Final report

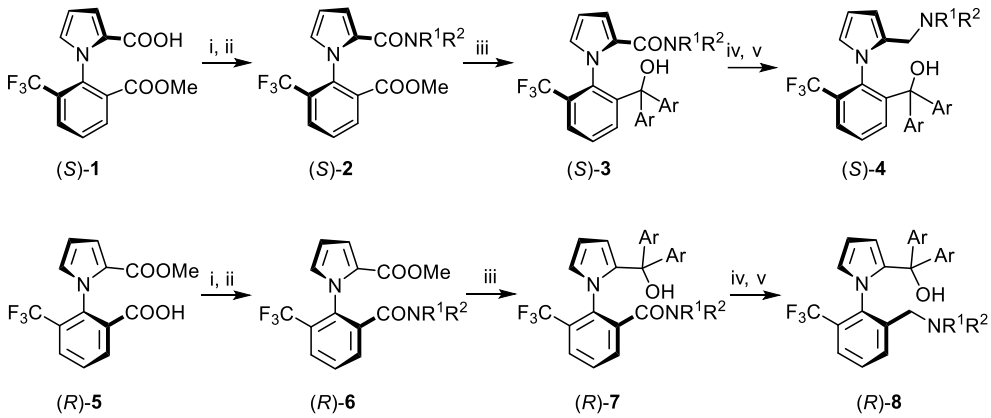
NKFIH – PD129652

Design and synthesis of new conjugated or atropisomeric hetero- and polycycles through organometallic methodologies

According to the workplan, we conducted our researches in the field of hetero- and polycyclic chemistry. The main aim of our project was the synthesis of novel 1-arylpyrrole based atropisomeric ligands and their investigation as asymmetric catalysts. Furthermore, the the development of new strategies for the syntesis of conjugated hetero- or polycycles was also aimed at.

1.1.) Synthesis of new atropisomeric ligands

First, a series of tertiary amino group containing optically active, atropisomeric 1-phenylpyrrole derivatives (**4** and **8**) were prepared successfully (Scheme 1) and applied in the asymmetric addition of diethyl zinc to benzaldehyde (Table 1).

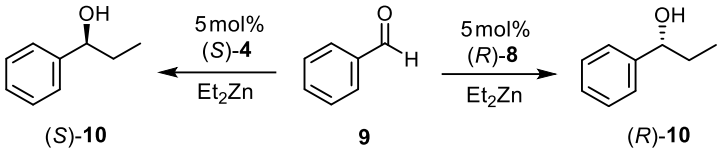


4 or **8**	NR^1R^2	Ar
a	NMe_2	Ph
b	NEt_2	Ph
c	NBu_2	Ph
d	pyrrolidino	Ph
e	NMe(*S*)-PE*	Ph
f	NMe(*R*)-PE*	Ph
g	NEt_2	3-$(CF_3)C_6H_4$
h	NEt_2	3,5-$(CF_3)_2C_6H_3$
i	NMe_2	3-$(CF_3)C_6H_4$
j	pyrrolidino	3-$(CF_3)C_6H_4$
k	morpholino	3-$(CF_3)C_6H_4$
l	NMe_2	3,5-$(CF_3)_2C_6H_3$
m	pyrrolidino	3,5-$(CF_3)_2C_6H_3$

Synthesis of (*S*)-**6a**-**h** and (*R*)-**7a**-**d**,**i**-**m**. (i: $SOCl_2$, toluene; ii: HNR^1R^2; iii: ArMgBr, DEE; iv: $BH_3.SMe_2$, toluene; v: NaOH, MeOH. *NMe(*S*/*R*)-PE: N-methyl-(*S* or *R*)-phenylethyl)

Scheme 1.

In some cases, the new ligands showed excellent catalytic activities in terms of enantioselectivity and yields. Quantum chemical calculations were also carried, which are in good accordance with our experimental results. The systematic comparative study of regioisomeric atropisomeric ligands confirmed that such isomerism may cause significant differences in the efficiency of the regioisomeric catalyst ligands. All together 13 new 1-arylpyrrole based amino alcohol ligands were synthesized and tested obtaining excellent asymmetric inductions (*ee* up to 96%). [1]



Entry[a]	Ligand (*S*)-**4**	(*S*)-**10** *ee*[b,c] (%)	Ligand (*R*)-**8**	(*R*)-**10** *ee*[b,d] (%)
1	**4a**	86	**8a**	82
2	**4b**	96	**8b**	9
3	**4c**	92	**8c**	2
4	**4d**	94	**8d**	70
5	**4e**	92	-	-
6	**4f**	26	-	-
7	**4g**	90	-	-
8	**4h**	87	-	-
9	-	-	**8i**	90
10	-	-	**8j**	86
11	-	-	**8k**	18
12	-	-	**8l**	94
13	-	-	**8m**	91

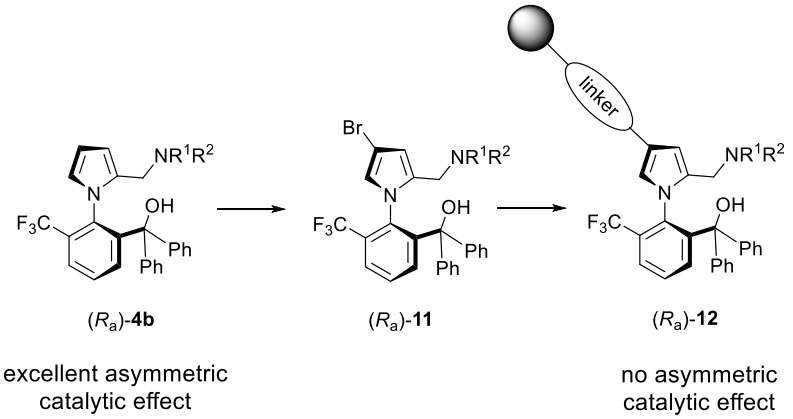
[a] The reactions were carried out with a 1 M solution of Et_2Zn in hexane (3 equiv).
[b] Determined by GC with a β-DEX™ 120 capillary column.
[c] Reactions carried out at 0 °C.
[d] Reactions carried out at 24 °C.

Table 1.

1.2.) Investigation of the preparation of polymer supported atropisomeric ligand

The most effective diethylamino-functionalized ligand was bounded to polymer. The individual ligand was brominated at the 4-position of the pyrrole ring, then following efficient Suzuki coupling with 4-vinylphenylboronic acid resulted our precursor for copolymerisation with styrene. However, the resulted chiral polymer catalysed the model reaction, it lost its asymmetric catalytic effect completely. Besides, the individual ligand of diethylamino derivative **4b** was thoroughly examined in the enantioselective addition of diethyl zinc and prochiral aldehydes and it showed a superior asymmetric and catalytic activity compared to

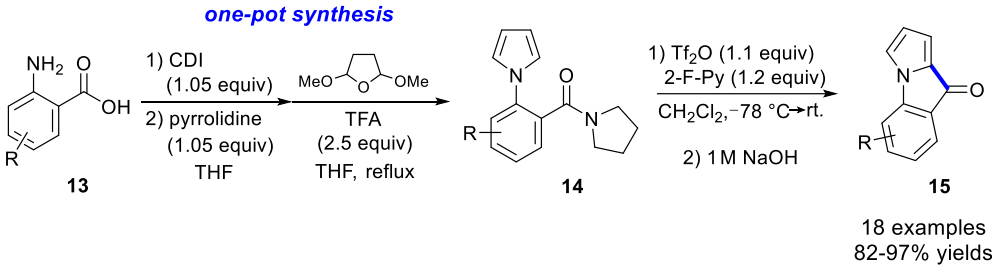
other 1-arylpyrrole based atropisomeric ligands described previously. Using this **4b** compound only 1 mol% of ligand is enough to achieve up to 98% *ee* in the presence of 1.1 equiv of diethyl zinc in the transformation of benzaldehyde into 1-phenylpropan-1-ol at 10°C.



Scheme 2.

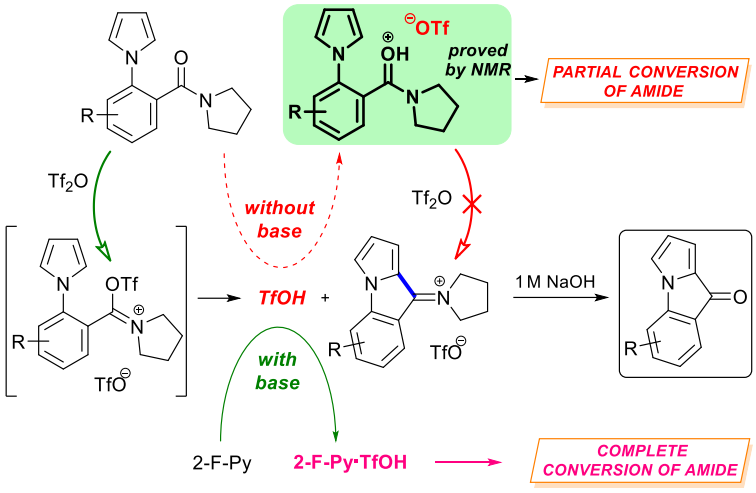
1.3.) Synthesis of arylpyrrole based fused heterocycles

The synthesis of fluorazones (9*H*-pyrrolo-[1,2-*a*]indol-9-ones, **15**) were studied to find a rapid and general access to these tricyclics from simple, easily accessible starting materials (Scheme 3.). A convenient two-step method was elaborated for the synthesis of these valuable tricycles from anthanilic acids. [2]



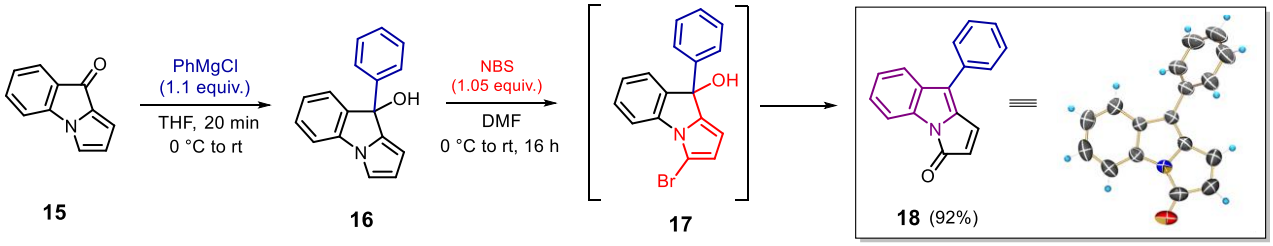
Scheme 3.

The key transformation for cyclization is a triflic-anhydride-triggered amide activation. However, the mechanism of this emerging approach for the construction of new C-C bonds was continuously studied in the last year, the specific role of the applied base additive was still uncleared. By a new mechanistic approach, it was proven via NMR experiment that the TfOH byproduct formed during the amide activation is able to protonate the unreacted part of the starting material amide, thus preventing it for further activation (Scheme 4). This mechanistic finding contributes to the completion of the mechanism of Tf_2O-triggered amide activations. [2]



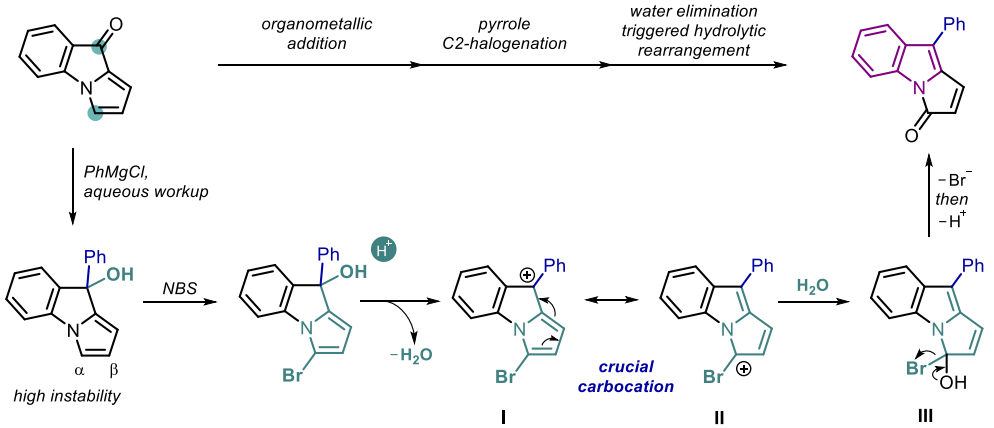
Scheme 4.

For the oxidative ring transformation of pyrroles an efficient method has been developed to synthetize fused indoles (9-substituted 3*H*-pyrrolo[1,2-*a*]indole-3-ones) on a novel way. In this way, a series of fluorazones were converted into aryl-substituted pyrrolo-indolones. [3] Extending the scope of the substrates, heteroaryl lithium species were also applied to obtain heteroaryl functionalized indoles (Scheme 5.).



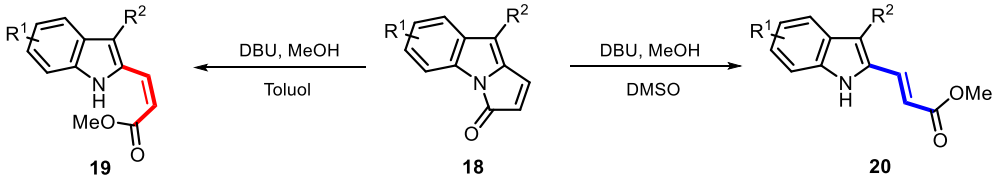
Scheme 5. *Ph group could be other aryl or herteroaryl moiety*

The mechanism of the bromination triggered oxidative ring transformation was studied in detail. It was found that the evaluation of a 2-bromo-5-hydroxymethyl species is necessary to achieve the desired reaction (Scheme 6.). Moreover, in case of N-heteroaryl derivatives an additional acid catalyst (Amberlyst-15) is necessary to achieve rearrangement.



Scheme 6.

As a continuation of the oxidative ring transformation of fused 1-arylpyrroles the ring opening reaction of pyrrolo-indolones synthetized were studied in order to obtain indole-2-acrylates (**19** or **20**). Methods have been exist for the synthesis of both the *cis* and *trans* indole-2-acrylates, respectively, however a general and stereodivergent strategy has not been described. We have studied the ring opening reaction of these N-acylindole derivatives in the presence of different bases and various solvents. We have found, that in the presence of methanol DBU has a superior effect over other commercial tertiary amine type bases. (using secondary amine the product would be a ring opened amide). Moreover, DBU is able to affect isomerization of the geometry of the double bond to afford the trans acrylate. The polarity of the solvent determines the accessible product. In less polar solvent such as DKM or toluene only the alcoholysis can occur to afford *cis* acrylates. In addition, using highly polar solvent such as DMSO a smooth isomerization could be observed, and in a feasible way trans acrylates can be easily obtain. These novel stereodivergent strategy rely on the fact that DBU can act as not only a base, but a catalyst via an N-acyl intermediate of DBU which can easily react with methanol to afford the methyl ester. Moreover, the application of a highly polar solvent can facilitate isomerization, which probably goes through ionic type transition states. The method elaborated can be applied for a wide range of pyrrolo-indolones affording *cis* (**19**) or *trans* (**20**) indol-2-acrylates selectively (Scheme 7).

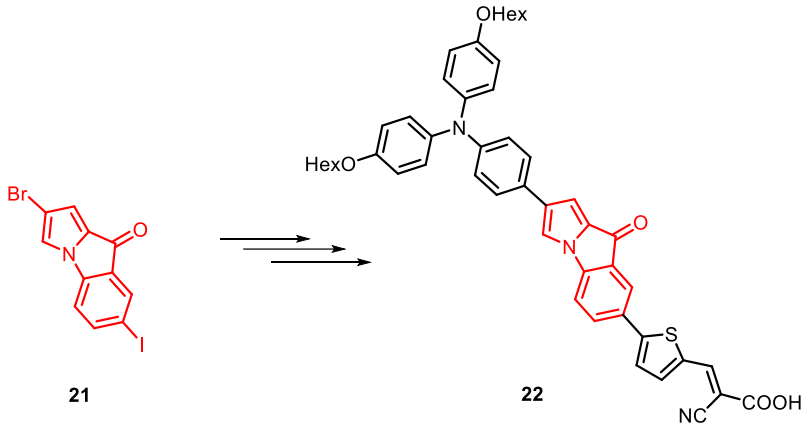


Scheme 7.

1.4.) Synthesis of new 1-phenylpyrrole based dyes

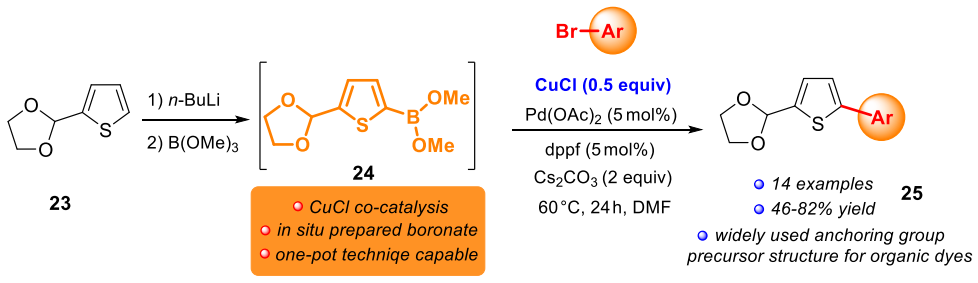
In this part of the project, a 1-arylpyrrole skeleton containing sensitizer for D-π-A type photovoltaic cells has been prepared on the basis of quantum chemical calculations. Extension of the conjugated system was carried out by means of Suzuki-Miyaura cross-coupling reactions of a 2,7-dihalofluorazon derivative. The designed sensitizer contained a single tiophene moiety between the novel fluorazone linker and the acceptor unit. In addition, the new dye has been tested in cooperation with an italian research group. The dye displayed intense absorption of visible light in dichloromethane solution. Moreover, its spectrum on nanocrystalline TiO_2 was much broader than that in solution, which was promising in view of the utilization of the dye as DSSC (dye-sensitized solar cell) sensitizer. In agreement with DFT computational analysis, cyclic voltammetry measurements, combined with the optical band-gap obtained from the UV-

Vis spectroscopy experiments, suggested that the compound had energy levels correctly aligned to be used in photovoltaic cell. Small-scale photovoltaic devices fabricated with the fluorazone dyes displayed moderate 2.1% power efficiency, which is promising for further structure optimization. [4]



Scheme 8.

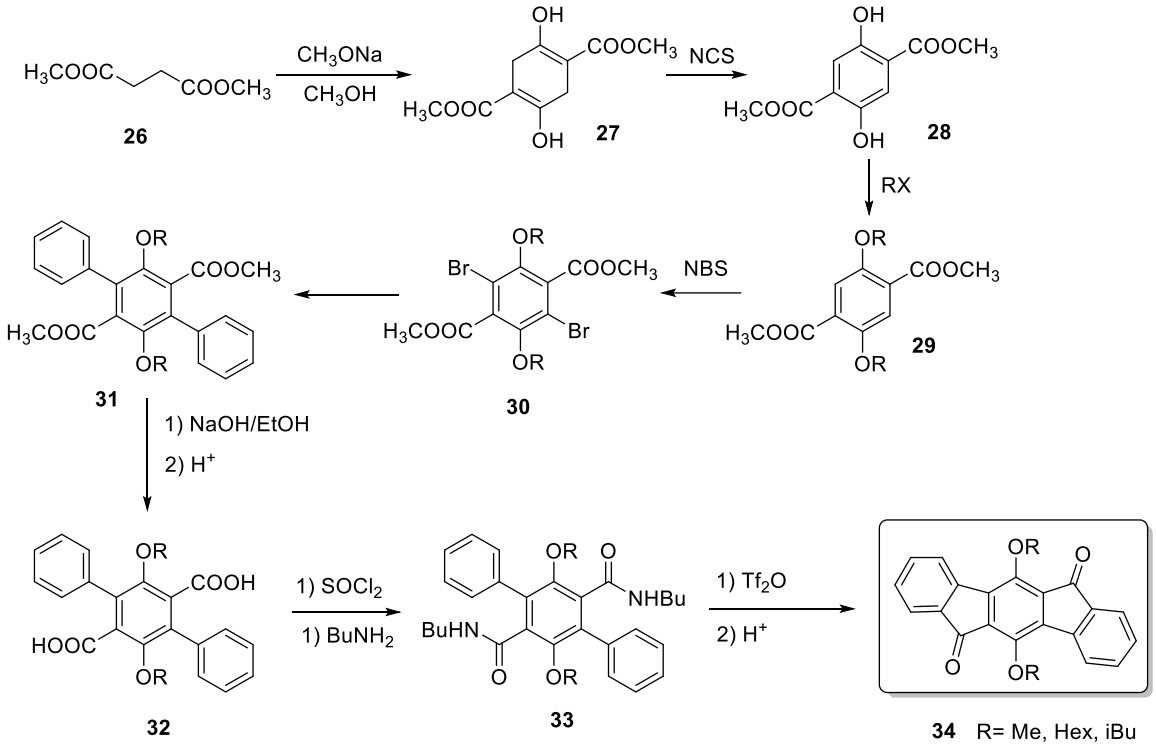
During the work directed towards the synthesis of metal-free organic dyes based on a fluorazone backbone, we have faced with those difficulties, that commonly occur during the construction of such extensively conjugated structures by Suzuki-Miyaura couplings: low stability of thiophne derived coupling parners, homocoupling and protodeborylation side reaction. Therefore the general synthtic conditions provide low yields, being affected by these problems. As a resolution, a successfully developement of a mild one-pot technique involving an in situ borylation and a copper-facilitated Suzuki-Miyaura cross-coupling reaction for the preparation of 1,3-dioxolane-protected 5-arylthiophene-2-carboxaldehydes was carried out. By means of this process the crucial acidic hydrolytic step to prepare 5-formyl-2-thiopheneboronic can be avoided, which significantly decrease the overall efficiencies of the corresponding cross-coupling reactions, in general. In addition, the versatile usefulness of the elaborated method was also shown on the improved synthesis of our fluorazon based metal-free organic dye. [5]



Scheme 9.

1.5.) Preparation of novel multiconjugated heterocyclic compounds

Finally, we have been successfully synthetized the first members of a novel family of indeno[1,2-*b*]fluorene-6,12-dione derivatives, namely the 5,11-alkoxy substituted compounds (Scheme 10). This highly electron rich pentacyclic system could not be synthetized using the known cyclization methods, due to its low stability against strong acids, such as concentrated sulfuric acid. The key of our unique approach for cyclization is a triflic-anhydride-triggered amide activation (**33** into **34**), which could open a novel way to electron rich derivatives. Determination of optical spectroscopic properties of the dimethoxy-substituted conjugated polycycle is currently under investigation in cooperation.



Scheme 10.

References

1. **Mátravölgyi, B.**; Deák, Sz.; Erdélyi, Zs.; Hergert, T.; Ábrányi-Balogh, P.; Faigl, F.: Effect of regioisomerism on the efficiency of 1-phenylpyrrole type atropisomeric amino alcohol ligands in enantioselective organometallic reactions, *Synlett*, **2018**, *29*, 2171-2175. [IF: 2,418]
2. **Mátravölgyi, B.**; Hergert, T.; Bálint, E.; Bagi, P.; Faigl, F.: Access to Fluorazones by Intramolecular Dehydrative Cyclization of Aromatic Tertiary Amides: A Synthetic and Mechanistic Study, *J. Org. Chem.*, **2018**, *83*, 2282–2292. [IF: 4,805]
3. Hergert, T, Faigl, F, **Mátravölgyi, B**: Új indolszintézis antranilsavból: indol-2-akrilészterek sztereospecifikus előállítása, MKE Vegyészkonferencia 2017; Program és előadásösszefoglalók, **2017** [IF:-]
4. **Mátravölgyi, B.**; Hergert, T.; Thurner, A.; Varga, B.; Sangiorgi, N.; Bendoni, R.; Zani, L.; Reginato, G.; Calamante, M.; Sinicropi, A.; Sanson, A.; Faigl, F.; Mordini, A.: Synthesis and Investigation of New Solar Cell Photosensitizers Having a Fluorazone Backbone, *Eur. J. Org. Chem.*, **2017**, *14*, 1843–1854. [IF: 2,882]
5. Hergert, T.; Bálint, V.; Thurner, A.; Faigl, F.; **Mátravölgyi; B.**: Copper-facilitated Suzuki-Miyaura coupling for the preparation of 1,3-dioxolane-protected 5-arylthiophene-2-carboxaldehydes, *Tetrahedron*, **2018**, *74*, 2002–2008. [IF: 2,379]

Submitted manuscript:

1. Hergert, T.; Posta, T.; Faigl, F.; Perdih, F.; **Mátravölgyi, B.**: Transition-Metal-Free Access to Pyrroloindolons via Oxidative Rearrangement of Fused Pyrroles, *manuscript submitted*

List of presentations:

1. Hergert, T.; Faigl, F.; **Mátravölgyi, B.**: Új indolszintézis antranilsavból: indol-2-akrilészterek sztereospecifikus előállítása. MKE Vegyészkonferencia 2017, Hajdúszoboszló, 2017. június 19 – 21. (poster presentation)
2. **Mátravölgyi, B.**: Indol szintézis fluorazonok gyűrűtranszformációjával: 2-indolakrilátok sztereoszelektív előállítása. Bruckner termi előadás, ELTE TTK Kémia épület (Bruckner terem), 2018. március 23. (invited oral presentation)
3. **Mátravölgyi, B.;** Hergert, T.; Faigl, F.: Redox-Neutral Ring Transformation of Fluorazones: A Stereoflexible Access to 2-Alkenylated Indoles *at the* 28th European Colloquium on Heterocyclic Chemistry, Lecce, September 2-5, 2018 (oral presentation)
4. **Mátravölgyi, B.**; Hergert, T.; Posta, T.; Faigl, F.; Perdich, F.: Ring Transformation of (Hydroxymethyl)Pyrroles: A Tool to Access Conjugated N-Heterocycles, 18th Blue Danube Symposium on Heterocyclic Chemistry, Ljubljana, Szlovénia, 2019. szeptember 18 – 21. (poster prezentation)
5. Hergert, T.; Posta, T.; Faigl, F.; **Mátravölgyi, B.**: A Stereoflexible Access to 2-Alkenylated Indoles, 21st European Symposium on Organic Chemistry, Wien, Austria 2019. július 14 – 18. (poster presentation)
6. **Mátravölgyi, B.;** Posta, T.; Faigl, F., Hergert, T.: Pyrroloindolones as a Versatile Buildig Block: A Synthetic Study and Application, 4th EuCheMS Conference on Green and Sustainable Chemistry, Tarragona, Spain, 2019. szeptember 21 – 28. (poster prsentation)