Design and application of fluorinated reagents

Theses of PhD dissertation

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INTRODUCTION

During the first part of our PhD work we dealt with sequential Sonogashira coupling. With this method, we were able to achieve terminal and disubstituted acetylenes, and heterocycles like indoles, benzofurans, and triazoles. These derivatives are valuable scaffolds for pharmaceutical and fine chemical industry. The synthesis of smaller molecules of this kind is well known and many methods are available for it. However, the synthesis of more complex systems mostly needs multistep reactions and functionalization.

Several methods are available for sequential and domino Sonogashira coupling in the literature, but these methods have disadvantages, like the high price of reagents such as tetrabutylammonium fluoride (TBAF) or the harsh conditions needed for deprotection of carbinol type protecting groups. To avoid these problems, we aimed for the use of hexafluorosilicic acid as a cheap, non-toxic fluorine reagent instead of TBAF. We planned to use TMS-acetylene as a C_2-source. We investigated our method in sequential Sonogashira-Sonogashira coupling, in the domino synthesis of benzofurans and Sonogashira-CuAAC sequence resulting 1*H*-1,2,3-triazoles. Furthermore, we expanded our method, and catalytic amount (1 mol%) of H_2SiF_6 was also screened for the same type of transformations mentioned above.

In the second part of our work, we designed a novel trifluoromethyl containing hypervalent alkenyl iodine reagents. Previously, we carried out quantum chemical calculation to predict the reactivity of our planned reagent. According to that, it was a promising C_2-CF_3 synthesis equivalent for this purpose, according to energy barriers calculated. These type of iodonium species are not described in literature, henceforth their synthetic application is unknown.

After the synthesis of the adequate (trifluoropropenyl)iodonium salt, we successfully applied in the synthesis of (2-trifluoromethyl)aziridines, having versatile substituents on the nitrogen atom of the small heterocycle. These (trifluoromethyl)aziridines are valuable compounds, as they can be used in treatment of aggressive malignant carcinoma. Although, they are more precious as starting materials or intermediates for the synthesis of hardly available CF_3 derivatives, where it is attached to aliphatic carbon.

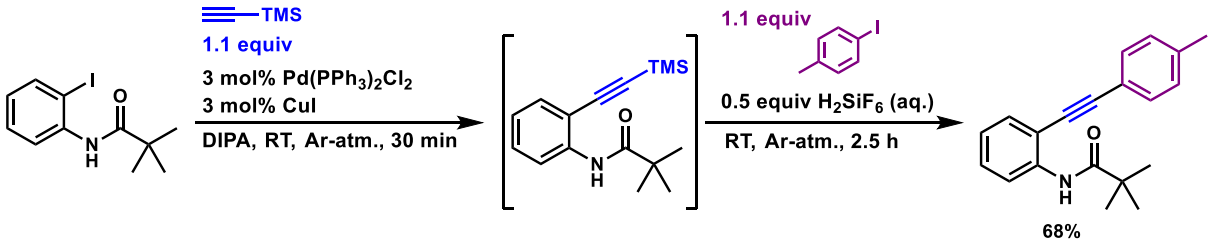
Our hypervalent iodonium salt proved to be adequate in the transformation of aliphatic and aromatic amines and even sulphamides to aziridines. This extensive usability has been unprecedented in the literature.

RESULTS

1. Sequential coupling in the presence of 50 mol% H_2SiF_6

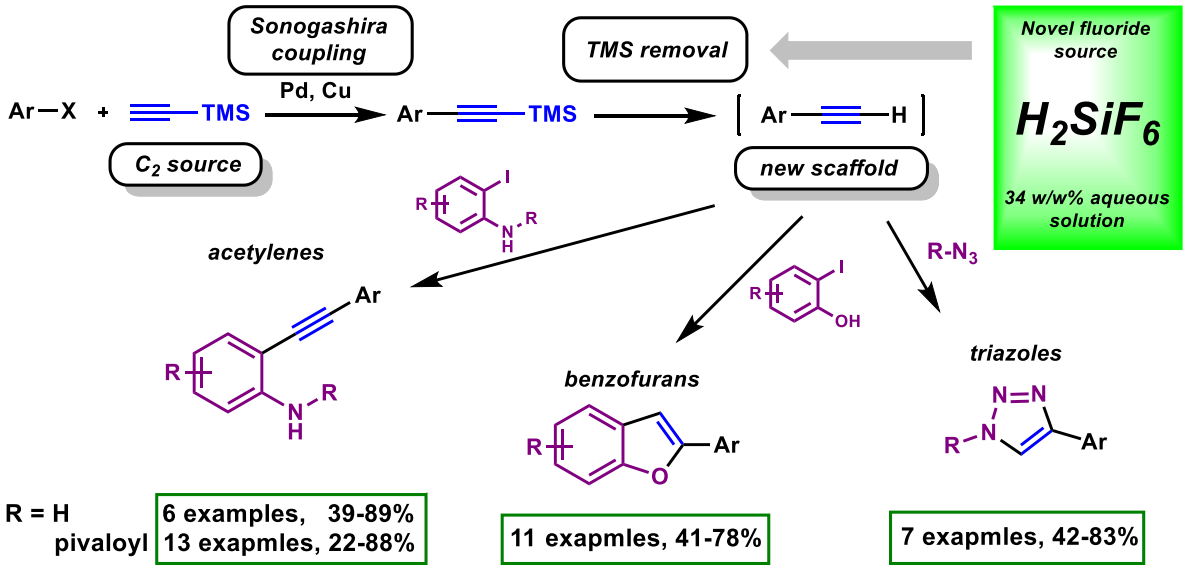
To replace the (mostly costly) pre-synthesized arylacetylenes in the synthesis of diarylacetylenes, we used an acetylene derivative, protected on one terminal end, ethynyltrimethylsilane. We used the conventional 3 mol% $Pd(PPh_3)_2Cl_2$ and 3 mol% CuI catalytic system, using different aryl iodides as starting materials. The formed TMS-ethynyl-arene intermediates were used in one pot process by adding another iodoarene, 2-iodophenol derivatives, or benzyl azides to achieve the desired moieties.

- Based on our research group's preliminary results, the amount of hexafluorosilicic acid can be lowered from 1.5 equivalents to 0,5 equivalent without any negative effect on conversion or without elongation of reaction time. We chose the reaction shown on Scheme 1 as a model reaction for optimization.



Scheme 1. Model reaction for sequential Sonogashira-Sonogashira coupling

- We proved through experiments, that the acidity of the hexafluorosilicic has not influence on its activity as in the desilylation reaction.
- Using the optimized reaction conditions, we accomplished the synthesis of non-symmetrically substituted diarylacetylenes, 2-(aryl)benzofurans and 1-benzyl-4-aryl-1*H*-1,2,3-triazoles.



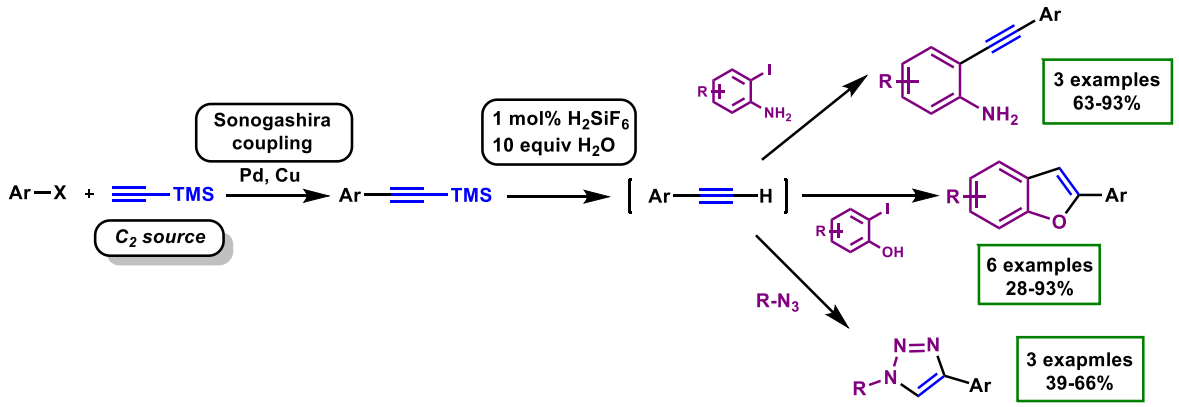
Scheme 2. Synthesized derivatives

2. Sequential coupling in the presence of 1 mol% H_2SiF_6

In the next step, we wanted to lower the amount of hexafluorosilicic acid to catalytic amount.

We only investigated the 2nd step of the sequence, because the conversion in the first step is simply full after 1 hour at 60 °C. We found the lowest loading of catalyst as 1 mol%. Parallel to this, the reaction time for full conversion increased significantly, but could be compensated with increasing the reaction temperature to 60 °C and we reached full conversion in acceptable 24 hours. Furthermore, addition of 10 equivalents of distilled water was needed, otherwise the conversion also dropped significantly. Further increasing of temperature gave place for side reactions.

- We investigated the role of H_2SiF_6, and we concluded, that none of hydrochloric acid, water or catalytic amount of fluoride sources like CsF or KF worked as efficient desilylating agent. Salts of H_2SiF_6, like Na_2SiF_6, K_2SiF_6, $NH_4)_2SiF_6$ were not sufficient and gave only traces of the desired products. We proposed the reason behind the low activity of hexafluorosilicate salt is the low solubility of these salts in diisopropylamine as solvent.
- We showed the utility of our method in synthesis of aniline and heterocyclic derivatives in good to excellent yields. In the case of 2-(arylethynyl)anilines the amino group remains intact even at higher temperature and elongated reaction time.
- Our method can be used for the synthesis of (2-aryl)benzofurans and 1-benzyl-4-aryl-1*H*-1,2,3-triazoles. Although in most cases we reached acceptable yields, but in case of identical structures, the application of 50% H_2SiF_6 has beneficial effects..

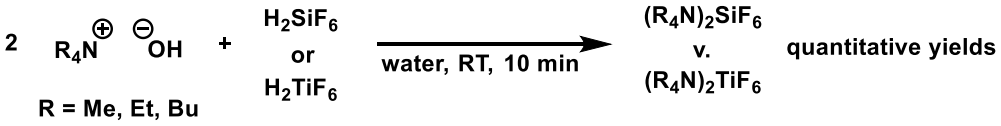


Scheme 3. Compound types synthesized using catalytic amount of H_2SiF_6

3. Reaction of silyl-enol-ethers and TMS-acetylene with electrophiles

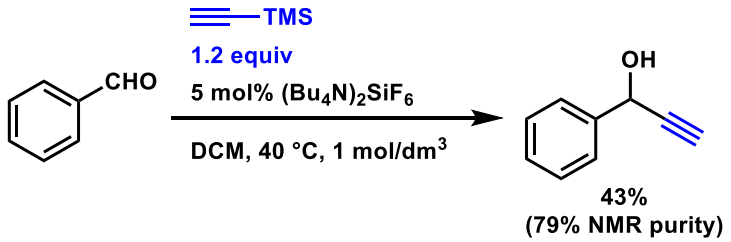
In the first two chapter, we presented the H_2SiF_6 to be a suitable substituent of TBAF for removal of TMS group, even in catalytic amount. Based on these results, we used the catalytic desilylation step in other desilylating methods requiring anhydrous reaction conditions.

- To achieve anhydrous catalytic transformations, we synthetized novel tetraalkyl ammomium hexafluorosilicate salts from aqueous solution of tetraalylammonium hydroxides and also aqueous solution of hexafluorosilicic acid to give the desired salts in quantitative yields.



Scheme 4. Synthesis of tetraalkylammonium salts

- We investigated the catalytic activity of the synthetized reagents, and experienced full conversion in the reaction of TMS-acetylene and benzaldehyde in the presence of catalytic amount of hexafluorosilicate.
- We optimized the reaction conditions and concluded that, for the best efficiency of carbinol addition, we have to use dichloromethane as a solvent at 40 °C, in the presence of 5 mol% hexafluorosilicate to obtain the corresponding ethynylcarbinol in 2 hours.

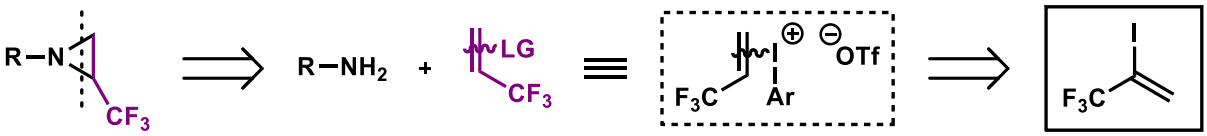


Scheme 5. Nucleophilic addition of TMS-acetylene to benzaldehyde

4. Synthesis of *N*-substituted (2-trifluoromethyl)aziridines

Objective

According to the literature, we aimed to design a C_2-CF_3 synthesis equivalent, which could be generally used not just for the production of *N*-alkylated, or sulfonylated, but also for *N*-arylated aziridines. Fluorine is a valuable target for bioactive compounds in pharmaceutical industry, which is reflected by the number of fluorine containing drugs accepted by the FDA.

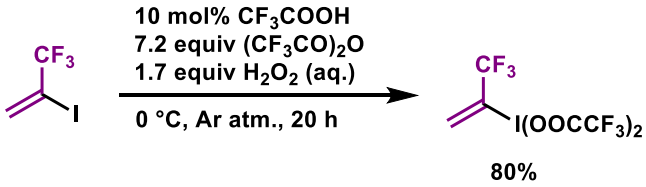


Scheme 6. Retrosynthesis of 2-(trifluoromethyl)aziridines

We planned to synthesize the corresponding iodonium salt from the commercially available 3,3,3-trifluoro-2-iodopropene, considering the extraordinary leaving ability of iodoarene from iodonium salts, which is 10^6-times better, than its triflate analogue's.

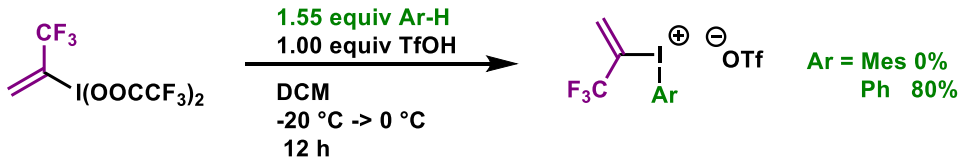
Based on quantum chemical calculations we ascertained the activation barrier of ring closing step to be much lower than in case of halides and sulfonium salts.

Based on the work of Umemoto and coworkers, we oxidized the commercially available 3,3,3-trifluoro-2-iodopropene to the appropriate bis(trifluoroacetate) (Scheme 7). The structure was verified by NMR.



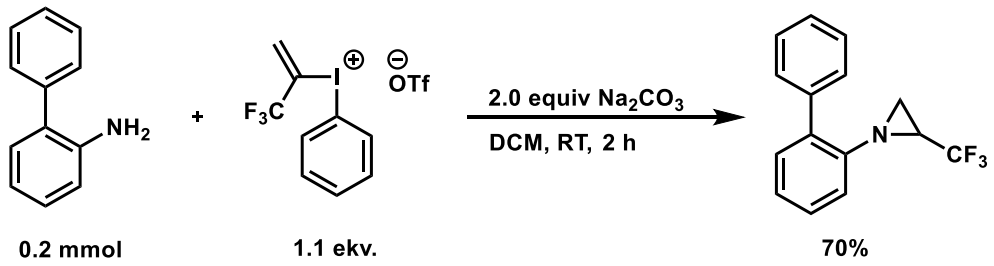
Scheme 7. Oxidation to the adequate bis(trifluoroacetate)

In the second step (Scheme 8), using mesitylene the reaction gave no trace of product, but using benzene as aryl source, we were able to isolate the desired iodonium salt in 80% yield. The structure of iodonium salt was verified by NMR.



Scheme 8. Synthesis of 2,2,2-trifluoropropenyl-phenyl-iodonium-triflate

- Considering the preliminary experiments, 2-aminobiphenyl gave the desired product in dichloromethane at room temperature, in presence of 2 equivalents of Na_2CO_3.

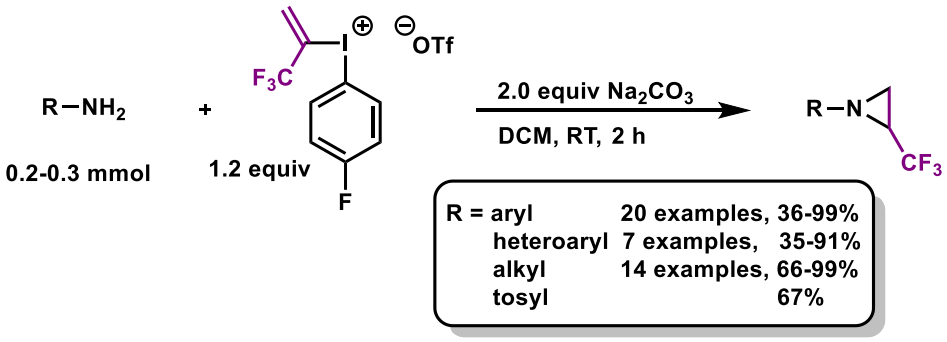


Scheme 9. First isolable scale aziridination

- We found the aryl group of iodonium salt has a significant impact on the stability and reactivity of iodonium salt. During these experiments, we were able to isolate the phenyl, 4-fluorophenyl, 4-chlorophenyl and 4-bromophenyl derivatives. Amongst them, the *p*-fluorophenyl derivative was outstanding in both of the chosen parameters.
- We optimized the reaction conditions for aziridination, and found the dichloromethane (DCM) the best solvent, and utility of 2 equivalents of Na_2CO_3 provided the highest

yield. The necessary amount of iodonium salt was also investigated, and we found no improving in yield above 1.2 equivalent of the used iodonium reagent.

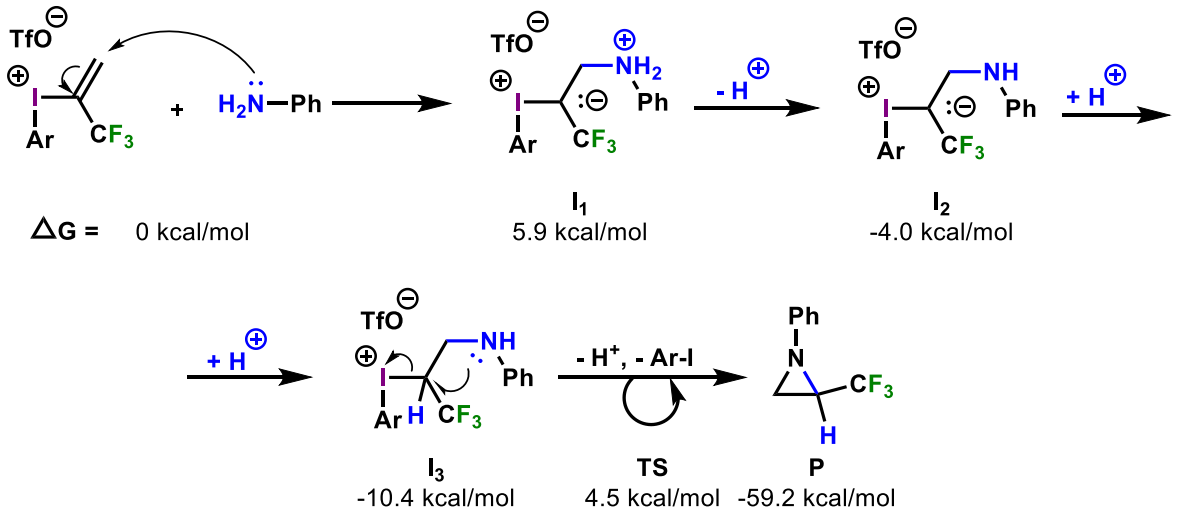
- With the optimized condotions in our hand, we investigated the scope and limitations of aziridination. We determined that anilines, aliphatic amines regardless of the order of the carbon core the amino group is attached to, are suitable starting materials to aziridination, and gave the desired trifluoromethylated aziridines in good yields.



Scheme 10. General equation for aziridination

These synthesized trifluoromethyl aziridines are promising starting materials for industry. Our results were highlighted in Organic Research and Development, where procedures valuable for both academic and industrial research are presented.

- We proposed a reaction mechanism, supported by quantum chemical calculations and deuteration experiments. (Scheme 11)



Scheme 11. Our proposed mechanism

According to our proposed mechanism, the hydrogen at position 2 on aziridine ring comes from the amino group. To support our mechanism, we used aniline-d_7 (98% D). According to the NMR, the incorporation of deuterium to that position was 76%.

The radical pathway was disproved by the 98% conversion in presence of 3 equivalents TEMPO to our model reaction. This way, under the original conditions the conversion was 98% after 2 hours.

Publications related to the dissertation

1) „Catalytic Activation of Trimethylsilylacetylenes: A One-Pot Route to Unsymmetrical Acetylenes and Heterocycles" Lasányi, D.; Mészáros, Á.; Novák, Z.; Tolnai, G. L. *J. Org. Chem.* **2018**, *83* (15), 8281-8291.; DOI: 10.1021/acs.joc.8b00998
2) „Design of Trifluoroalkenyl Iodonium Salts for a Hypervalency-Aided Alkenylation–Cyclization Strategy: Metal-Free Construction of Aziridine Rings" Mészáros, Á.; Székely, A.; Stirling, A; Novák, Z. *Angew. Chem. Int. Ed.* **2018**, *57* (22), 6643-6647.; DOI: 10.1002/anie.201802347
3) „Hexafluorosilicic Acid as a Novel Reagent for the Desilylation of Silylacetylenes: Application in Sequential Sonogashira Coupling and Click Reaction" Sinai, Á.; Mészáros, Á.; Balogh, Á.; Zwillinger, M.; Novák, Z. *Synthesis* **2017**, *49* (11), 2374-2388.; DOI: 10.1055/s-0036-1588981

Other publications

1) „Copper-Catalyzed N-Arylation of Nitroenamines with Diaryliodonium Salts" Aradi, K.; Mészáros, Á.; Tóth, B. L.; Vincze, Z.; Novák, Z. *J. Org. Chem.* **2017**, *82* (22), 11752-11764.; DOI: 10.1021/acs.joc.7b01591
2) „Computational Prediction and Rationalization, and Experimental Validation of Handedness Induction in Helical Aromatic Oligoamide Foldamers" Liu, Z.; Abramyan, A. M.; Mészáros, Á.; Csékei, M.; Kotschy, A.; Huc, I.; Pophristic, V. *Chem. Eur. J.* **2016**, *23* (15), 3605-3615.; DOI: 10.1002/chem.201605082
3) „Controlling Helix Handedness in Water-Soluble Quinoline Oligoamide Foldamers" Dawson, S. J.; Mészáros, Á.; Pethő, L.; Colombo, C.; Csékei, M.; Kotschy, A.; Huc, I. *Eur. J. Org. Chem.* **2014**, *2014* (20), 4265-4275.; DOI: 10.1002/ejoc.201402247
4) „Copper-Catalyzed Oxidative Ring Closure and Carboarylation of 2-Ethynylanilides" Sinai, Á.; Mészáros, Á.; Gáti, T.; Kudar, V.; Palló, A; Novák, Z. *Org. Lett.* **2013**, *15* (22), 5654-5657.; DOI: 10.1021/ol402600r

Oral presentations

1) „Hypervalency aided route to 3,3,3-trifluoropropenylated heterocycles, 1,2-diamines and *N*-aryl-2-(trifluoromethyl)aziridines" Mészáros, Á.; Székely, A.; Tóth, Á.; Csenki, J. T.; Stirling, A.; Novák, Z. *257th ACS National Meeting & Exposition*, **2019**, Orlando, Florida, USA
2) „Hipervalens alkenil-jódvegyületek fejlesztése és felhasználása fluorozott aziridinek szintézisében" Mészáros, Á.; Székely, A.; Stirling, A.; Novák, Z. *MTA Heterociklusos és Elemorganikus Kémiai Munkabizottsági ülés*, **2018**, Balatonszemes, Magyarország

Poster presentations

1) „Hypervalency aided route to 3,3,3-trifluoropropenylated heterocycles” Mészáros, Á.; Csenki, J. T.; Stirling, A.; Gonda, Z.; Novák, Z. *Markovnikov Congress on Organic Chemistry*, **2019**, Kazan, Russia
2) „Hypervalency aided alkenylation-cyclization: simple and efficient construction of aziridine ring” Mészáros, Á.; Székely, A.; Stirling, A.; Novák, Z. *16th Belgian Organic Synthesis Symposium*, **2018**, Brussels, Belgium
3) „Hypervalency aided alkenylation-cyclization: simple and efficient construction of aziridine ring” Mészáros, Á.; Székely, A.; Stirling, A.; Novák, Z. *6th International Conference on Hypervalent Iodine Chemistry*, **2018**, Cardiff, Wales
4) „Új deszililező ágens használata szekvenciális Sonogashira-kapcsolásban és heterociklusok szintézisében” Mészáros, Á.; Sinai, Á.; Zwillinger, M.; Balogh, Á.; Novák, Z. *Vegyészkonferencia*, **2017**, Hajdúszoboszló, Magyaroroszág
5) „Simple and efficient transition metal free synthesis of 2-(trifluoromethyl)aziridines from primary amines” Mészáros, Á.; Székely, A.; Stirling, A.; Novák, Z. *18th Tetrahedron Symposium*, **2017**, Budapest, Hungary
6) „Synthesis of new benzoxazine derivatives via copper-catalyzed oxidative cyclization utilizing aryethynyl-pivalanilides and diaryliodonium salts” Mészáros, Á.; Sinai, Á.; Gáti, T.; Kudar, V.; Palló, A.; Novák, Z. *20th International Conference on Organic Synthesis*, **2014**, Budapest, Hungary