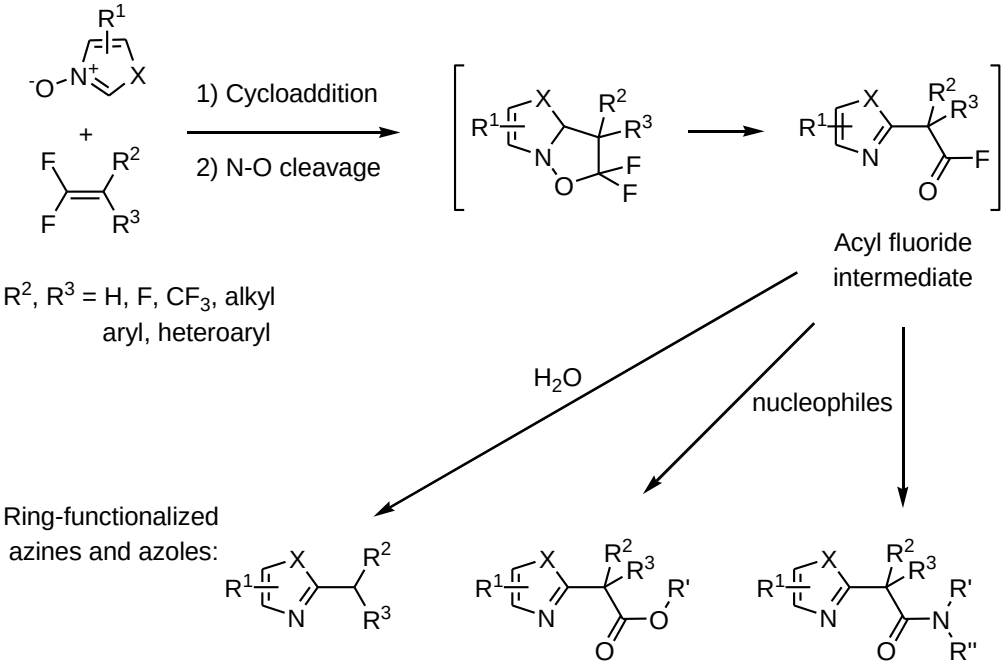
Highly functionalized azines and azoles are important as pharmaceuticals, ligands, synthetic intermediates, etc. A synthetic approach to the problem of selective introduction of new substituents into hydrogen–occupied position of the heteroaromatic ring will be presented. 1,3-Dipolar cycloaddition of difluoroalkenes with *N*-oxides of azines and azoles allows to obtain various heterocyclic products, such as fluoroalkyl heterocycles, amides and esters of α-heteroarylcarboxylic acids or unsymmetrical bis(heteroaryl)methanes. NMR characterization of the key intermediate, α-heteroaryl acyl fluoride, provides evidence for the mechanism proposed for this reaction.



SL-3

Applications of Fluorinated Carbohydrazides, Nitrones and β-Amino Alcohols in Syntheses of Selected Azaheterocycles

Emilia Obijalska, Marcin K. Kowalski, Aneta Wróblewska, Grzegorz Mlostoń*

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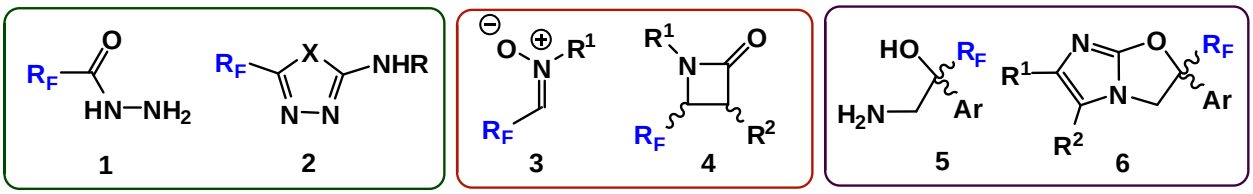
Fluooroorganic compounds containig fluoroalkyl groups *e.g.* CF_3, CHF_2 found many applications as pharmaceuthicals, agrochemicals and materials with spacial properties [2]. Due to our continuing interest in synthesis of fluorinated building blocks and heterocyclic compounds we developed several methods for the synthesis of azaheterocycles **2**, **4**, **6** based on exploration of fluorinated hydrazides **1**, nitrones **3** and β-amino alcohols **5**. Carbohydrazides and their derivatives are known as building blocks widely applied in syntheses of heterocyclic compounds with diverse ring size [1]. Surprisingly, applications of hydrazides derived from fluorinated carboxylic acids have scarely been reported. Hydrazides **1** were prepared starting with *N*-protected hydrazines and fluorinated anhydrides. Reactions of **1** with isocyanates or isotiocyanates gave semicarbazides or thiosemicarbazides, respectively which subsequently were cyclized to corresponding 1,3,4-oxadiazoles (X = O), 1,3,4-thiadiazoles (X = S) and 1,3,4-selenodazoles (X = Se) **2**. Nitrones are known as useful building blocks widely applied for synthesis of heterocyclic systems via 1,3-dipolar cycloaddition [3]. To date, 'fluorinated' nitrones derived from trifluoro- and difluoroacetaldehyde are less well known and rarely used for preparation of heterocyclic products [4]. 'Fluorinated' nitrones **3** are accessible via reactions of fluorinated aldehydes with appropriate *N*-hydroxylamines. In the next step, they were used as a substrates for the reactions with terminal alkynes (*Kinugasa* reaction). Desired β-lactams **4** were obtained in moderate to good yields as the mixtures of *cis*- and *trans*- diastereoisomers. Enantiomerically pure β-amino-α-(trifluoromethyl) alcohols **5** [5] were used as key starting materials for the preparation of fluorinated bicyclic heterocycles **6**. Initially, β-amino alcohols **5** were converted into imidazole *N*-oxides bearing the *N*(1)-β-hydroxyalkyl substituent via reaction with formaldehyde and corresponding α-hydroxyimino ketone. Next, treatment with acetic anhydride led to bicyclic, fused heterocycles **6** via a multi-step reaction pathway. Mechanisms of this conversion will be presented in detail.



$R_F = CF_3, CHF_2$

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Alphabetical Author Index

Notes