

Institute of Organic Chemistry NAS of Ukraine

Scientific Annual Report 2016

**Prof. Kalchenko V. I.
On behalf of IOCh NASU team**

Department of Chemistry, Natl. Acad. of Sci. of Ukraine, 10.03.2017

Institute of Organic Chemistry of the National Academy of Sciences of Ukraine is one of the leading research institutions in Ukraine founded in 1939. The scientists of the Institute made an important contribution to the world science. Investigations of our scientists in the field of color of organic compounds theory, mechanisms of organic reactions, chemistry of heterocyclic compounds, chemistry of phosphorus-, fluorine-, and sulfurorganic compounds, chemistry of biologically active compounds, supramolecular chemistry have deserved public recognition all over the world.

Large quantities of the elaborations of the Institute have been introduced to medicine, veterinary, national economy. As for today, 221 employees work in the Institute, there are 18 Doctors of Science, 78 Candidates of Science, 73 engineers and specialists, 26 technicians among them. The scientists of the Institute have published more than 7500 original scientific papers, 80 monographs, received more than 1500 Patents and Author's Certificates, prepared 66 Doctors of Science and more than 400 Candidates of Science.

Technical Area Keywords: Fine Organic Synthesis; Organophosphorus, Fluoroorganic, Sulfurorganic and Heterocyclic Chemistry, Organic Dyes, Supramolecular Chemistry.

- **ORGANO PHOSPHORUS COMPOUNDS CHEMISTRY DEPARTMENT**
Dr Sci Kostyuk A.N.
- **COLOUR AND STRUCTURE OF ORGANIC COMPOUNDS DEPARTMENT**
Prof. Ishchenko A.A.
- **ORGANO-ELEMENT COMPOUNDS CHEMISTRY DEPARTMENT**
Prof Onys'ko P.P.
- **ORGANIC REACTIONS MECHANISM DEPARTMENT**
Prof. Vovk M. V.
- **PHOSPHORANES CHEMISTRY DEPARTMENT**
Prof. Kalchenko V. I.
- **BIOLOGICALLY ACTIVE COMPOUNDS DEPARTMENT**
Dr Sci Volochnyuk D. M.
- **DEPARTMENT OF PHYSICOCHEMICAL INVESTIGATIONS**
Dr Sci Rozhenko A. B.
- **ORGANO FLUORINE COMPOUNDS CHEMISTRY DEPARTMENT**
Prof. Yagupolskii Yu.L.
- **SULFUR ORGANIC COMPOUNDS CHEMISTRY DEPARTMENT**
Prof. Shermolovich Yu. G.

Life science

- Biologically active compounds for medicine, veterinary, agriculture

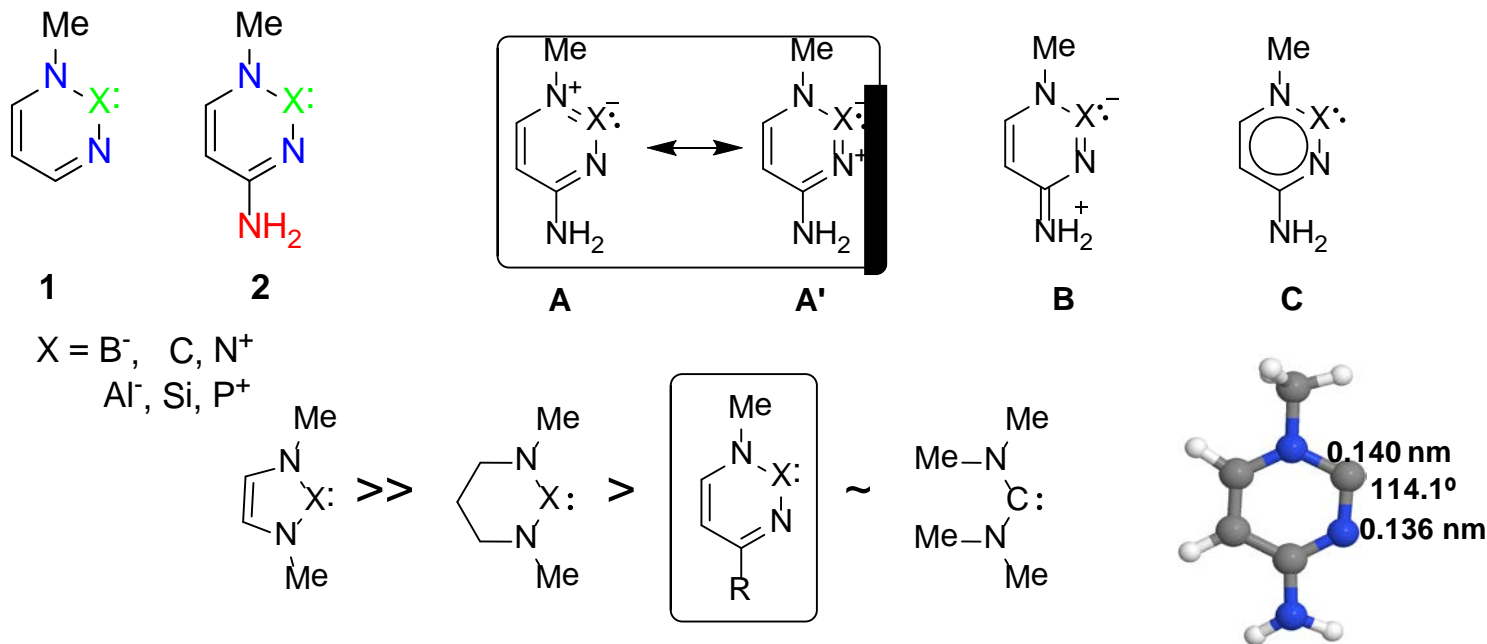
Material science

- Dyes for lasers, holography, solar cells
- Catalysts
- Compounds for MOFs gas storage
- Receptors for sensor devices

Ecology

- Selective complexants and extractants
- Sorbents of toxic radionuclides

On Structure and Stability of Pyrimidine Ylidenes and Their Homologues

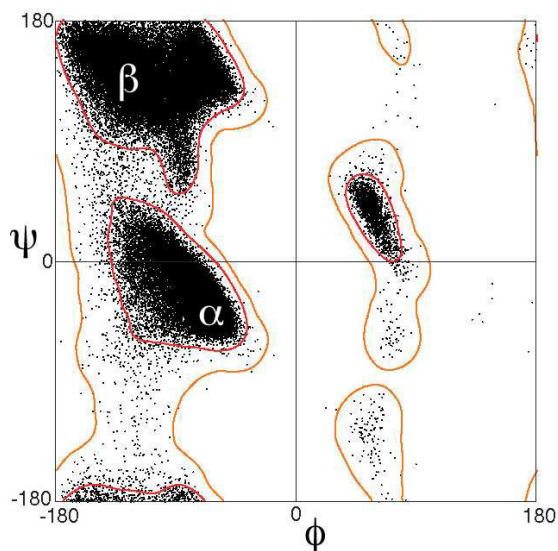


Structure of six-membered cyclic aminoiminocarbenes (pyrimidine ylidenes) and their group 13-15 homologues was studied by quantum chemical calculations. Isodesmic and dimerization reaction energies, NICS values, frontier molecular orbitals, as well as NBO, Bader's "atoms in molecules" and Laplacian bond order (LBO) analyses were employed for estimating relative stability of the studied carbenes (carbene homologues). They show a low degree of aromatic delocalization and considerable variation of electronic structure depending on the nature of divalent element. The predicted stability for the series of interest is lower than that for the corresponding five-membered Arduengo carbenic structures, but comparable with Alder's bis(dimethylamino)carbene.

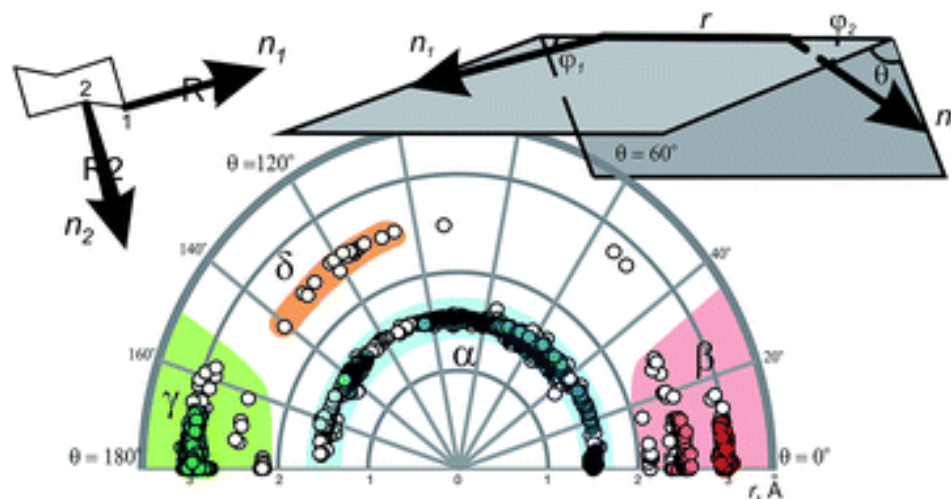
Kirilchuk, A. A.; Rozhenko, A. B.; Leszczynski, J. *Comput. Theor. Chem.* 2017, 1103, 83–91.

DOI: <http://dx.doi.org/10.1016/j.comptc.2017.01.024>

Following Ramachandran: exit vector plots (EVP) as a tool to navigate chemical space covered by 3D bifunctional scaffolds. The case of cycloalkanes



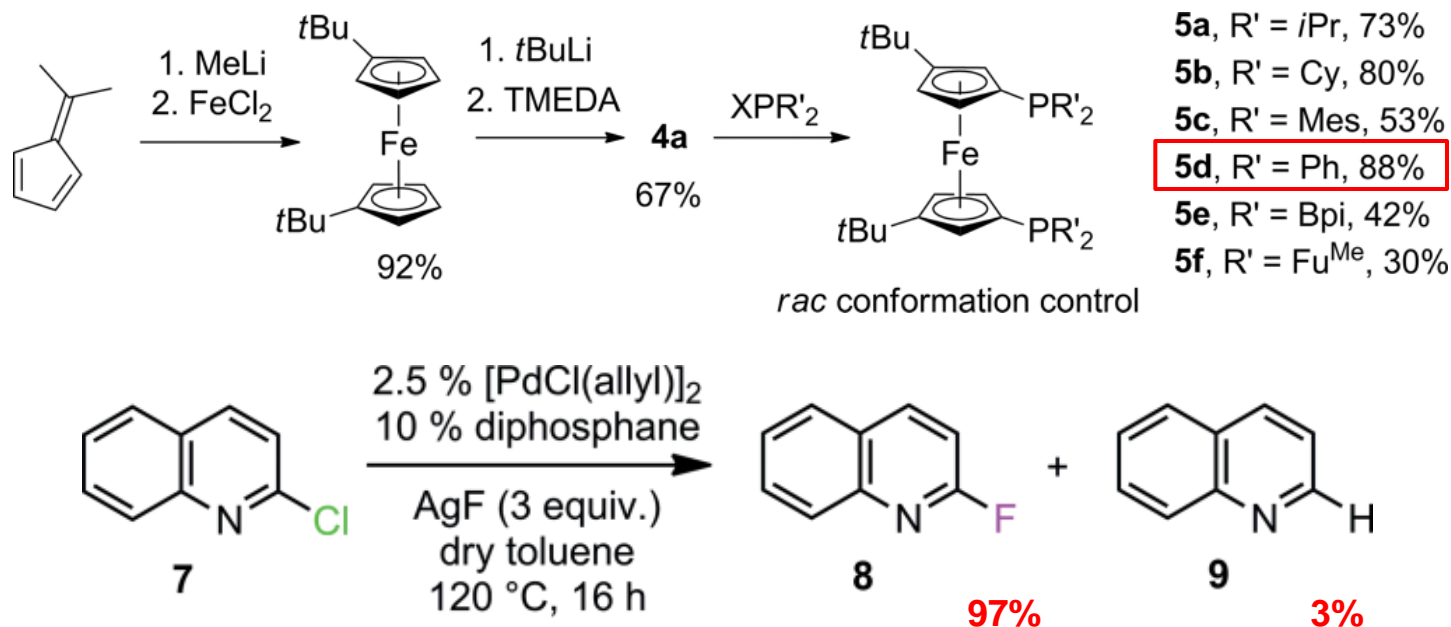
Ramachandran 1963



Grygorenko and Volochnyuk 2016

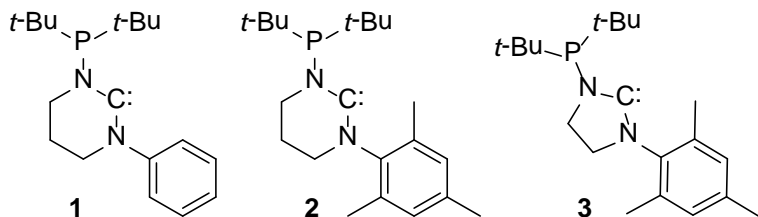
An approach to analysis and visualization of chemical space covered by disubstituted scaffolds, which is based on exit vector plots (EVP), is used for analysis of the simplest disubstituted cyclic cores – cycloalkanes, deposited in the Cambridge Structural Database (CSD). It is shown that four clearly defined regions are found in EVP of the cycloalkanes, similar to those observed in Ramachandran plots for peptides. These results can be used for directed design of more complex scaffolds, classification of conformational space for the disubstituted scaffolds, rational scaffold replacement, or SAR studies

Diastereoselective Synthesis of Dialkylated Bis(phosphino)ferrocenes: Their Use in Promoting Silver-Mediated Nucleophilic Fluorination of Chloroquinolines



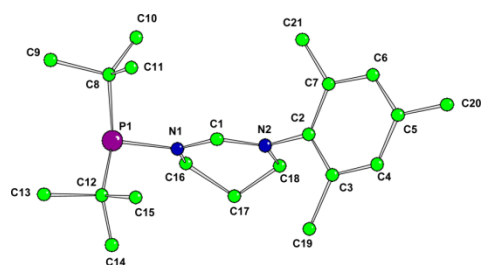
The diastereoselective synthesis of dialkylated ferrocenyl bis(phosphane)s bearing aryl, alkyl, and hetero- or polycyclic substituents on the phosphino groups is reported, together with their characterization in the solid state by X-ray structure analysis and in solution by multinuclear NMR spectroscopy. A significant favorable effect from the ferrocenyl phosphanes is evidenced by using the commercial AgF reagent for this fluorination that renders any palladium addition useless. This innovative nucleophilic fluorination thus avoids harsh conditions (strictly anhydrous) and highly specialized reagents.

Chelate Palladium(II) Complexes with Saturated N-Phosphanil-Nheterocyclic Carbene Ligands: Synthesis and Catalysis

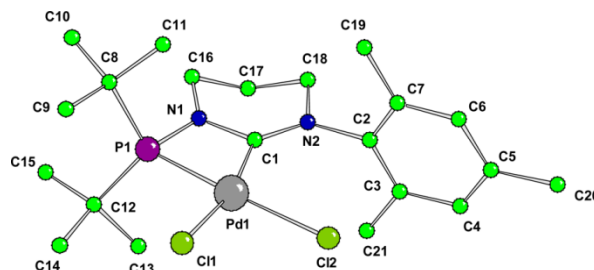


1*PdCl₂ in 1% mol gives > 80% preparative yields in Suzuki coupling using aryl bromides and aryl chlorides as well as Sonogashira coupling using aryl bromides

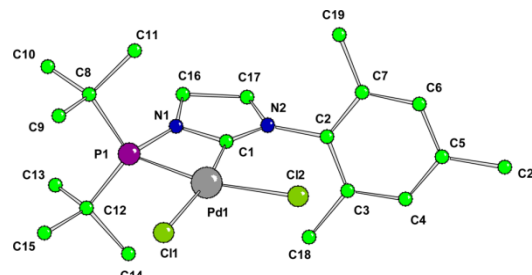
✓ X-Ray of complexes with PdCl₂



1 * PdCl₂



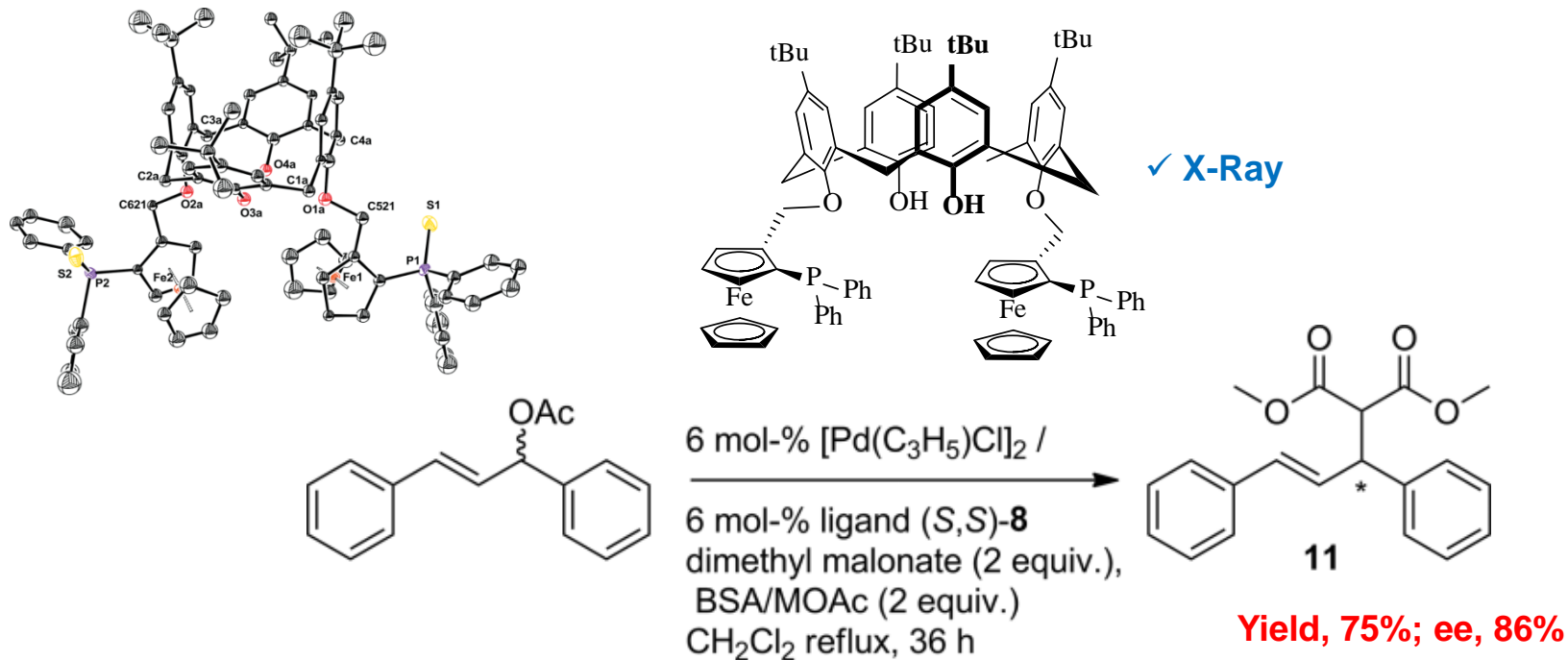
2 * PdCl₂



3 * PdCl₂

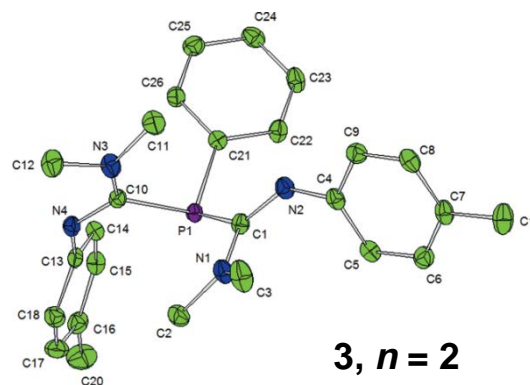
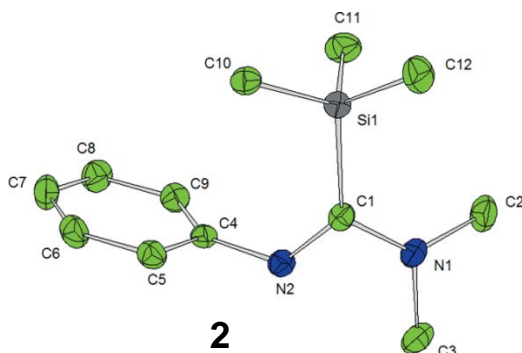
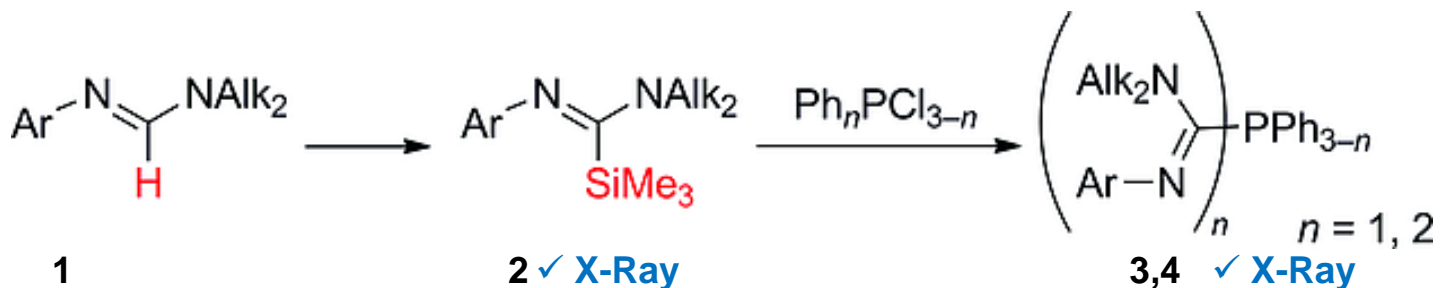
N-Phosphanil-N-heterocyclic carbenes (NHCPs) featuring a saturated imidazolin-2-ylidene or tetrahydropyrimidin-2-ylidene ring have been synthesized and characterized. The free carbenes are capable of acting as chelating ligands toward palladium(II), forming very stable mononuclear complexes that have been structurally characterized. The catalytic potential of the complexes has been preliminarily assessed in cross-coupling reactions, most notably in the Suzuki coupling of aryl chlorides, where these complexes display promising activity, and in the copper- and amine-free Sonogashira coupling of aryl bromides.

Asymmetric Tsuji–Trost Reaction Catalyzed by the Chiral Phosphinoferrocenyl-Calixarene



The Mitsunobu alkylation of 4-tert-butylcalix[4]arene with (S)-(2-diphenylthiophosphinoferrocenyl)methanol followed by desulfuration of the thiophosphine nit using tris(dimethylamino) phosphine afforded enantiomerically pure calixarene mono- and di(ferrocenylphosphine) ligands in high yields. The calixarene mono(ferrocenylphosphine) ligands exhibited good catalytic activity. The di(ferrocenylphosphine) ligand displayed both good catalytic activity and enantioselectivity (ee values up to 86 %) when employed in the asymmetric Tsuji–Trost allylic alkylation of 1,3-diphenylprop-2-enyl acetate with dimethyl malonate.

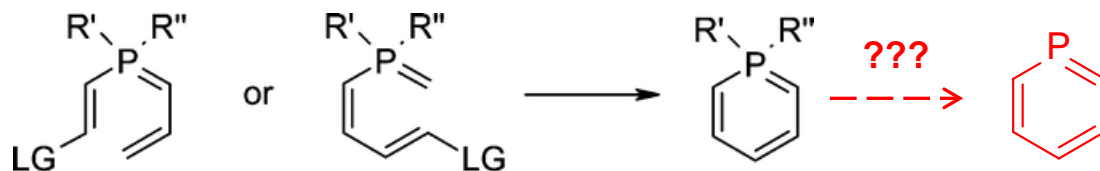
C-Silyl-N,N-dialkyl-N'-arylformamidines: Synthesis and Reactions with Phosphorus(III) Chlorides



A convenient preparative method for the synthesis of C-silyl-N,N-dialkyl-N'-arylformamidines was developed. These derivatives were employed as nucleophiles in reactions with phosphorus(III) chlorides to afford phosphanes that feature one or two formamidine substituents. We were unable to introduce three formamidine substituents into the final product.



Reduction of λ^5 -Phosphinines – first way to λ^3 -Phosphinines able to scale up



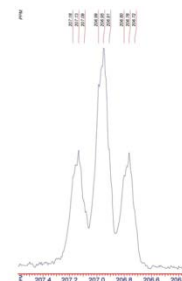
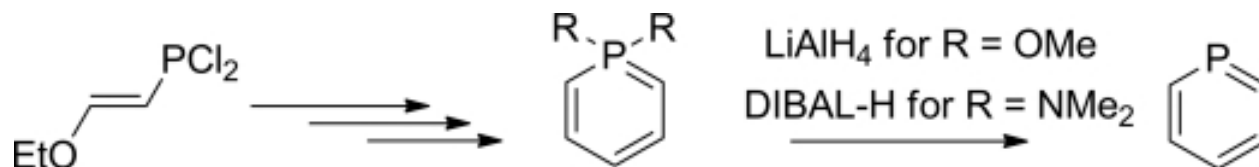
LG = OEt, NMe₂

R' = R'' = NAlk₂, Ph, Me

or
R' = NMe₂; R'' = Ph, Me

was questioned till 2016

Dr Svyaschenko, Dr. Sci Kostyuk
J. Org. Chem., 2011, 76, 6125–6133

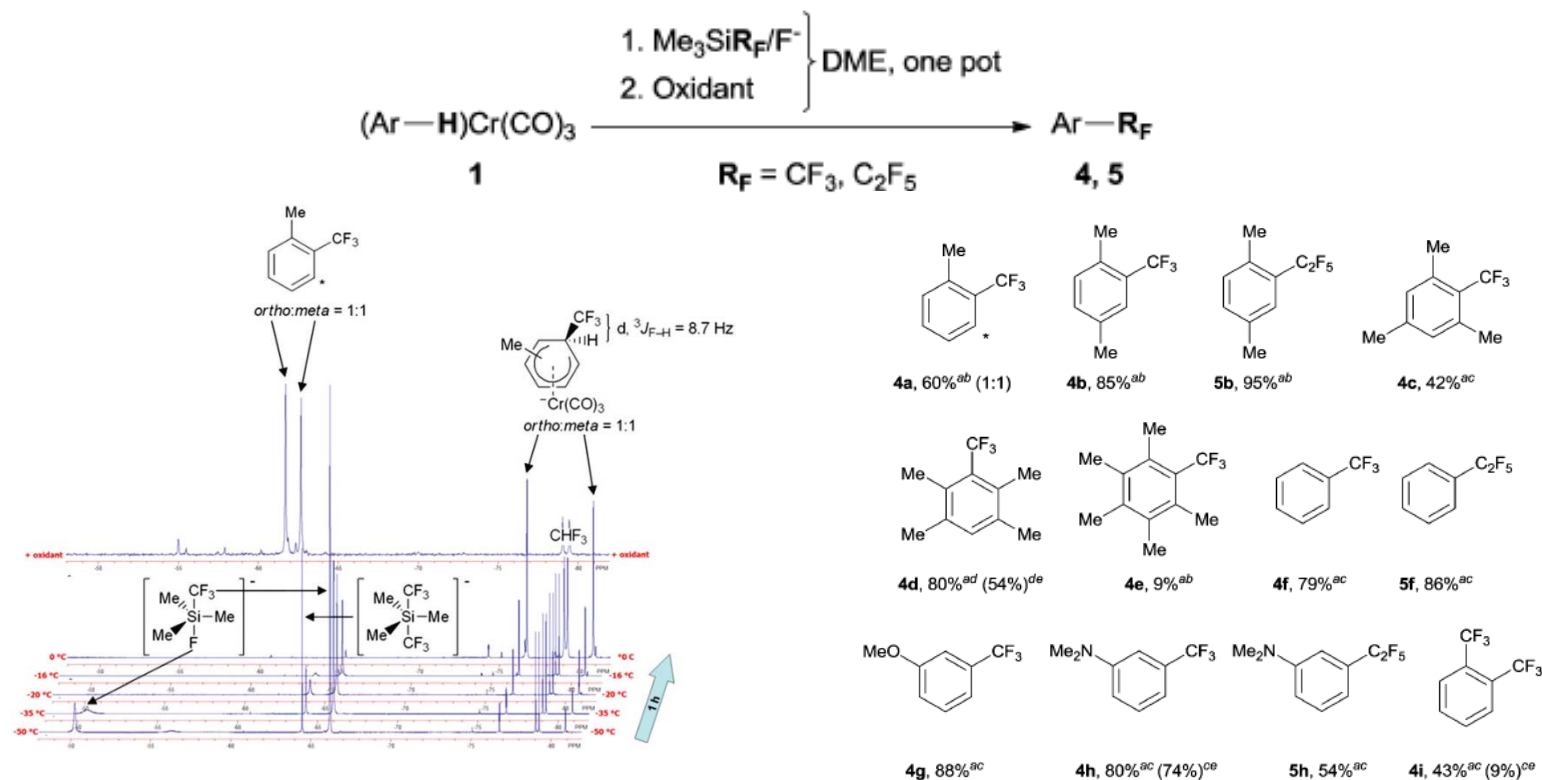


Total yield 30% from vinyl ethyl ether
gram quantities accessible

A convenient method to easily prepare parent λ^3 -phosphinine from easily accessible λ^5 -precursors was developed. A series of λ^5 -phosphinines bearing heteroatom substituents OMe, SMe, and/or NMe₂ at the phosphorus atom were prepared by electrocyclization of phosphahexatrienes generated in situ. Reaction conditions for the synthesis of λ^5 -phosphinines were optimized. The molecular structure of 1,1-dimethoxy- λ^5 -phosphinine was determined by an X-ray diffraction analysis. A series of reducing agents were tested in order to prepare λ^3 -phosphinine. 1,1-Dimethoxy- λ^5 -phosphinine was reduced by LiAlH₄. The method of choice appeared to be the reduction of bis(dimethylamino)- λ^5 -phosphinine with diisobutylaluminium hydride (DIBAL-H) in 30 % overall yield starting from vinyl ethyl ether

Dr. Savateev, Dr. Sci Kostyuk *Eur. J. Inorg. Chem.* 2016 , 628–632
DOI: 10.1002/ejic.201500856

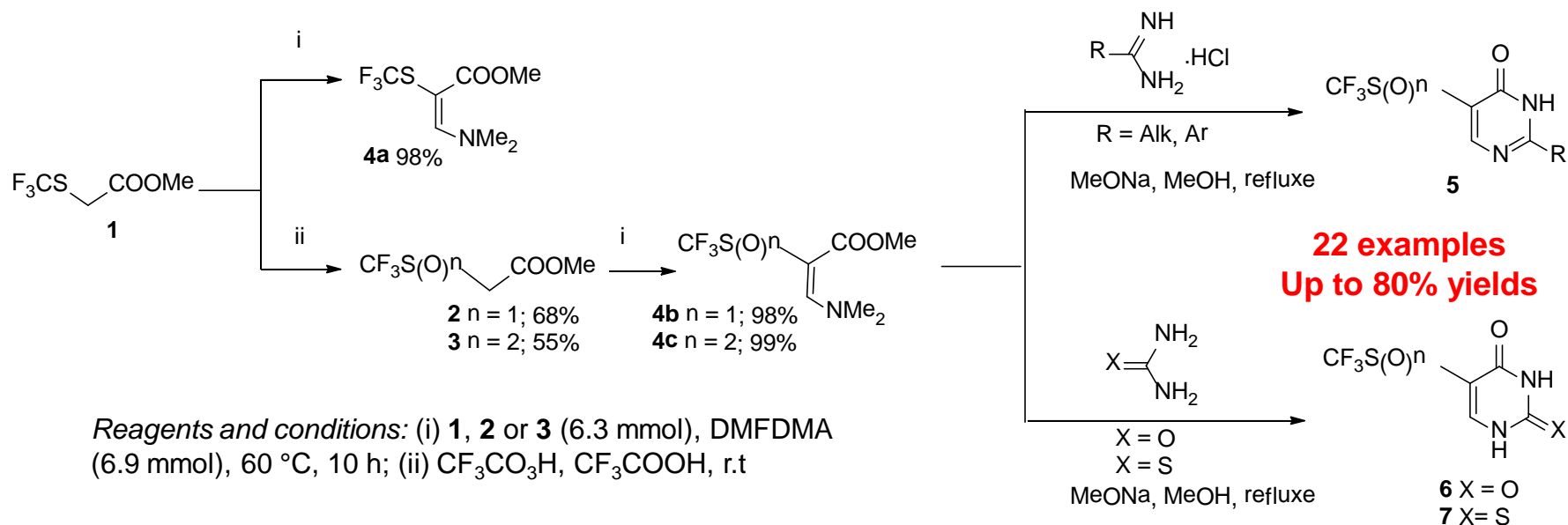
The first nucleophilic C–H perfluoroalkylation of aromatic compounds *via* (arene)tricarbonylchromium complexes



The first nucleophilic perfluoroalkylation of arenes is based on the arene π -system activation via (γ^6 -arene)tricarbonylchromium complexes. Perfluoroalkyl anions generated from $\text{Me}_3\text{SiR}_\text{F}$ and a fluoride ion source $[\text{Me}_4\text{N}]\text{F}$ exclusively attack the arene ligand under mild conditions. The formed negatively charged analogs of Meisenheimer adducts readily undergo a one-pot oxidation to perfluoroalkyl arenes.



$\text{CF}_3\text{S}(\text{O})_n$ -Containing Enaminones as Precursors for the Synthesis of Pyrimidine-4(3H)-ones

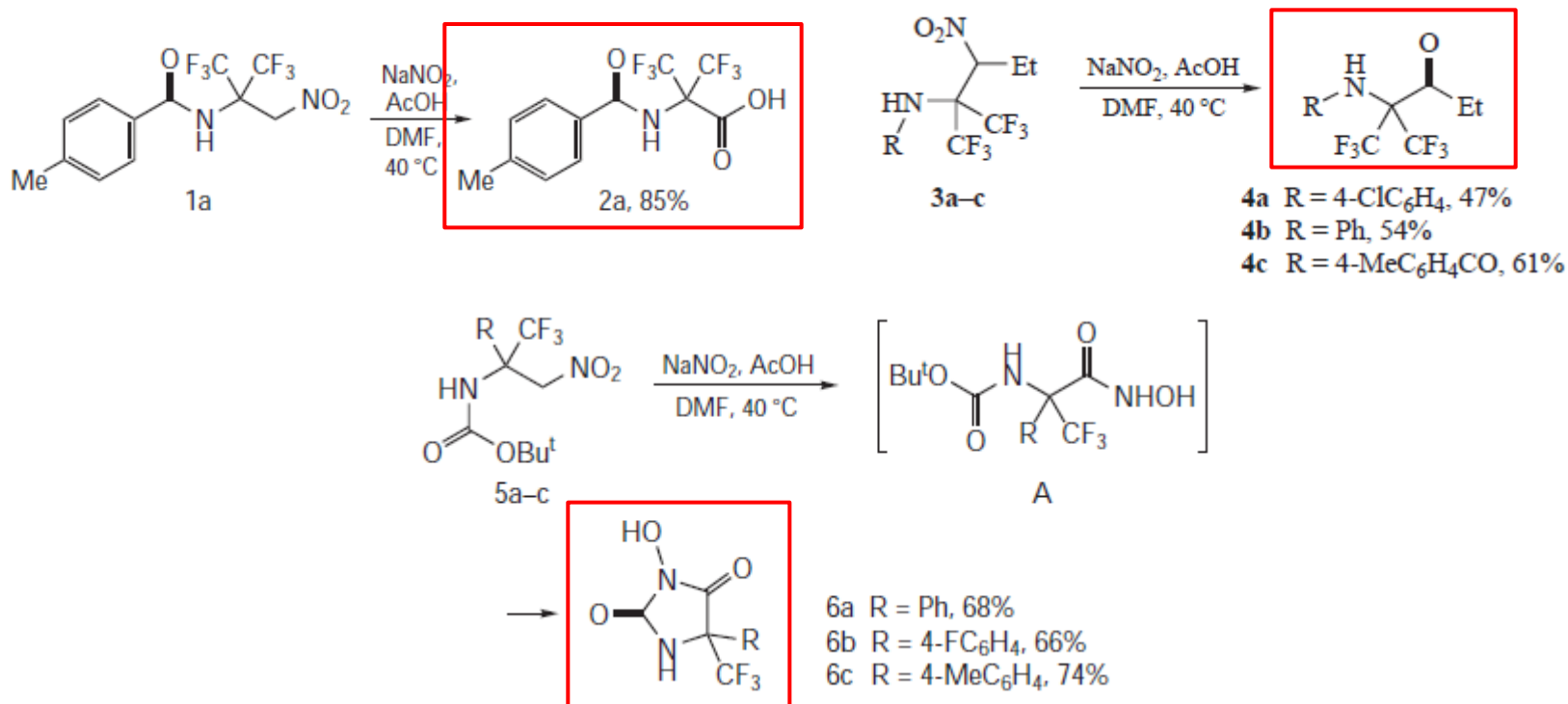


Reagents and conditions: (i) **1**, **2** or **3** (6.3 mmol), DMFDMA (6.9 mmol), 60 °C, 10 h; (ii) $\text{CF}_3\text{CO}_3\text{H}$, CF_3COOH , r.t

Methyl 3-(dimethylamino) acrylates containing trifluoromethylsulfenyl-, trifluoromethylsulfinyl-, and trifluoromethylsulfonyl groups were synthesized and their utility demonstrated by reactions with aliphatic and aromatic amidines to produce 2,5-substituted 4(3H)-pyrimidones. Cyclization reactions of enaminones with urea or thiourea led to 5-substituted uracil or 2-thiouracil derivatives, respectively.

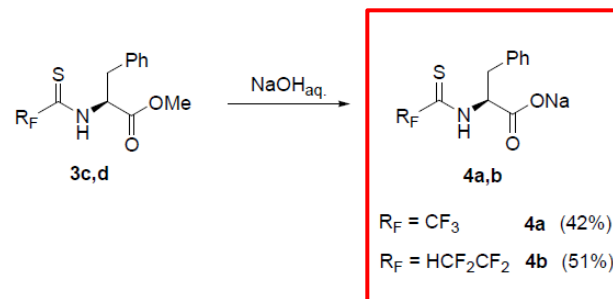
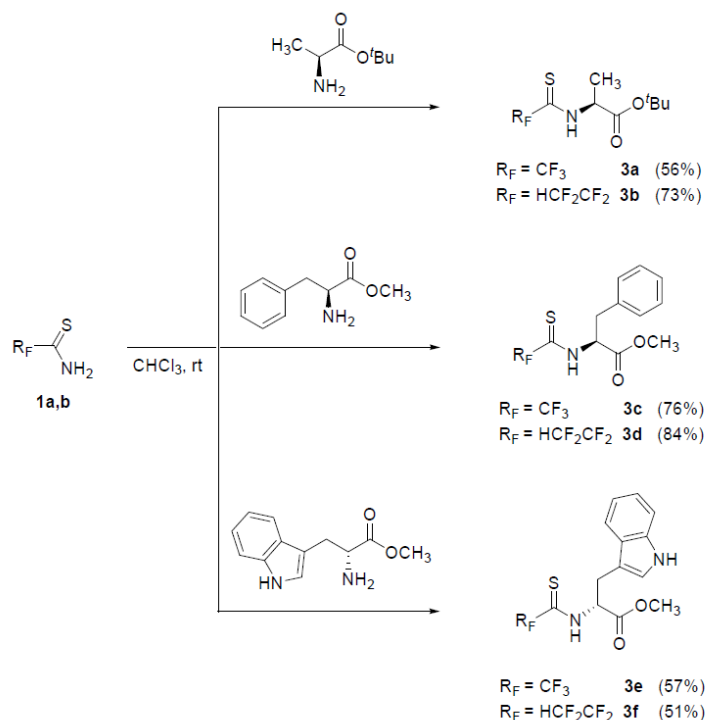


Oxidative Nef reaction of trifluoromethylated 2-nitroalkanamines



Oxidative Nef reaction of 2-nitroalkanamines or N-(2-nitroalkyl) carboxamides bearing trifluoromethyl group affords amino acids, amino ketones or hydroxyhydantoin depending on structure of the starting compounds.

Primary polyfluoroalkanethioamides as mild thioacylating reagents for alkyl amines and α -amino acid esters



Primary screen against HSV-1:
 $\text{EC}_{50} = 71$ (for **4a**) and 14 (for **4b**) $\mu\text{g/mL}$

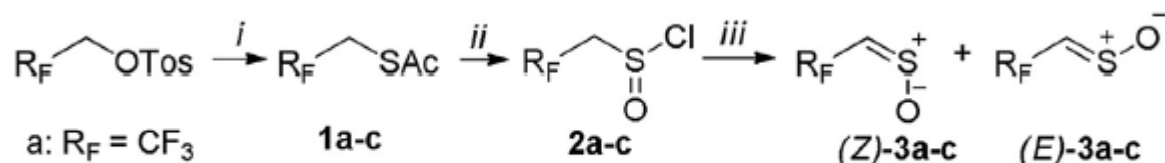
Compound **4b** showed 68 % inhibition of HSV-1
DNA replication at 125 $\mu\text{g/mL}$ meanwhile
 $\text{CC}_{50} > 1000$ $\mu\text{g/mL}$

Biology study with **Dr. Zagorodnya** from Institute of
Microbiology and Virology NASU

New fluorinated N-alkylthioamides were obtained by the transamidation reactions of primary amides of polyfluoroalkanethiocarboxylic acids with alkyl amines. Thionation of 2,2,3,3-tetrafluorosuccinamide with P_4S_{10} in the presence of hexamethyldisiloxane gave 3,3,4,4-tetrafluoropyrrolidine-2,5-dithione. The latter compound and primary polyfluoroalkanethioamides were shown to react with α -amino acid esters under mild conditions affording their new polyfluoroalkanethioyl derivatives.



Polyfluoroalkyl sulfines derived from 1,1-dihydropolyfluoroalkanesulfinyl chlorides: Decomposition and [4+2]-cycloaddition reactions

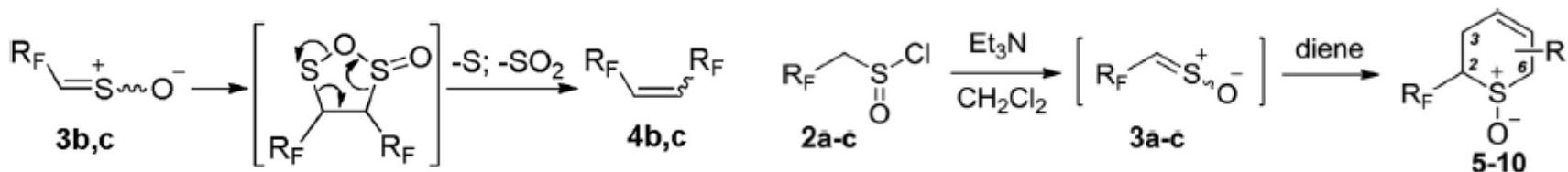


a: $\text{R}_\text{F} = \text{CF}_3$

b: $\text{R}_\text{F} = \text{H}(\text{CF}_2)_2$

c: $\text{R}_\text{F} = \text{H}(\text{CF}_2)_4$

Reagents and conditions: (i) AcSK, DMSO, 45 C; (ii) Cl_2 , AcOH, rt; (iii) Et_3N , CDCl_3 , 10 C to rt.

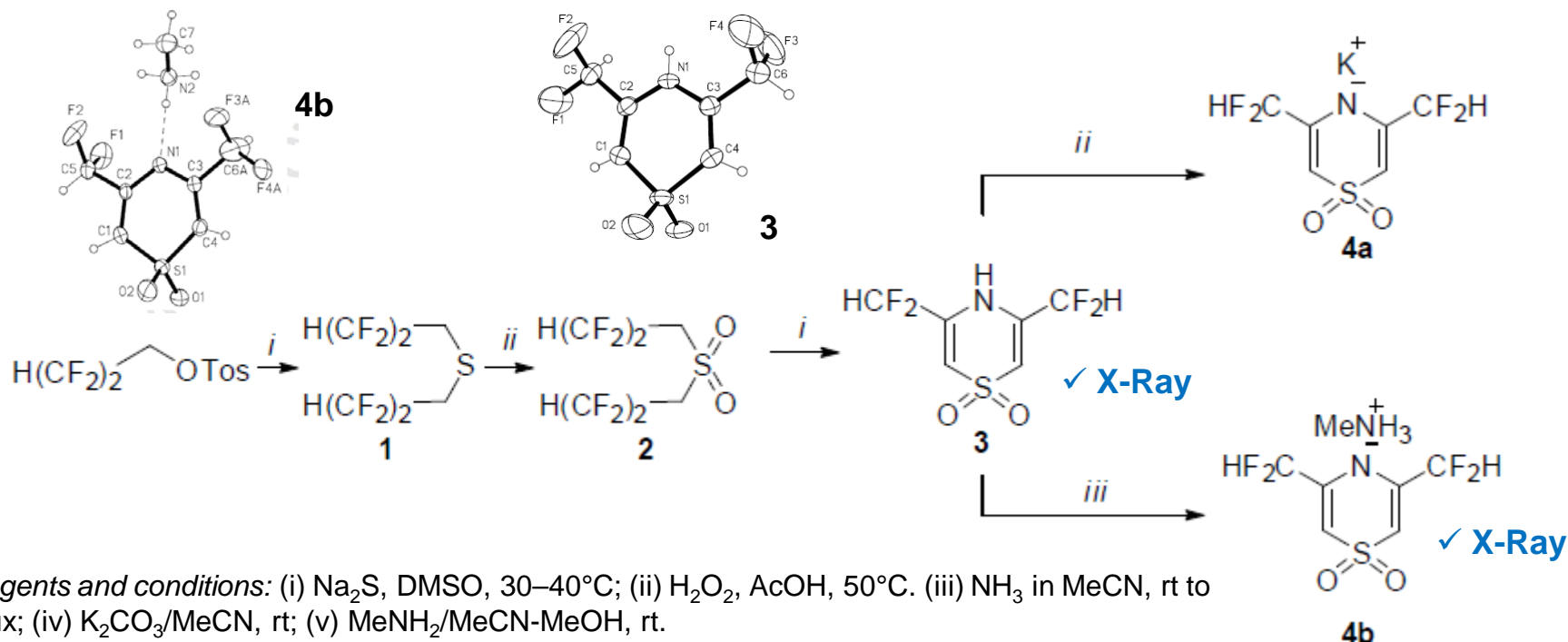


6 examples, 49-55% yields

✓ X-Ray

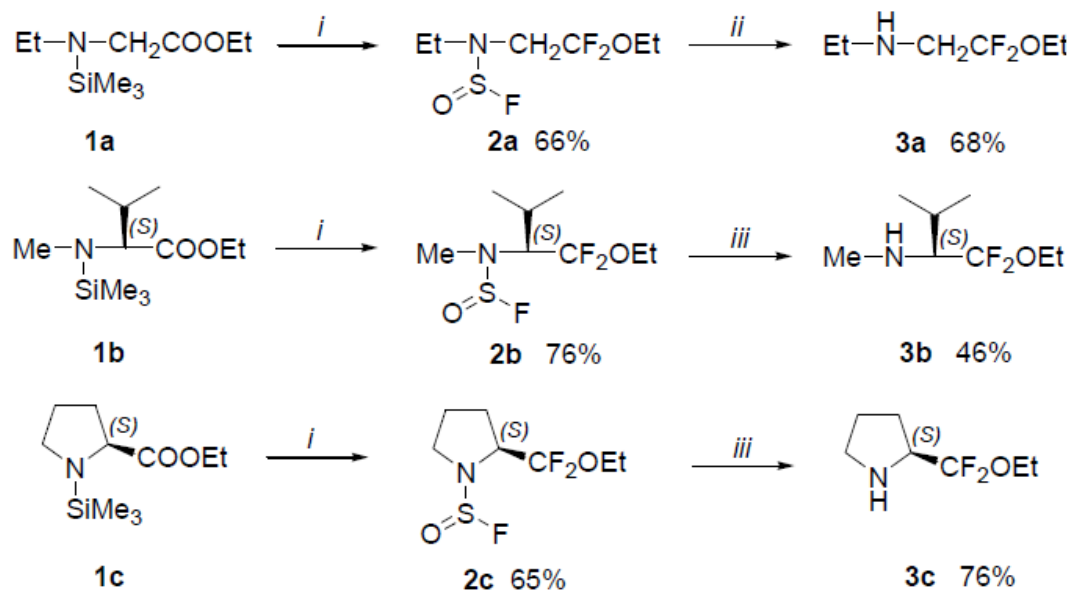
A convenient method for the preparation of 1,1-dihydropolyfluoroalkanesulfinyl chlorides has been developed basing on the oxidative chlorination of 1,1- dihydropolyfluoroalkyl thioacetates. The dehydrochlorination of the sulfinyl chlorides leads to the formation of new polyfluoroalkylsulfines (fluorinated thioaldehyde-S-oxides). The thermal decomposition of the sulfines results in formation of the symmetrical polyfluorinated alkenes, whereas the reactions of the sulfines with 1,3-dienes afford 2 - (polyfluoroalkyl)-3,6-dihydro-2H-thiopyran-1-oxides.

Synthesis of The Symmetrical 3,5-bis(difluoromethyl)-1,4-thiazine 1,1-dioxides



A convenient synthesis of the symmetrical bis(difluoromethyl)-1,4-thiazine 1,1-dioxides was carried out via heterocyclization of bis(2,2,3,3-tetrafluoropropyl)sulfone with ammonia and primary amines. The reaction with excess of ammonia leads to the formation of 3,5-bis(difluoromethyl)-4H-1,4-thiazine 1,1-dioxide. The result of the reaction with primary amines is determined by spatial nature of substituent at the nitrogen atom. 3,5-Bis(difluoromethyl)-4-propyl-4H-1,4-thiazine 1,1-dioxide and 3,5-bis(difluoromethyl)-4-(p-tolyl)-4H-1,4-thiazine 1,1-dioxide were prepared by the reactions of bis(2,2,3,3-tetrafluoropropyl)sulfone with n-propylamine and p-toluidine accordingly. The reaction of bis(2,2,3,3-tetrafluoropropyl)sulfone with tert-butylamine gives the 1,1'-sulfonylbis(N-(tert-butyl)-3,3-difluoroprop-1-en-2-amine).

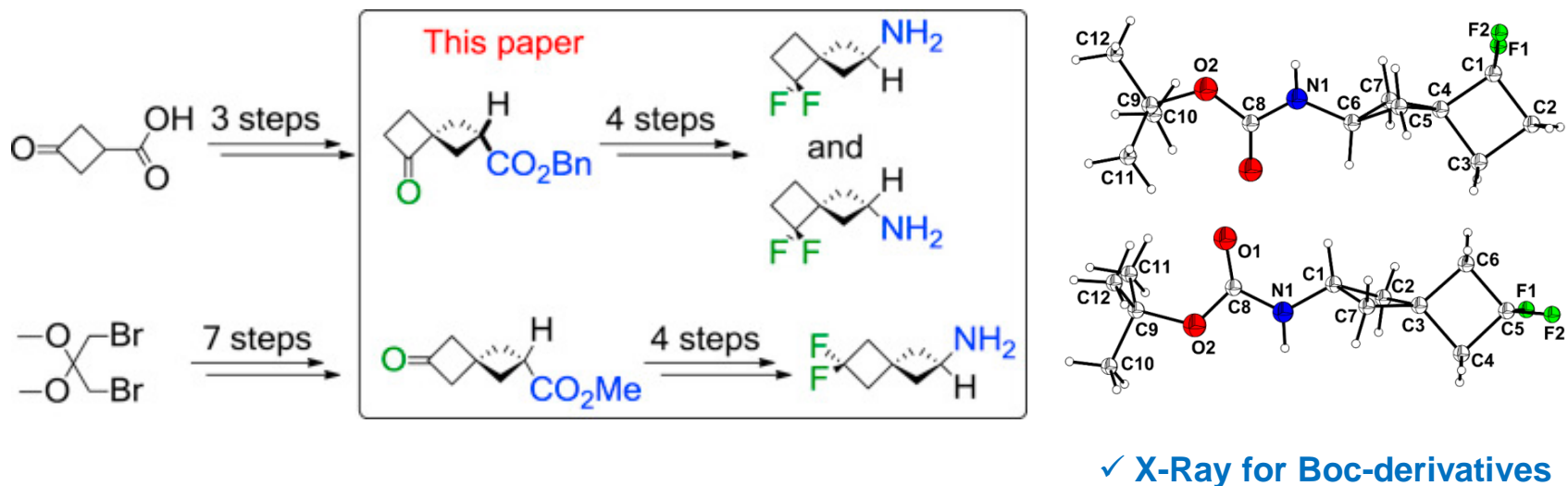
The first synthesis of chiral dialkylamines with α,α -difluoroethers fragments



Reagents and conditions: (i) SF_4 , Et_2O , -78°C to rt.; (ii) $\text{NaHCO}_3/\text{H}_2\text{O}$, CH_2Cl_2 , rt; (iii) $\text{C}_6\text{H}_6/\text{H}_2\text{O}$, Et_3N , rt.

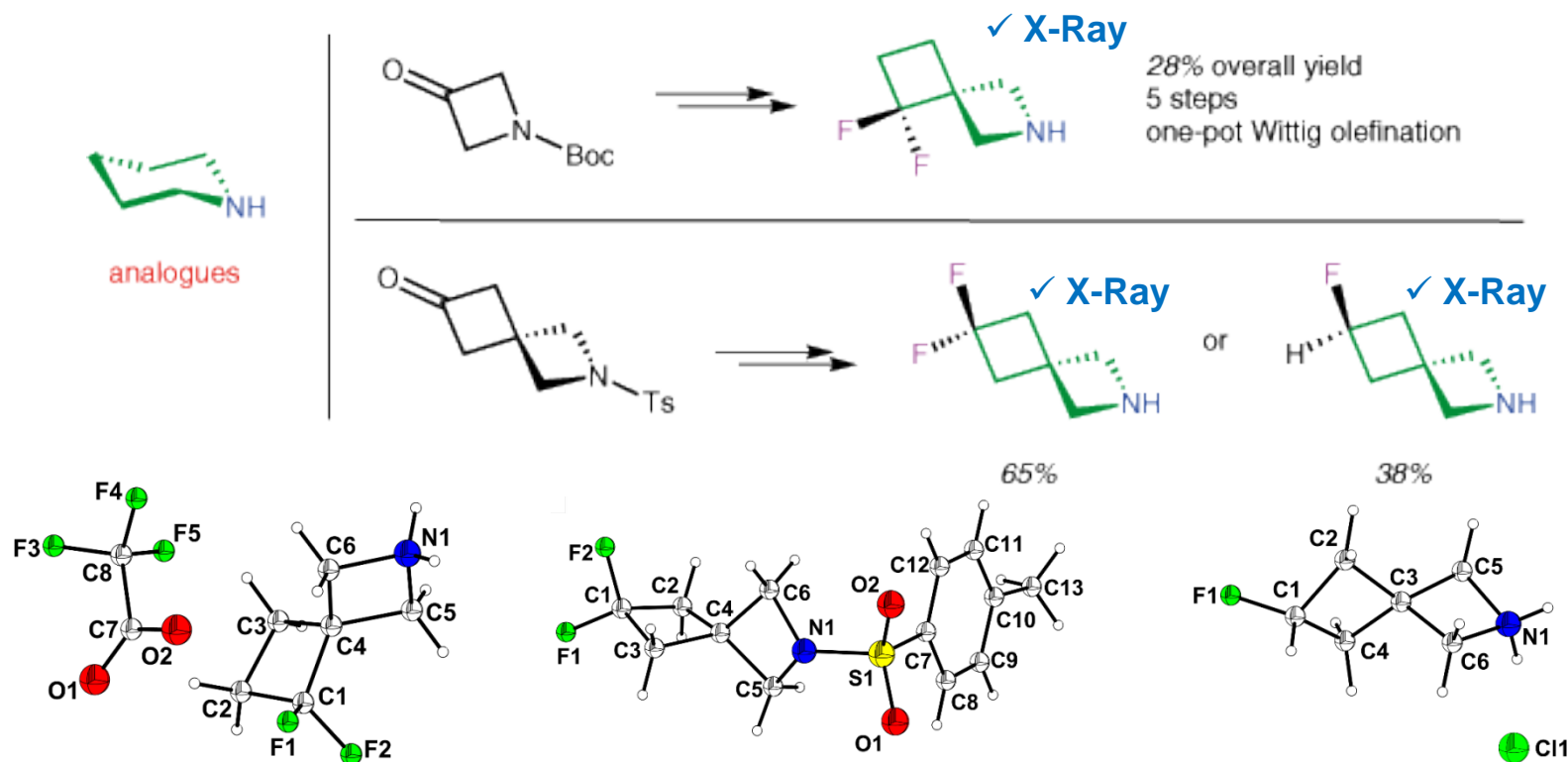
The reaction of *N*-trimethylsilylated esters of α -aminoacids with sulfur tetrafluoride provides the convenient route to previously unknown (2-ethoxy-2,2-difluoro-ethyl)-alkylamines containing α,α -difluoroether and secondary amino functions in one molecule. We consume, that the reaction proceeds through the formation of intermediate dialkylaminosulfur trifluorides which fluorinate carbonyl function in the same molecule giving (2-ethoxy-2,2-difluoro-ethyl)-alkylamino sulfinyl fluorides as the reaction products. Use of chiral aminoacids as the starting reagents gave route to chiral dialkylamines containing α,α -difluoroether substituents on the nitrogen atoms in their pure enantiomeric forms.

Synthesis of fluorinated building blocks based on spiro[3.3]heptane scaffold



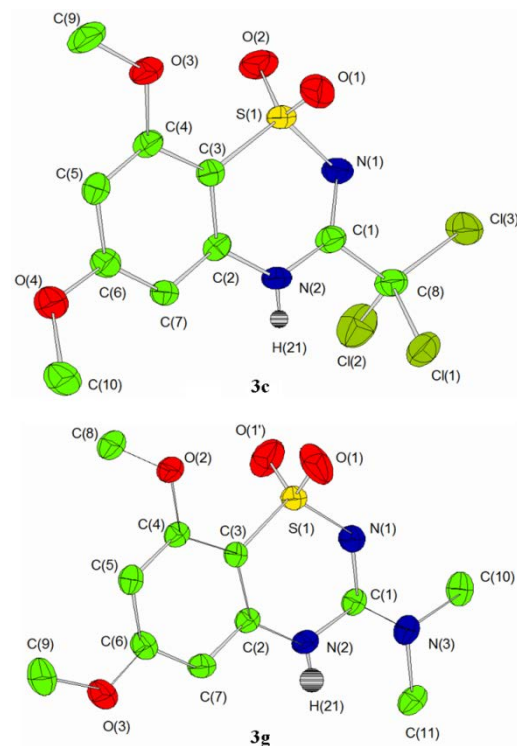
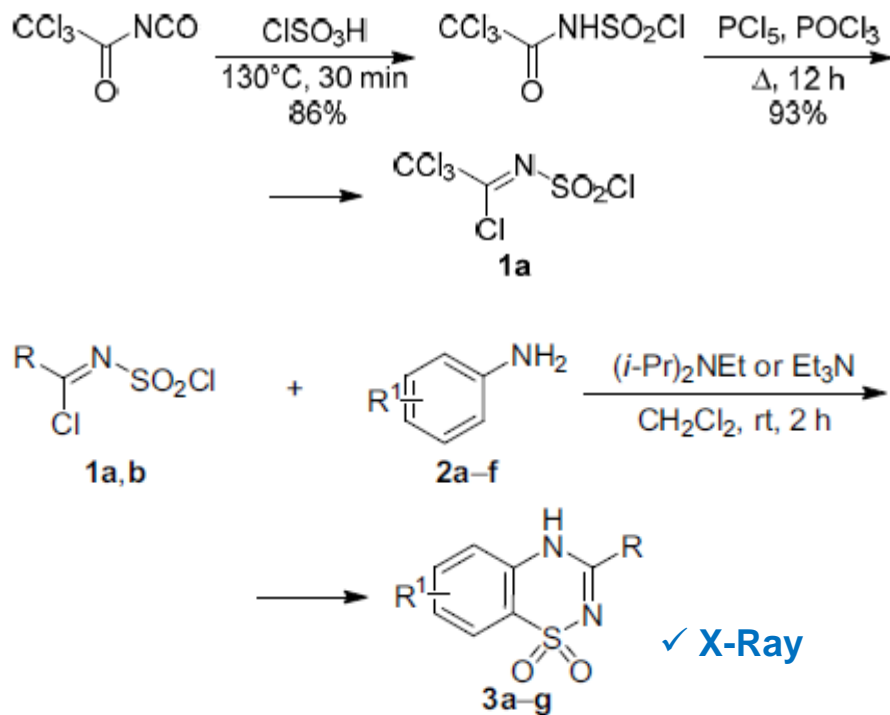
New non-flattened amino group-containing building blocks and fluorinated analogs based on the spiro[3.3]heptane motif were synthesized. The syntheses included a challenging deoxofluorination of sterically hindered carbonyl groups via an intermediate carbocation. XtaFluor-M was found to be the reagent of choice for deoxofluorination of the ketones. The synthesized compounds could be useful in medicinal chemistry due to their three-dimensional shape, and a different pattern of the fluorine substitution.

Synthesis of fluorinated building blocks based on spiro[3.3]heptane scaffold



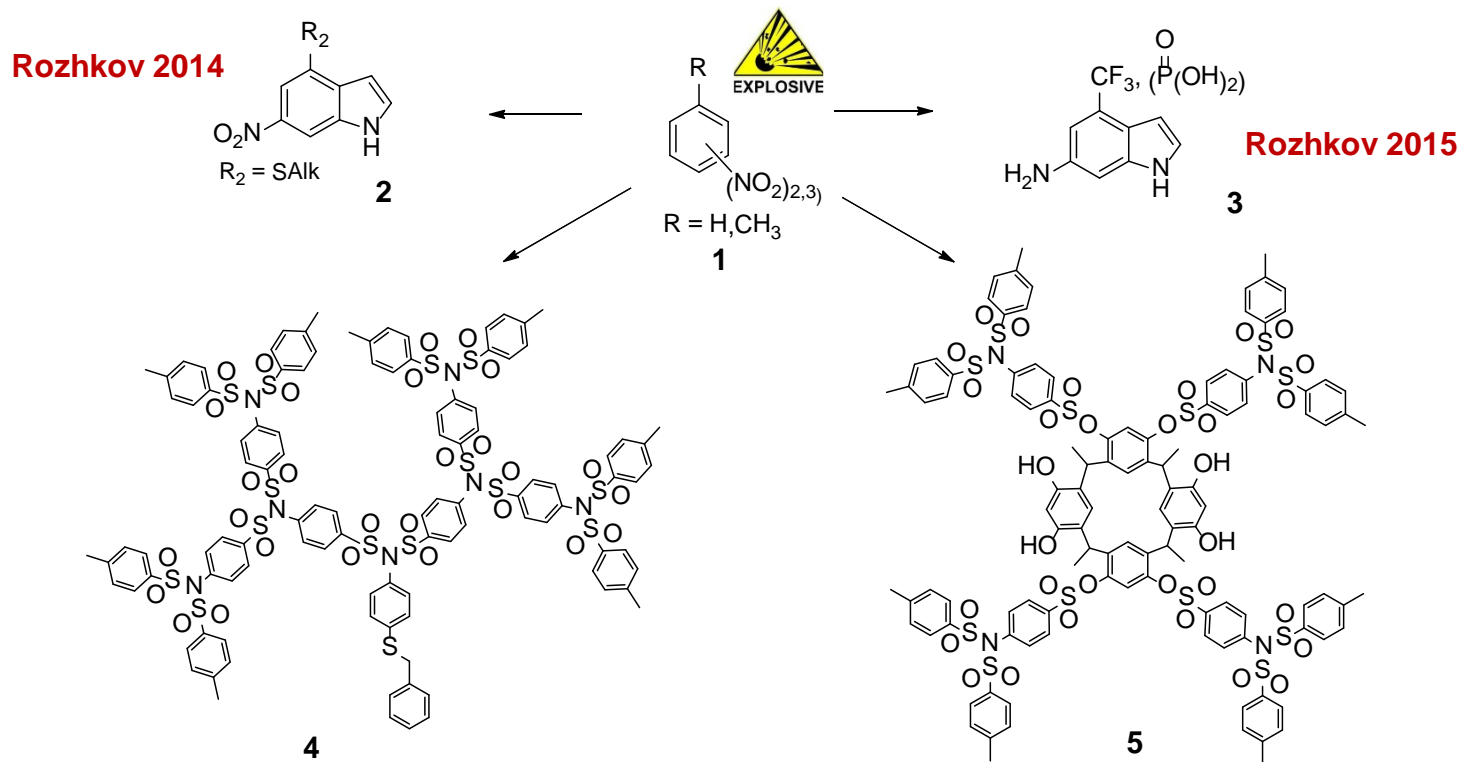
The synthesis of a set of conformationally restricted fluorinated analogues of piperidine, based on a 2-azaspiro[3.3]heptane scaffold, is reported. Different pattern of fluorine substitution within the rigid skeleton make the analogues excellent candidates for use in drug design. The overall simplicity of the experimental procedures and the availability of inexpensive starting materials allow for multigram-scale syntheses of the described compounds.

Heterocyclization of N-(chlorosulfonyl)imidoyl chlorides with anilines, a new method of synthesis of 1,2,4-benzothiadiazine 1,1-dioxides



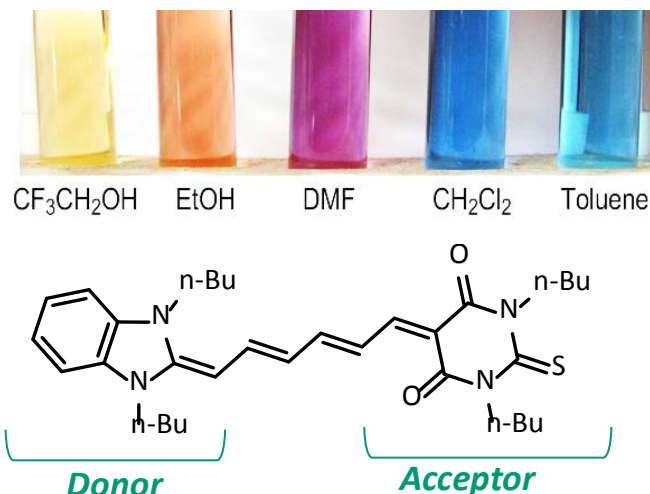
N-(Chlorosulfonyl)imidoyl chlorides react regioselectively with anilines, 2-aminomethylnaphthalene, or 1,2,3,4-tetrahydroquinoline leading to derivatives of 1,2,4-benzothiadiazine 1,1-dioxide. Heterocyclization occurs at the sterically less hindered C-6 atom in the case of 3-methoxy- and 3,4-dimethoxyaniline, while the reaction with 3-methylaniline leads to a mixture of cyclization products at the C-2 and C-6 atoms of aniline.

Conversion of hazardous polynitrocompounds (TNT surrogates) into practically valuable substances

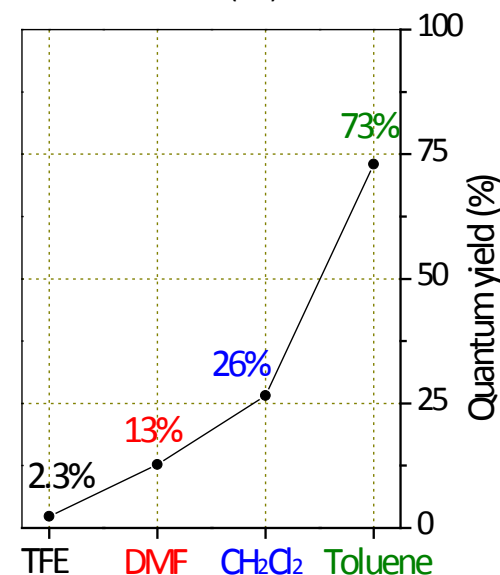
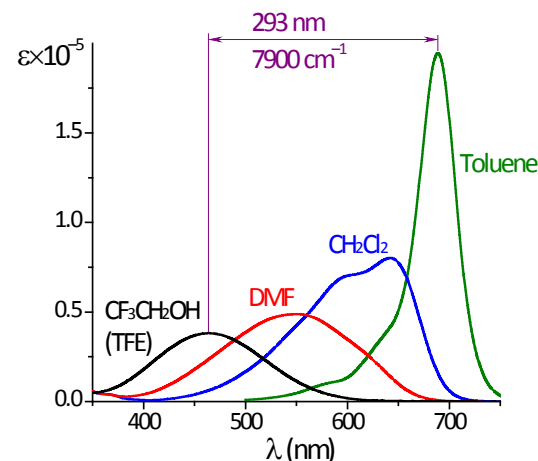


A four-step synthesis of two branched arylsulfonyl chlorides bearing a sulfonimide branching point is described. The protocol consists of the nucleophilic substitution of a nitro group or a halogen in the corresponding nitro aromatic compounds with benzyl mercaptide and reduction of the remaining nitro group to the amino group. The latter was persulfonated with 4-toluene sulfonyl chloride and, finally, the benzylsulfide group was converted into a sulfonyl chloride moiety.

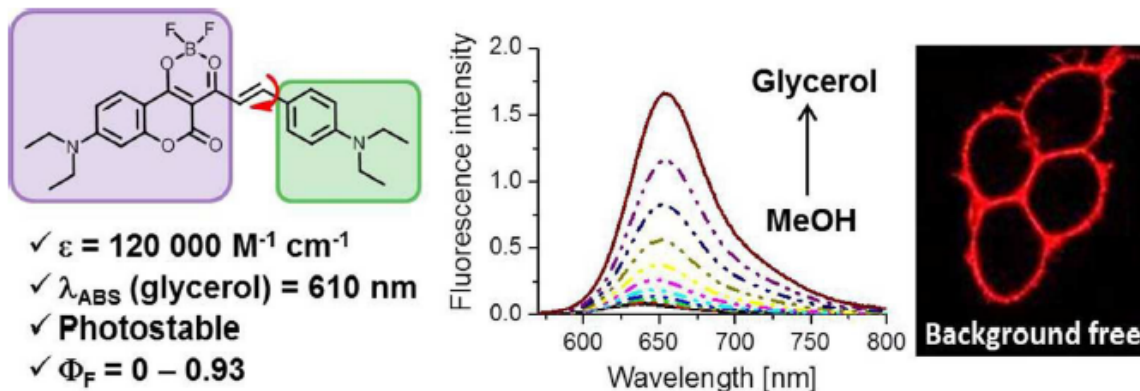
Highly solvatochromic merocyanines



A vinylogous series of highly dipolar merocyanines were designed to study their solvatochromism in a wide range of solvents including low-polarity alkanes. It has been revealed that the lower vinylogues indeed have negative solvatochromism in the full range of solvent polarities starting from n-hexane, while the hexamethinemerocyanine exhibits reversed solvatochromism. With the extreme ranges of solvatochromism, the studied dyes possess 5–7 times weaker solvatofluorochromism, which can be rationalized via their decreased dipolarity in the fluorescent state. They also demonstrate an inverse dependence of their fluorescence quantum yield on solvent polarity and have near-record Stokes shifts in high-polarity media. The experimental data are supplemented by the results of DFT quantum chemical analysis of dye electronic structures in both the ground and excited states with PCM solvent field simulation.

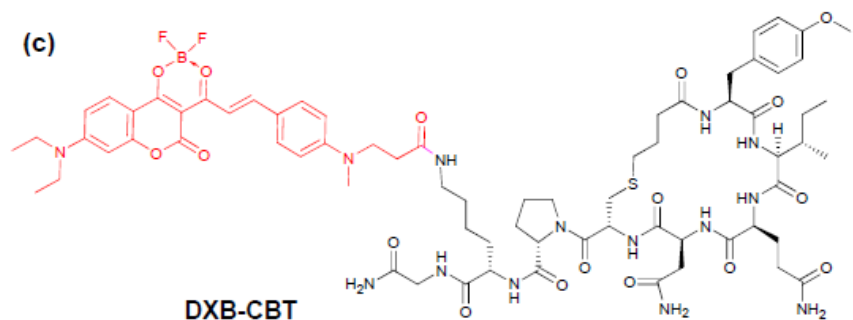


Push-pull dioxaborine as fluorescent molecular rotor: far-red fluorogenic probe for ligand-receptor interactions

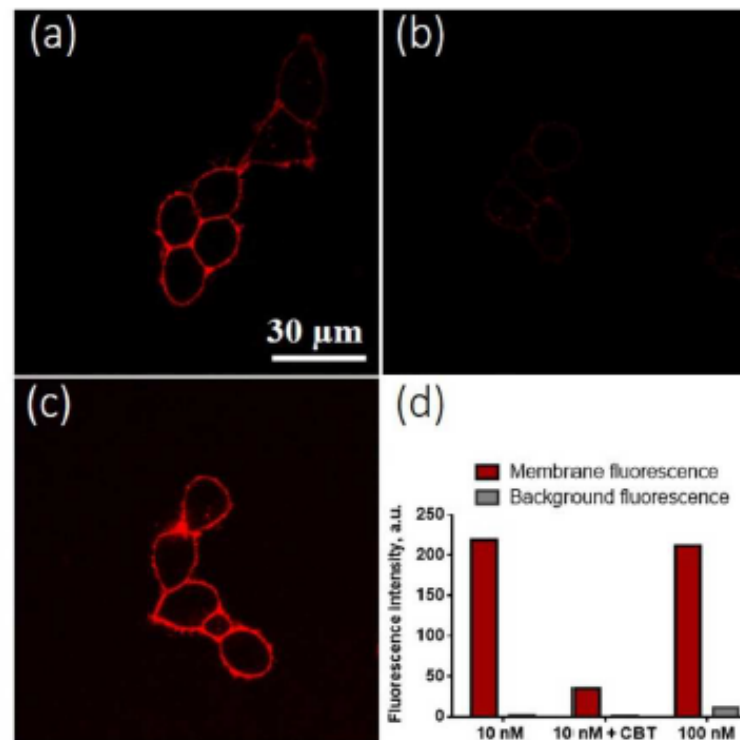


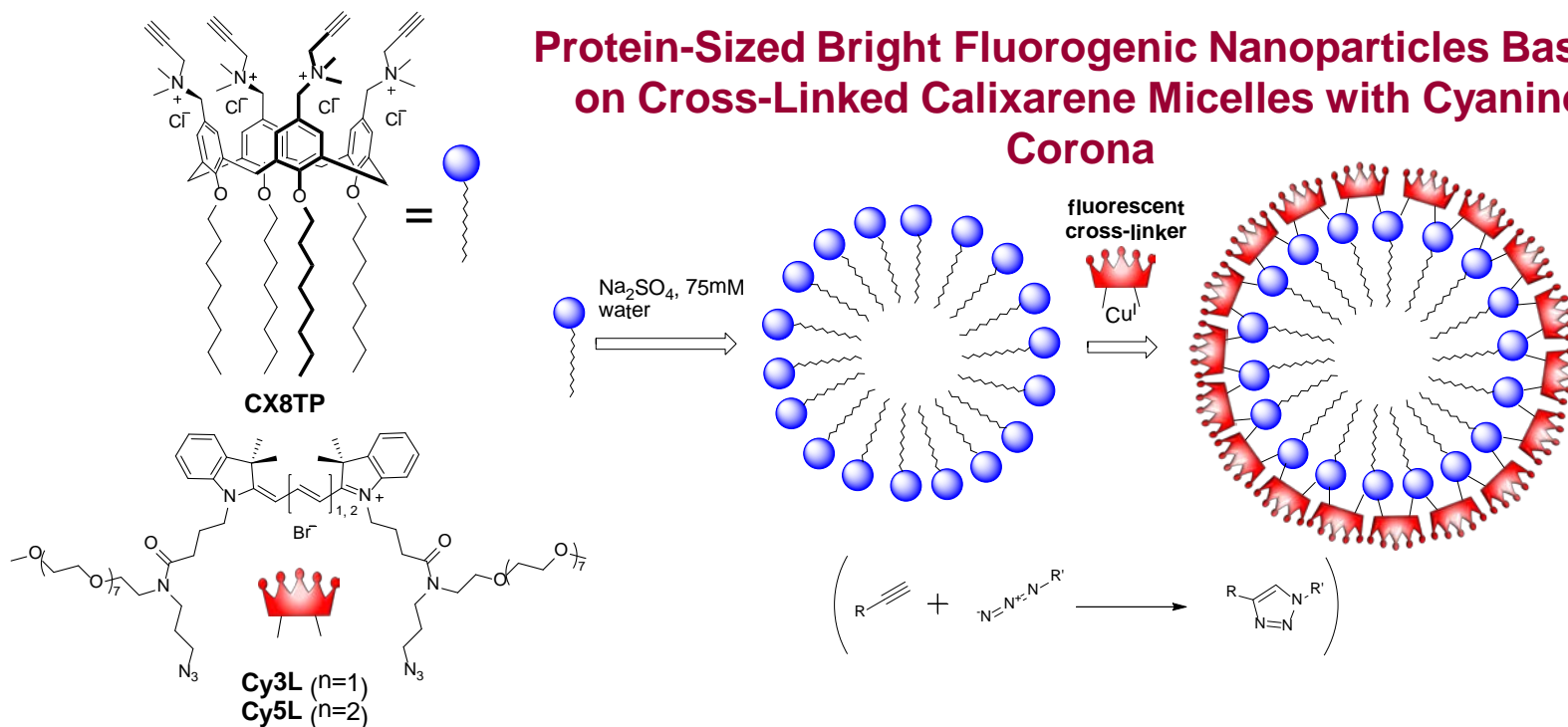
Fluorescent solvatochromic dyes and molecular rotors have attracted considerable attention as fluorogenic probes because of background-free detection of biomolecules in live cells in no-wash conditions. Herein, we introduce a push-pull boron-containing (dioxaborine) dye that presents unique spectroscopic behavior combining solvatochromism and molecular rotor properties. Indeed, in organic solvents, it shows strong red shifts in the absorption and fluorescence spectra upon increase in solvent polarity, which is typical for push-pull dyes. On the other hand, in polar solvents, where it probably undergoes twisted intramolecular charge transfer (TICT), the dye displays strong dependence of its quantum yield on solvent viscosity, in accordance with the Förster–Hoffmann equation. In comparison to solvatochromic and molecular rotor dyes, the dioxaborine derivative shows an exceptional extinction coefficient ($120\,000\text{ M}^{-1}\text{ cm}^{-1}$), high fluorescence quantum yields and a red/far-red operating spectral range. It also displays much higher photostability in apolar media as compared to Nile Red, a fluorogenic dye of similar color. Its reactive carboxyl derivative has been successfully grafted to carbetocin, a ligand of the oxytocin G protein-coupled receptor. This conjugate exhibits a >1000-fold turn on between apolar 1,4-dioxane and water. It targets specifically the oxytocin receptor at the cell surface, which enables receptor imaging with excellent signal-to-background ratio (>130).

Push-pull dioxaborine as fluorescent molecular rotor: far-red fluorogenic probe for ligand-receptor interactions



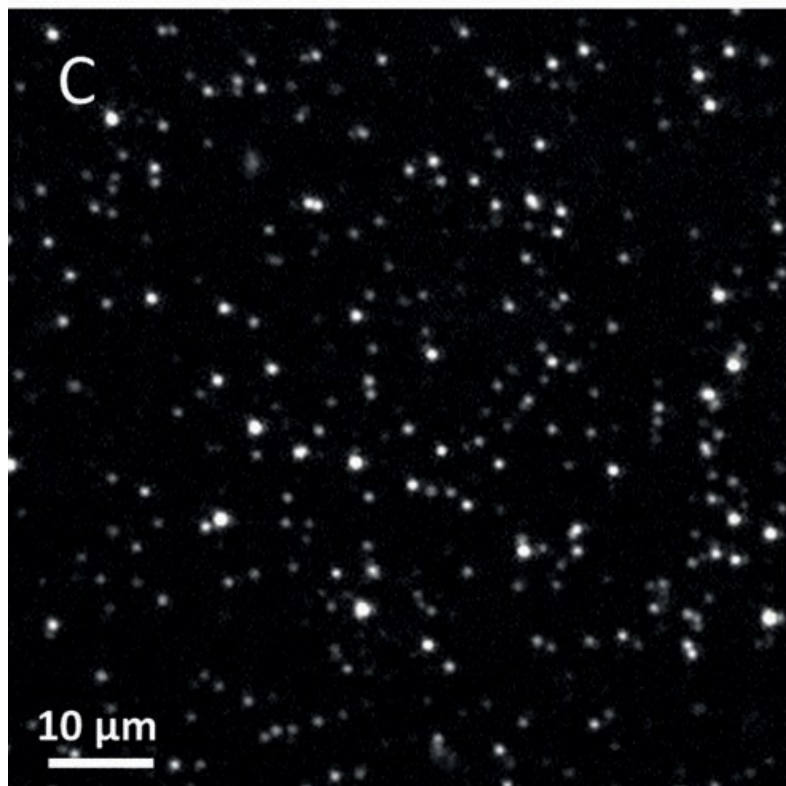
Confocal microscopy studies. Confocal images of OTR cells with 10 nM of DXB-CBT (a), 10 nM of DXB-CBT and 2 μ M of CBT competitor (b), or 100 nM of DXB-CBT (c). Fluorogenic properties of DXB-CBT: average membrane and background fluorescence for all the images (d). DXB-CBT was incubated with cells 5 min before imaging. Laser excitation was done at 561 nm and the emission was collected at 575-750 nm interval.



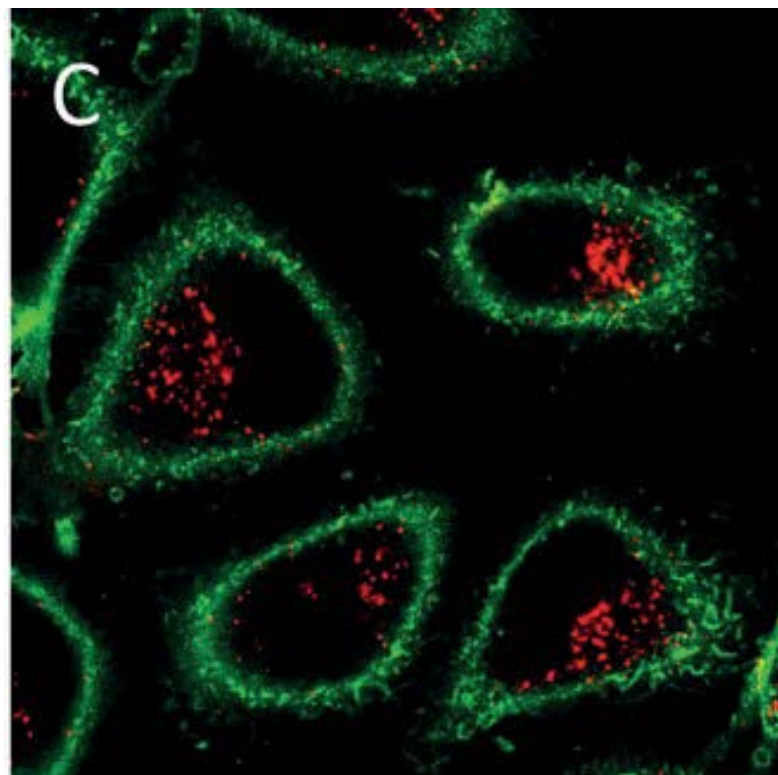


The key challenge in the field of fluorescent nanoparticles (NPs) for biological applications is to achieve superior brightness for sizes equivalent to single proteins (3–7 nm). We propose a concept of shell-cross-linked fluorescent micelles, in which PEGylated cyanine 3 and 5 bis-azides form a covalently attached corona on micelles of amphiphilic calixarene bearing four alkyne groups. The fluorescence quantum yield of the obtained monodisperse NPs, with a size of 7 nm, is a function of viscosity and reached up to 15 % in glycerol. In the on-state they are circa 2-fold brighter than quantum dots (QD-585), which makes them the smallest PEGylated organic NPs of this high brightness. FRET between cyanine 3 and 5 cross-linkers at the surface of NPs suggests their integrity in physiological media, organic solvents, and living cells, in which the NPs rapidly internalize, showing excellent imaging contrast. Calixarene micelles with a cyanine corona constitute a new platform for the development of protein-sized ultrabright fluorescent NPs.

Protein-Sized Bright Fluorogenic Nanoparticles Based on Cross-Linked Calixarene Micelles with Cyanine Corona

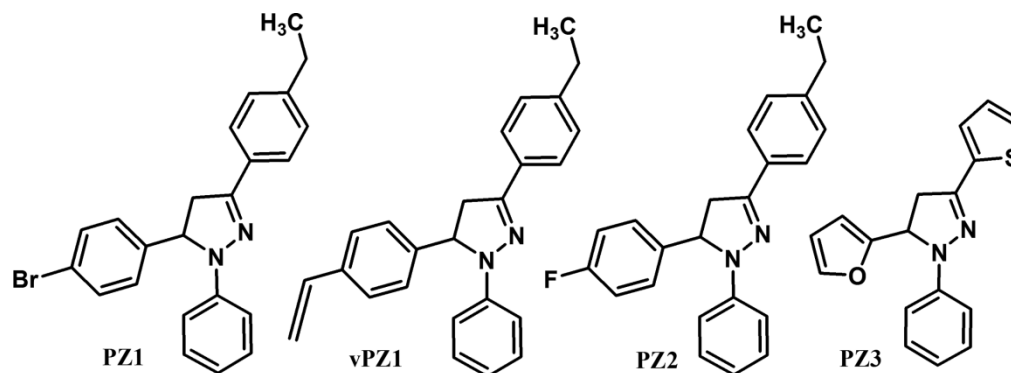
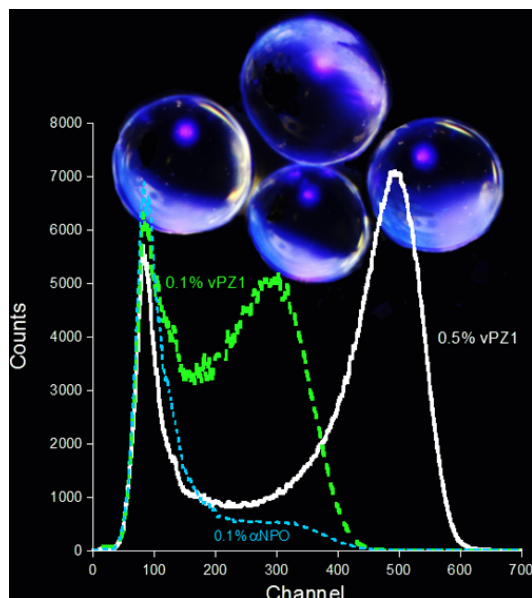


Fluorescence image of NPs
deposited on glass



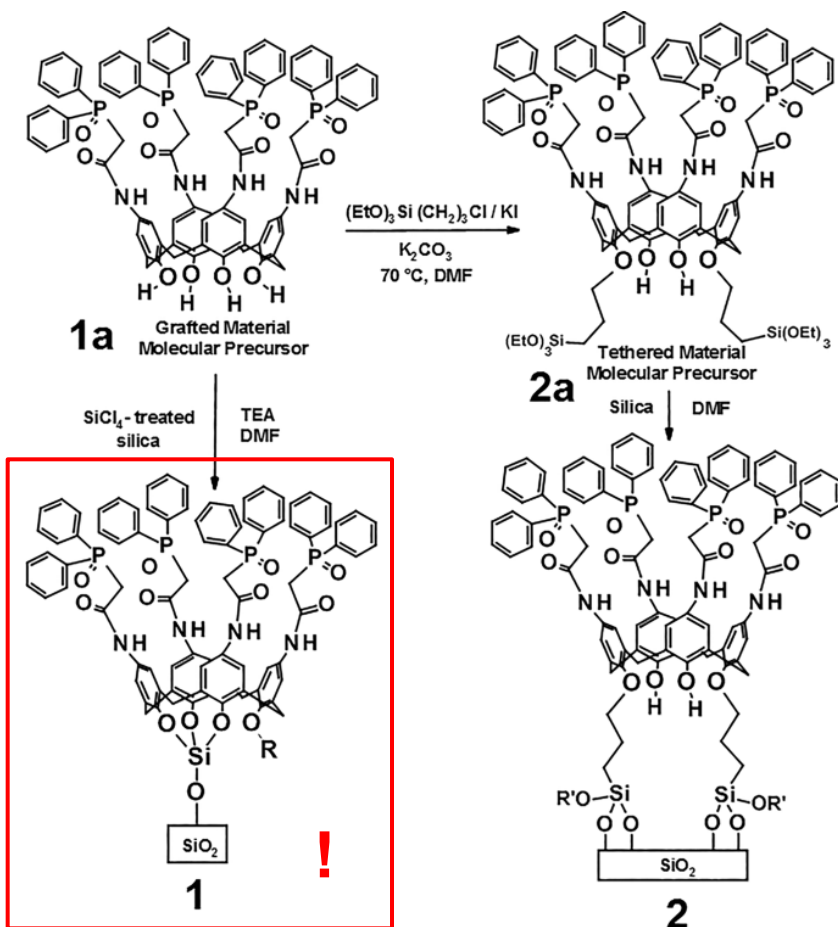
Fluorescence confocal imaging
of HeLa cells incubated with NPs

New Efficient Organic Scintillators Derived from Pyrazoline



We report on the synthesis, spectroscopic and scintillation properties of three new pyrazoline core based fluorophores. Fluorescence properties of the fluorophores have been studied both in a solution state and in a solid polyvinyltoluene (PVT) resin matrix of different porosity. The synthesized fluorophores were found to be promising candidates for application in plastic scintillators for detection of ionizing radiation (alpha, beta particles, γ rays and neutrons) and demonstrated superior efficiency in comparison to the existing commercially used fluorophores (2-(1-naphthyl)-5-phenyloxazole (α NPO), 9,10-diphenylanthracene, etc.). Moreover, the suggested synthetic route allows functionalization of the fluorophores with a vinyl group for further covalent bound to the PVT or other vinyl polymer matrices, which dramatically improves chemical stability of the system simultaneously improving the photoluminescence quantum yield. Possible mechanisms of the enhanced scintillation properties are discussed based on preliminary quantum mechanical calculations and spectroscopic characteristics of the fluorophores under study.

Lanthanide–Actinide Separation



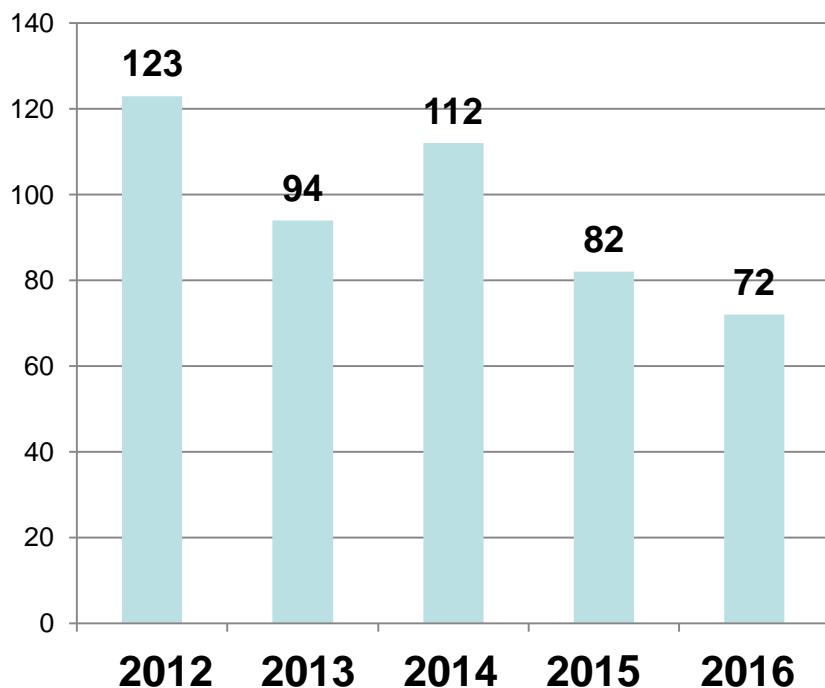
Unprecedented Increase in Affinity for Eu^{III} over Am^{III} through Silica Grafting of a Carbamoylmethylphosphine Oxide-Calix[4]arene Site

Surface area	$274 \text{ m}^2 \cdot \text{g}^{-1}$
CMPO-calixarene loading	$125 \mu\text{mol} \cdot \text{g}^{-1}$
$K_D(\text{Eu})$	170
$K_D(\text{Am})$	7.5
Separation factor	22
$K_D(\text{Eu}) / K_D(\text{Am})$	

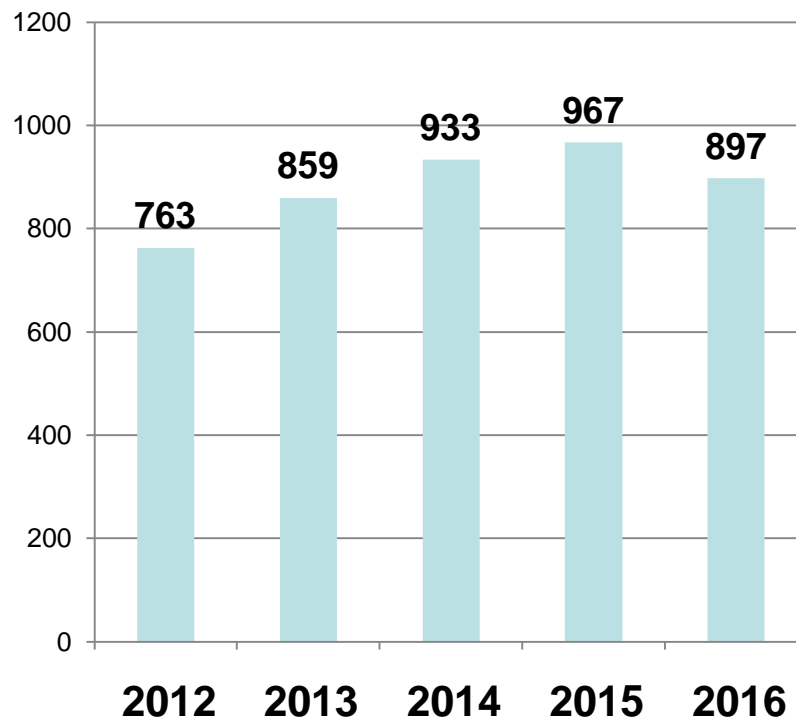
A grafted CMPO-calix[4]arene site on silica demonstrates affinity for Eu^{III} over Am^{III} , which is unique when compared with a more flexible propoxy-tethered CMPO-calix[4]arene site as well as all previously reported CMPO-calix[4]arene ligands. The results highlight the importance of rigidity when anchoring sites for cation recognition on solid surfaces.



Publications, Citations, H-index, SCOPUS, 2012-2016



Publications, 483



Citations, 4419

H-Index = 44



MANY THANKS!

