Report on the new scientific results achieved
in the 01 November 2012- 31 October 2017 period

At the beginning of the project, aim of our research work was summarised as follows:

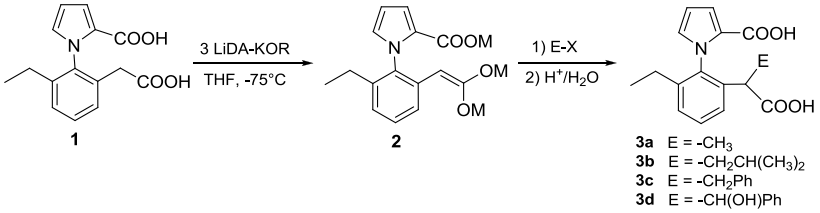
- we supposed that the atropisomeric 1-phenylpyrrole derivatives can be used as efficient enantioselective organocataysts and/or optically active ligands in transition metal containing cataysts;
- the superbase induced rearrangement reaction of the corresponding benzylamino group containing oxiranes could provide 1,2,3-trisubstituted azetidines in high stereoselectivity;
- reductive catalytic ring opening and deprotection reaction of the optically active 1,2,3-trisubstituted azetidines should yield 4-aminoalkan-1-ols which could be transformed into optically active 2,3-disubstituted pyrrolidines by a simple ring closure reaction.
- the optically active azetidines and pyrrolidines could be used as organocatalysts and/or valuable intermediates of active pharmaceutical ingredients.

The new scientific results we have achieved in the above mentioned research fields are summarized below in four main sections as follows:

1. Stereoselective synthesis and applications of new atropisomeric 1-phenylpyrrole derivatives

1.1. Diastereoselective metalation –alkylation reactions of 1-(substituted phenyl)pyrrole derivatives

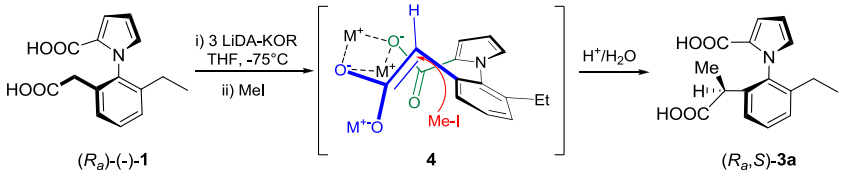
Axial chirality determined, highly diastereoselective metalation - alkylation reaction sequence of a new, atropisomeric dicarboxylic acid derivative (**1**) of 1-phenylpyrrole was invented. Compound **1** reacted with of potassium *tert*-butoxide activated lithium diisopropylamide (LiDA-KOR) superbase in tetrahydrofuran (Scheme 1). Clean benzylic metalation occurred under these conditions and the organometallic intermediate (**2**) readily reacted with different electrophiles (iodomethane, isobutyl bromide, benzyl bromide and benzaldehyde).



Scheme 1. Diastereoselective metalation - alkylation reaction sequence of **1**

Beside the axial chirality, the product (**3a-d**) contains a new asymmetric carbon atom in benzylic position and the configuration of that new chiral carbon atom was completely determined by the axial chirality element of the starting material (confirmed by spectroscopic evidences). In order to prove this supposition, the methylation reaction was repeated with optically active ((*R*)-(-)-**1**) starting material, resulting in a single enantiomer as the only product. Single crystal X-ray diffraction measurements were also carried out

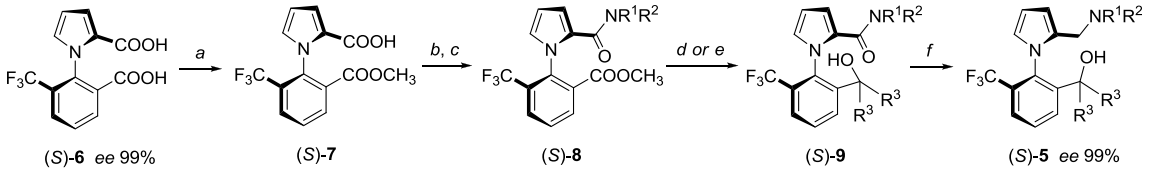
to determine the absolute configuration of the new asymmetric carbon atom in **3a**. The high stereoselectivity of the reaction could be explained by the supposed structure of the intermediate enolate: structure of **4** is stabilized by the Coulomb interactions among the two alkali cations and the negatively charged oxygen atoms of the two carboxylate groups, respectively. This way the axial chirality of **4** strictly determines the configuration of the new asymmetric center because the methyl group could only join to the benzylic carbon atom from the *Si* face of the organometallic intermediate. (Scheme 2). Similar reactions of the diester and/or diamide derivatives yielded diastereoisomeric mixtures of the desired products.



Scheme 2. Synthesis of (R_a,*S*)-(+)-**3a** (possible diisopropyl amine and THF ligands of the metal cations (M^+) are not depicted in **4** for clarity)

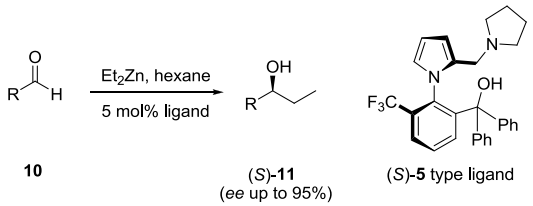
1.2 Synthesis of new aminoalcohol type atropisomeric ligands containing 1-phenylpyrrole skeleton

On the basis of our previous experience, two series of tertiary amino group containing aminoalcohol type ligands were designed. In the first series, the *tert*-aminomethyl group was connected to the C2 position of the pyrrole ring and the hydroxyl group was sticked to the benzylic carbon atom of the side chain of the phenyl ring in the atropisomeric 1-phenylpyrrole skeleton ((*S*)-**5** in Scheme 3).



Scheme 3. Synthesis of (*S*)-**5**. a) $SOCl_2$, MeOH 80%, b) $SOCl_2$, toluene, 80 °C, 2 h, c) amine, toluene, 0 °C, 92–98%, d) PhMgCl, Et_2O, 0 °C → r.t., 93–97%, e) $NaBH_4$, 10% EtOH/THF, 25 °C, 48h, 92–96%, f) $BH_3 \cdot SMe_2$, toluene, 60-80 °C, 24 h; MeOH, NaOH, 50 °C, 24h, 65–82%, R^1 = H, Et, 2-Pr, R^2 = H, Et, 2-Pr, Bn, (*R*)-1-phenylethyl, or R^1+R^2 = -$(CH_2)_4$)-, R^3 = H, Ph.

The new ligands were tested in enantioselective addition of diethylzinc to benzaldehyde. The best results were achieved with the pyrrolidine-derived compound ((*S*)-**5** type ligand; (S_a)-1-[2-diphenylhydroxymethyl-6-(trifluoromethyl)phenyl]-2-(1-pyrrolido)methyl-1*H*-pyrrole) therfore it was applied in the enantioselective addition of diethylzinc to series of prochiral aldehydes (Scheme 4).



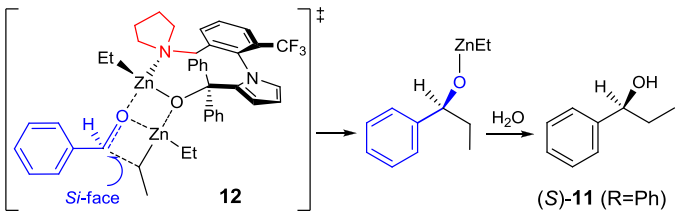
Scheme 4. Enantioselective addition of diethylzinc to aldehydes in the presence of (*S*)-**5** type ligand

Table 1. Results of the enantioselective addition of diethylzinc to aldehydes in the presence of (*S*)-**5** type ligand

R	Yield[a] (%)	*Ee*[b] (%)	Config.[c]
Ph	92	93	(*S*)
2−MeC_6H_4	93	94	(*S*)
3−MeC_6H_4	94	93	(*S*)
4−MeC_6H_4	96	92	(*S*)
2−$MeOC_6H_4$	93	93	(*S*)
3−$MeOC_6H_4$	92	93	(*S*)
4−$MeOC_6H_4$	88	92	(*S*)
3−BnO−4−$MeOC_6H_3$	94	95[d]	(*S*)[e]
2−BrC_6H_4	91	88	(*S*)
2−ClC_6H_4	92	90	(*S*)
2−FC_6H_4	90	93	(*S*)
3−FC_6H_4	95	92	(*S*)
4−FC_6H_4	91	93	(*S*)
1−Naphth	93	90	(*S*)
2−Naphth	92	90	(*S*)
Ph−CH=CH	91	63[d]	(*S*)

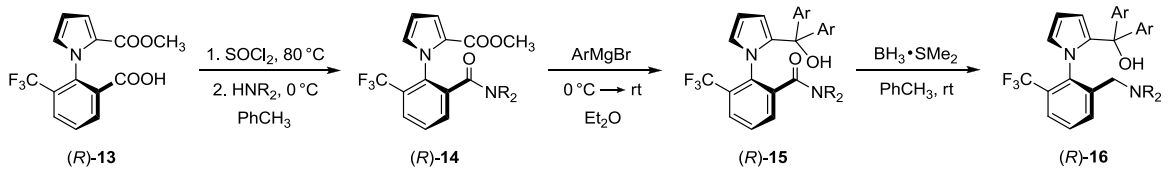
[a] Isolated yields.
[b] Determined by GC analysis using a Supelco b-DEX 120 chiral capillary column.
[c] Absolute configurations of the alcohols were assigned by comparison of the direction of optical rotation of the samples with literature data.24–34
[d] Determined by HPLC analysis using a Phenomonex Lux Cellulose-1 chiral column. The reaction was carried out in toluene.
[e] Absolute configuration of the alcohol was assumed based on the stereochemistry of the reaction.

The conversion rates were close to quantitative in each cases and good to excellent enantiomeric excesses (up to 95% ee) could be achieved (Table 1). The great success due to the five-membered ring skeleton which presents a certain degree of rigidity was explained with the fact that this chiral system could provide a transition state having a well-defined chiral environment (**12**, Scheme 5). Consequently, a more efficient control is attained in the enantioselective transformations.



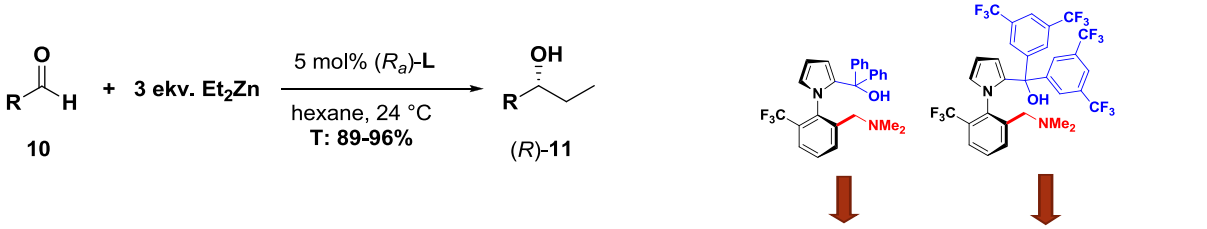
Scheme 5. Visualisation of a plausible transition complex **12** in the formation of (*S*)-**11** (R=Ph).

In order to compare the effect of the regioisomerism in chiral ligands, another series of aminoalcohol type atropisomeric 1-phenylpyrrole derivatives were synthesized ((*R*$_a$)-**16** type products, Scheme 6). In these compounds the functions were exchanged: the *tert*-aminomethyl group was sticked to the phenyl ring while the diarylhydroxymethyl group was placed to the α position of the pyrrole moiety.



Scheme 6. Synthesis of (*R*)-**16** type ligands. R=Me, Et, *n*Bu, or NR_2= yrrolidinyl, Ar=Ph, 3-CF_3Ph, 3,5-$(CF_3)_2$Ph

Results of the test reactions with benzaldehyde and diethylzinc showed the excellent activities and selectivities of the *N*,*N*-dimethyl and the pyrrolydinyl group containing ligands, but the best results were achieved with the *N*,*N*-dimethyl group containing compound when the aryl groups of the hydroxymethyl moiety contained two-two trifluoromethyl groups (Scheme 7).



Product (*R*$_a$)-**11**, R:	*ee** (%)	*ee** (5)
Ph	82	94
2-Me-Ph	85	83
3-Me-Ph	69	92
4-Me-Ph	45	94
2-MeO-Ph	10	77
3-MeO-Ph	65	93
4-MeO-Ph	72	90
2-F-Ph	78	94
2-Cl-Ph	80	93
2-Br-Ph	83	94
3-F-Ph	-	94
4-F-Ph	-	96
4-Cl-Ph	-	95
1-Naft	-	93
2-Naft	-	93
Ph-CH=CH	-	58**
3-BnO-4-MeO-Ph	-	93**

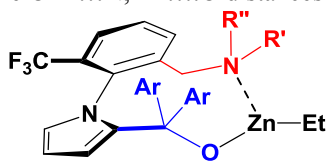
* determined by chiral GC
** determined by chiral HPLC

Scheme 7. Enantioselective addition of diethylzinc to aldehydes in the presence of (*R*)-**16** type ligands

In order to shed light the detailds of these reactions the pK_a values of the OH and the *tert*-amino groups in the ligands were calculated. In the same time quantumchemical calculations were carried out and the energy values of the intermediates and supposed transition states were compared in the cases of the

differen ligands. It turned out, that there is an optimum pK_a value of the OH groups which influences the O…Zn and the N…Zn distances in the active catalyst and these distances determine the energy differences between the two diastereoisomeric transition states. These findings were documented in a PhD thesis work, defended succesfully in 2017 by Mrs. Bodnár. The calculated energy values of several catalyst-complexes are collected in Table 2.

Table 2. The calculated energy levels and the OZn…N, Zn….O distances in the catalyst complexes

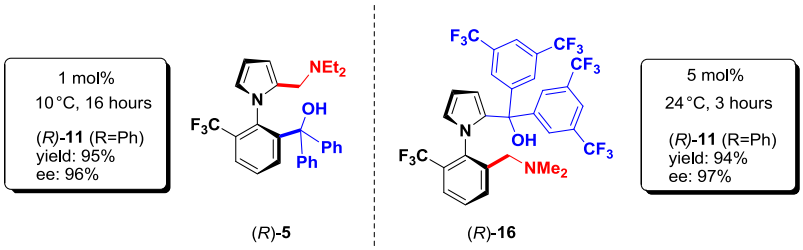


NR^1R^2 in (*R*)-**16**	**Ar**	***ee****	$\Delta G_{OZn...N}$ (kJ/mol)**	$l_{OZn...N}$ (Å)	$l_{Zn...O}$ (Å)
NBu_2	Ph	2%	14,3	2,428	1,849
NEt_2	Ph	9%	31,6	2,426	1,849
pirrolidine	Ph	70%	81,0	2,401	1,856
NMe_2	Ph	82%	55,2	2,399	1,852
NMe_2	3-CF_3-C_6H_4	88%	56,8	2,371	1,863
NMe_2	3,5-$(CF_3)_2$-C_6H_3	94%	66,8	2,338	1,869

* Enantiomeric excess measured in the reaction of benzaldehyde and diethyl zinc
** Gaussian 09: B3LYP-6-31g(d,p) for H, C, N, O, F atoms, B3LYP-SDD-MDF10 for Zn atom

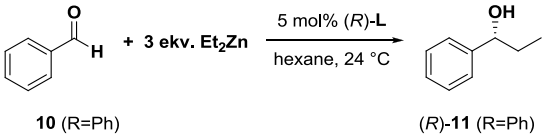
The calculated energy data of the OZn…N bond are in good correlation with the *ee* values measured in the test reactions. The strongest the OZn…N bond the highest the *ee* of the reactions within the series of the NMe_2 group cointaining catalysts. Electron withdrawing groups (eg CF_3) in the aromatic substituents of the hydroxymethyl moiety incerase the acidity of the OH group and decrease the energy of the O…Zn bond. Tha is why the Zn atom can move closer to the N atom. Electron donor character of the amino group depends on the N substituents at it seems to be optimal in the case of the dimethylamino group.

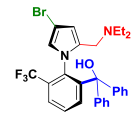
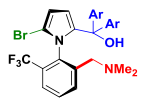
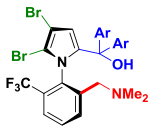
Comparison of the best ligands of the two regioisomeric series let us to conclude, that both compounds can be used as highly efficient catalyst ligands in enantioselective addition reactions of diethylzinc to numerous substituted aromatic aldehydes. The (*S*)-**5** type ligand was effective even in 1 mol% concentration at 0-10 ^oC (using optimum conditions) while the (*R*)-**16** type ligand can be used at ambient temperature but in 5 mol% concentration (Scheme 8). This latter mentioned ligand is less sensitive to the substituents of the aromatic aldehyde and it gave good results with cinnamaldehyde, too. Both enentiomers of the ligands can be synthesized using our methods. The (*S*)-**5** and (*S*)-**16** type ligands prefer the formation of the (*S*)-**11** type alcohols, the (*R*)-**5** and (*R*)-**16** type ligands provided the (*R*)-**11** type alcohols with good to excellent yields and ee values.



Scheme 8. Comparison of the efficiencies of the two regioisomeric catalyst ligands

Further modifications of the best ligands were carried out with the aim of insertion of such function into the molecules which would be suitable for immobilization of the lignads. Therefore mono- di- and tribrominated derivatives of of (*R*)-**5** and (*R*)-**16** were prepared and the catalytic activities of these compounds were also tested in the same organometallic reaction (Scheme 9). The results demonstrated that the monobrominated derivative of the (*R*)-**5** and the mono- and dibrominated derivatives of (R)-**16** are even more efficient than the original ligands.

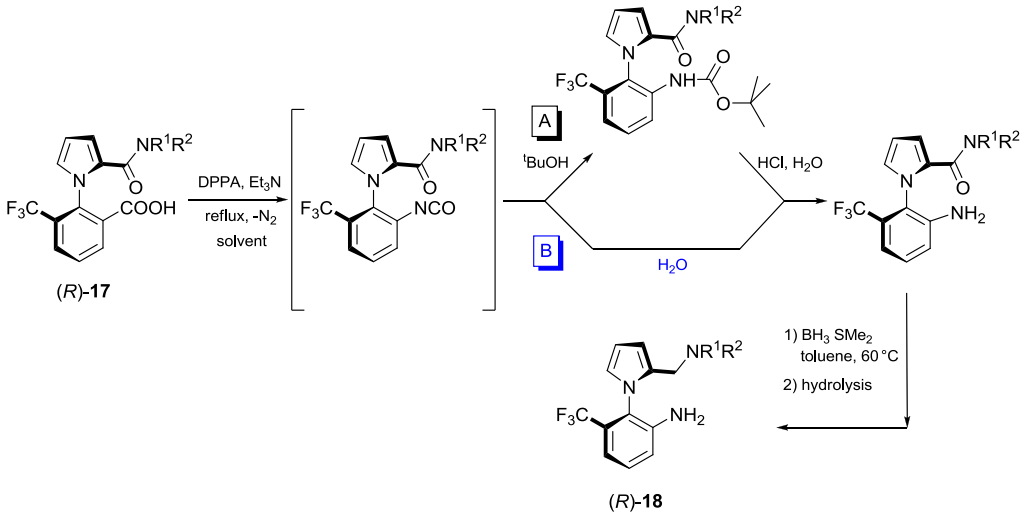


(R)-L	*ee**
	**97%**
	**97%**
	**97%**

Scheme 9. Results of test reactions accomplished with the brominated derivatives of the ligands

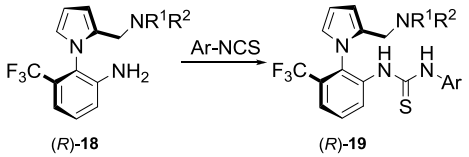
1.2 New bifunctional atropisomeric organocatalysts with 1-phenylpyrrole skeleton

An efficient, highly stereoconservative synthesis has been developed for preparation of aniline derived 1-arylpyrrole-2-carboxamide atropisomers using diphenylphosphoryl azide (DPPA). The classical azide synthesis, involving reaction with active acylating agents prepared from axially chiral benzoic acid derivatives, showed significant racemization coused by intramolecular tricyclic izoimidium salt formation. In order to avoid the ring closure reaction, the azid synthesis was carried out with DPPA on a stereoconservative way, and Curtius rearrangement followed by hydrolysis resulted in enantiopure products. The application of DPPA for a the novel racemization-free synthetic method of axially chiral anilines from atropisomeric benzoic acid derivatives was demonstrated by the preparation of secondary as well as tertiary amine functions containing 2-(2-substituted-1*H*-pyrrole-1-yl)aniline type diamines (**18**) starting from the corresponding optically active (*R*)-**17** benzoic acid derivative (Scheme 10).



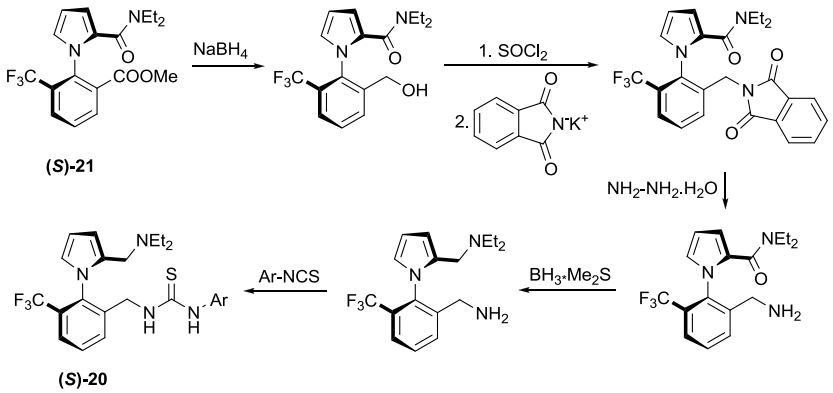
Scheme 10. Synthesis of atropisomeric diamines (*R*)-**17** (-NR^1R^2=-NMe_2, -NEt_2, -NBu_2, -$NHCH_2Ph$, pyrrolidine, -NH_2, (*S*)-N-(1-phenylethyl)-N-methylamino)

These optically active diamines were used for the preparation of amino and thiourea groups containing new organocatalysts ((*R*)-**19**, Scheme 11).



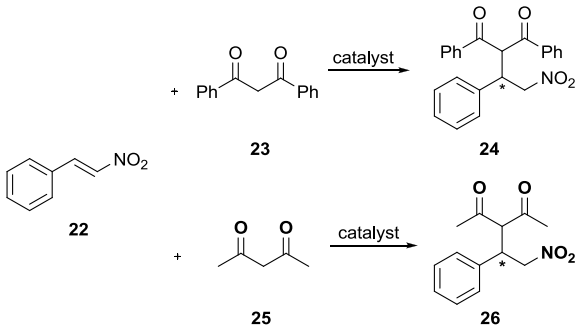
Scheme 11. Synthesis of (*R*)-**19** organocatalysts (-NR^1R^2=-NMe_2, -NEt_2, -NBu_2, -$NHCH_2Ph$, pyrrolidine, -NH_2, (*S*)-N-(1-phenylethyl)-N-methylamino)

Two more flexible atropisomeric organocatalysts ((*S*)-**20**) were also prepared on a stereoconservative route, starting from the optically active amide-ester type intermediate (*S*)-**21** (Scheme 12).



Scheme 12. Synthesis of organocatalysts (*S*)-**20** (Ar=3,5-bis(trifluoromethyl)phenyl, phenyl)

The new organocatalysts were tested in Michael addition reactions starting from nitrostyrene (**22**) and dibenzoyl- (**23**) or diacetylmethane (**25**) as it is depicted in Scheme 13. Experimental results of the test reactions served as proof of concept: compounds (*R*)-**19** and (*S*)-**20** can be treated as a new class of atropisomeric bifunctional organocatalysts. The more flexible (*S*)-**20** efficiently catalysed both investigated reactions, the products were formed in 95-97% yields. On the other hand, the more rigid (*R*)-**19** (NR_2= NEt_2, Ar= 3,5-di(trifluoromethyl)phenyl) performed slower reactions, but higher asymmetric induction effects (up to ee 54%).



Scheme 13. Test reactions with organocatalysts (*R*)-**19** and (*S*)-**20**

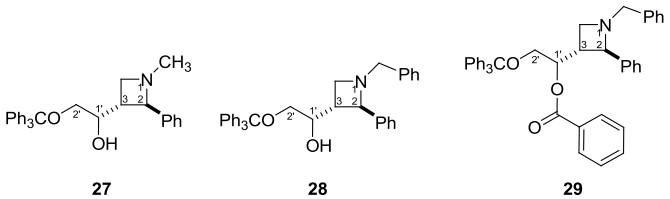
1.3. Synthesis and test reactions of phosphine amide containing atropisomeris 1-phenylpyrrole derivatives

Tertiary and primary amino groups containing optically active, atropisomeric 1-phenylpyrrole derivatives were also prepared successfully, then the primary amino groups were acylated with dinaphtylphosphinic acid chloride to prepare the designed new bifunctional ligands containing phosphine amide moieties. The new ligands were preliminarily tested in the asymmetric addition of diethyl zinc to benzaldehyde. The first results showed excellent catalytic activities, but in terms of enantioselectivities were low.

2. Investigation of the novel stereoselective synthesis and chemical transformations of azetidines and pyrrolidines.

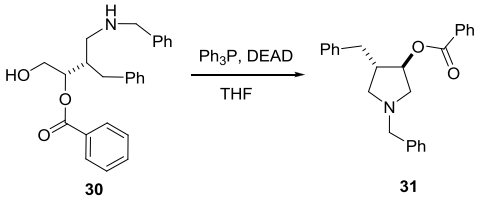
2.1. Hydrogenolysis of N- and O-protected hydroxyazetidines

Heterogeneous catalytic hydrogenolyses of several *N*- and *O*-protected hydroxyazetidine derivatives (**27**-**29**, Scheme 14), over palladium on carbon were investigated in detail. The corresponding amines, formed in hydrogenolytic ring opening and/or deprotecting reactions, are potential starting materials for preparing optically active, practically important pyrrolidine derivatives.



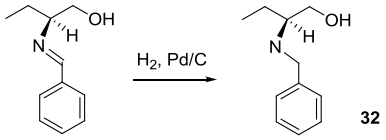
Scheme 14. Modell compounds of hydrogenolysis reactions

Detailed investigation of the effects of the solvents, the temperature, the pressure, amount of the catalyst (Pd/C) and the reaction time let us to find such conditions in which various amino compounds were formed selectively. Depending on the solvents (methanol, dichloromethane or tetrahydrofuran) and reaction conditions (30–60 ^{o}C, 1–10 bar) used, the products were prepared with 75–80% yields. In case of compound **29**, due to the vulnerability of its benzoyl ester moiety, a two-step method (selective hydrolytic O-detritylation and opening the azetidine ring) was applied to get a practically important 1,4-aminoalcohol derivative (**30**) with high cumulative yield (70%). Thus, the hydrogenolysis of N- and O-protected hydroxyazetidines proved to be an alternative reaction route for preparing different 1,4-aminoalcohols which can be promising starting materials for synthesis of valuable and important pyrrolidine derivatives, like compound **31** (Scheme 15), a key intermediate of the synthesis of Balanol analogues.



Scheme 15. Synthesis of a pyrrolidine derivative (**31**) from the product (**30**) of hydrogenolysis.

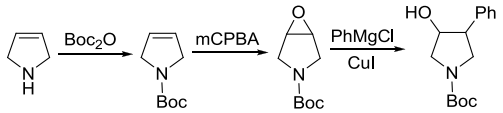
The selective heterogenous catalytic hydrogenation method was used for the preparation of a practically important resolving agent **32** (Scheme16) containing N-benzyl moiety which is also sensitive to certain conditions of catalytic hydrogenation.



Scheme 16. Preparation of resolving agent **32** by selective hydrogenation

2.2. New method for the preparation of an optically active pyrrolidine derivative

Substituted pyrrolidines are common structural subunits found in a variety of natural and synthetic bioactive compounds. Recently, *tert*-butyl-3-hydroxy-4-phenylpyrrolidine-1-carboxylate (*N*-Boc-*trans*-3-hydroxy-4-phenylpyrrolidine, **33**) was described as an intermediate of a potential neurokinin-1 (NK1) receptor antagonist, which could be effective for treatment of emesis, depression and anxiety (R.L. Barreto, M.J.S. Carpes, C.C. Santana, C.R.D. Correia, *Tetrahedron: Asymmetry* 2007, *18*, 435). However, the enantiomers of **33** could only be separated by high performance liquid chromatography using chiral stationary phase containing column. Compound **33** is a structural analogue of **31** prepared in our laboratory using our novel method (see in point 2.1). Therefore racemic **33** was also synthesized from pyrroline (**34**) via Boc protection, epoxidation and copper catalyzed phenylmagnesium bromide addition (Scheme 17).

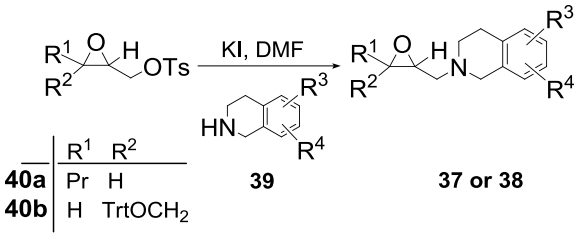


Scheme 17. Synthesis of *rac*-**33**.

The synthesis provided *rac*-**33** as pure *trans* isomer. Then a new, enzime catalysed kinetic resolution was developed for separation of the enantiomers of *rac*-**33**. Acetylation of the OH group was investigated in the presence of different lipases, then the best enzyme was tested under different conditions and solvents. It has been found that Novzyme 435 and BUTE-3 lipases are suitable catalysts for the kinetic resolution of *rac*-**33**. The enzymes initiate the acetylation of (+)-(3*S*,4*R*)-**33** while (-)-(3*R*,4*S*)-**33** remains intact. The best separation could be achieved with Novozyme 435 using vinyl acetate in methyl *tert*-butyl ether at 50 °C. Under these conditions the enantioselectivity E = 40 and (-)-(3*S*,4*R*)-**33** could be isolated in 94% yield (ee>97.3%). Absolute configuration of the (-)-(3*R*,4*S*)-**33** enantiomer was determined by single crystal X-ray diffraction method because such a measurement was missing from the literature until now.
High enantioselectivities could be achieved during the alcoholysis of the racemic acetate of **33**. The Novozyme 435 catalyzed reaction was the most selective and the fastest in *2*-propanol and *terc*-butanol (E > 200). The reactions were quite slow at 30 °C, 47% conversion could be achieved within 70 hours at 60 ^{o}C, while the enantioselectivity remained high (E > 200) and practically enantiopure (+)-(3*R*,4*S*)-**33** could be prepared (ee = 99.7%).

2.3. Controlling the metalation of oxiranylmethyl-tetrahydroisoquinolines coupled with regio- and stereoselective rearrangement reactions

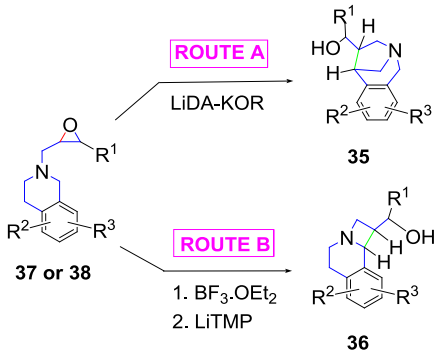
The azetidine- and pyrrolidine-fused 1,2,3,4-tetrahydro-isoquinolines are among the most frequently used heterocycles in medicinal chemistry due to the wide range of physiological activities of their representatives. Tetrahydroazeto[2,1-*a*]isoquinolines have hypotensive and anti-aggregant activities (Nelson NA, Tamura Y. *Can. J. Chem.* 1965, *43*, 1323), and pyrrolidine fused tetrahydroisoquinolines are abundant in Nature, and occur in many Amaryllidaceae alkaloids (Kano T, Hayashi Y, Maruoka K. *J. Am. Chem. Soc.* 2013, *135*, 7134). However, only a few approaches for the synthesis of these azetidine- and pyrrolidine-fused tetrahydroisoquinolines have been developed. Therefore we developed a new, stereoselective rearrangement into pyrrolidine (**35**) and azetidine (**36**) fused heterocycles from oxiranylmethyl group-substituted tetrahydroisoquinoline derivatives, along with the results of quantum chemical calculations, for the confirmation of the proposed reaction mechanism.
In order to prepare the target compounds type **35** and **36**, the key intermediates **37** and **38** were synthesized from tetrahydroiso-quinolines (**39a-n**) and 3-substituted-(oxiran-2-yl)methyl 4-toluene-sulfonate (**40a** or **40b**) derivatives (Scheme 18). The results are collected in Table 3.
The obtained key intermediates **37a-n** and **38a**,**b** were treated with an excess of LiDA-KOR superbase (mixture of lithium diisopropylamide and potassium tert-butoxyde) in tetrahydrofuran at –78 °C. On the basis of spectroscopic evidence, it was clear that the *trans* five membered ring-containing fused tricyclic compounds **35a-j** and **36a**,**b** were formed regio- and diastereoselectively (Scheme 19, Table 4, Route A).



Scheme 18. Synthesis of **37** and **38**

Table 3. Results of *N*-alkylation reactions

Starting material	Reagent			Product	
		R^3	R^4	Yield	Compound
40a	**39a**	H	H	98%	**37a**
	39b	6-OMe	7-OMe	88%	**37b**
	39c	6-OMe	H	74%	**37c**
	39d	5-F	H	81%	**37d**
	39e	7-F	H	84%	**37e**
	39f	6-^{t}Bu	H	94%	**37f**
	39g	7-^{t}Bu	H	95%	**37g**
	39h	5-Me	H	91%	**37h**
	39i	6-Me	H	89%	**37i**
	39j	7-Me	H	88%	**37j**
	39k	7-CF_3	H	66%	**37k**
	39l	5-Cl	H	91%	**37l**
	39m	6-Cl	H	98%	**37m**
	39n	7-Cl	H	87%	**37n**
40b	**39a**	H	H	89%	**38a**
	39b	6-OMe	7-OMe	77%	**38b**



Scheme 19. Superbase induced rearrangements of compounds **37** and **38**

The oxirane reacted only on its C2' position, excluding the formation of some other possible tricyclic products. This observation is in accordance with the literature data in which, in general, the C4 benzylic position of the 1,2,3,4-tetrahydroisoquinolines is mentioned as more reactive in metalation reactions than the C1. The formed organometallic intermediates can be stabilized via an intramolecular nucleophilic reaction with the C2' carbon atom of the oxiranyl moiety within the substrate. Parallel oxirane ring-opening and pyrrolidine ring closure procedures provide **35a-j** and **35o**,**p**. The dehalogenated starting material (**37a**) could only be isolated from the reaction mixtures of the chlorinated starting materials (**37l-n**), which could occur via chlorine/metal exchange followed by hydrolysis. Experimental data and quantum chemical calculations confirmed the high diastereoselectivity of the novel rearrangement reactions described above.

However, addition of boron trifluoride to the starting materials before metalation resulted in a new rearrangement reaction which has been unknown from literature until now. Metalation of **37a-k** and **38a**,**b** boron trifluoride complexes followed by the intramolecular nucleophilic reaction with the oxirane moiety could produce azetidine or pyrrolidine-fused tricyclic products. These new reactions were accomplished

with lithium 2,2,6,6-tetramethylpiperidide (LiTMP) providing exclusively the corresponding 1,4,5,9*b*-tetrahydro-2*H*-azeto[2,1-*a*]isoquinoline derivatives (Scheme 19 and Table 4, Route B). In most of the cases, typically the *cis* isomer was formed as the major product, but for **37d**–**j** the *trans* isomers were also isolated as minor products (ca. 30% of the overall product).

Table 4. Results of consecutive metalation rearrangement reactions

	Starting material			ROUTE A		ROUTE B	
	R^1	R^2	R^3	Yield	Product	Yield	Product
37a	Pr	H	H	66%	**35a**	45%	**36a**
37b	Pr	6-OMe	7-OMe	71%	**35b**	46%	**36b**
37c	Pr	6-OMe	H	56%	**35c**	40%	**36c**
37d	Pr	5-F	H	76%	**35d**	44%	**36d**
37e	Pr	7-F	H	70%	**35e**	46%	**36e**
37f	Pr	6-^{t}Bu	H	76%	**35f**	32%	**36f**
37g	Pr	7-^{t}Bu	H	83%	**35g**	36%	**36g**
37h	Pr	5-Me	H	70%	**35h**	28%	**36h**
37i	Pr	6-Me	H	73%	**35i**	33%	**36i**
37j	Pr	7-Me	H	58%	**35j**	30%	**36j**
37k	Pr	7-CF_3	H	-	**-**	47%	**36k**
38a	$TrtOCH_2$	H	H	36%	**35o**	25%	**36o**
38b	$TrtOCH_2$	6-OMe	7-OMe	30%	**35p**	30%	**36p**

The compounds **36a-k** were isolated with medium yields, while the trityloxymethyl group-containing products (**36o**,**p**) could be prepared after flash chromatography in lower yields. In addition, triphenylmethanol (about 20-40%) was also isolated in the cases of products **35o**,**p** and **36o**,**p**.

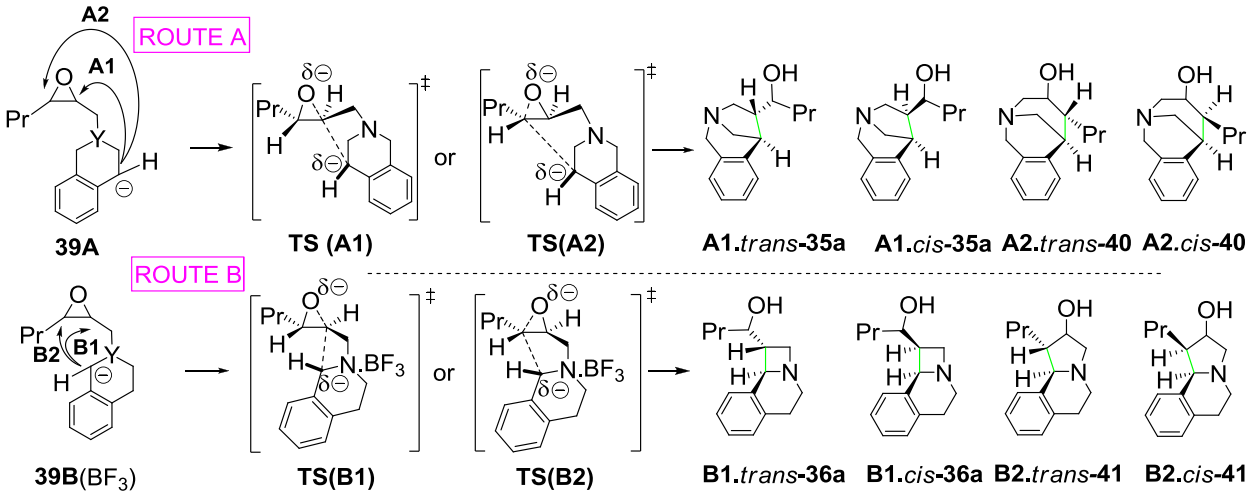
During the reaction mechanism studies, we focused only on the ring closure steps from the metalation, leading to products. Metalation of **37a** could occur at two positions (C1 and C4), resulting in two anions (**39A**, **39B**(BF3)). In addition, all the theoretically possible products which could be formed from anion **39A** or **39B**(BF3) in routes A1, A2, B1 or B2 are depicted in Scheme 20.

The starting metalation positions were selected according to the reaction conditions (without or with BF3). The computations were carried out at B3LYP/6-31G(d,p) level of theory, considering explicit solvation, including explicit Li, K ions and two THF solvent molecules.

Experimentally, mostly *cis*-**36a** could be prepared as the product, consequently the question arises whether kinetically preferred *trans*-**36a**.BF_3 could be transformed into the thermo-dynamically more stable *cis*-**36a**.BF_3 under the reaction conditions applied. We supposed that the excess of the base could deprotonate the product *trans*-**36a**.BF_3 and the formed double anion (*trans*-**36a**.BF_3–H^+) could be stabilized as *cis*-**36a**.BF_3–H^+ and that mechanism was confirmed by calculations, too. The very low activation gap (4 kJ.mol^{-1}) between the deprotonated *trans*-**36a**.BF_3–H^+ toward the thermodynamically more stable product *cis*-**36a**.BF_3–H^+, allows this process.

In summary, a novel, highly stereo- and diastereoselective method has been developed for preparation of pyrrolidine and azetidine fused 1,2,3,4-tetrahydroisoquinolines (**35a-j**,**o**,**p**; **36a-k**,**o**,**p**), by using strong alkali amide-type bases. Results of quantum chemical investigation of the mechanism is in good

accordance with the experimental findings and shed light on the details of the novel rearrangement reactions. The developed new synthetic methods can be widely used in the preparation of pharmaceutically interesting new pyrrolidine and azetidine fused 1,2,3,4-tetrahydroisoquinolines.



Scheme 20. The mechanism of formation of possible products without or with BF_3. Enthalpy (ΔH, kJ.mol^{-1}) and free enthalpy (ΔG, kJ.mol^{-1}) changes computed for TSs and deprotonated products from anion **39A** or **39B**(BF3) are given in Table 5. In the case of route A, one explicit Li and one K ion, solvated by two-two THF molecules, for route B, two explicit Li ions, solvated by two-two THF molecules are implemented. All the data were calculated at B3LYP/6-31G(d,p).

Table 5. Calculated energy levels of the transition states and the possible products

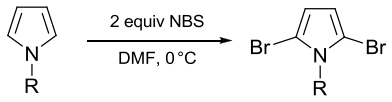
		ΔH	***ΔG***			***ΔH***	***ΔG***
A1	**TS**	37.5	47.8	B1	**TS**	60.3	62.4
cis-**35a**–H^+		-96.2	-81.6	*cis*-**36a**(BF_3)–H^+		-78.8	-74.2
A1	**TS**	29.2	38.4	B1	**TS**	49.1	49.2
trans-**35a**–H^+		-118.6	-106.6	*trans*-**36a**(BF_3)–H^+		-45.0	-42.7
A2	**TS**	48.3	57.9	B2	**TS**	72.3	75.7
cis-**40**–H^+		-120.2	-104.1	*cis*-**41**(BF_3)–H^+		-97.9	-88.7
A2	**TS**	61.4	71.2	B2	**TS**	89.9	92.6
trans-**40**–H^+		-105.5	-89.9	*trans*-**41**(BF_3)–H^+		-106.3	-98.9

3. A novel, convenient method for the preparation of 5-(diphenylmethylene)-1*H*-pyrrol-2(5*H*)-ones and derivatives

In the framework of our research project we have investigated several alternative synthesis of multifunctionalised 1-phenylpyrrole derivatives. One among the tested routes was the selective bromination of 1-substituted pyrroles in their α, α,α' or β and β' positions. We planned the transformation of these brominated compounds into atropisomeric products which could fit to the preparation of chiral catalysts ligands and organocatalysts mentioned in point 1 of this report.

According to our plan, a series of N-substituted 2,5-dibromo-1*H*-pyrroles were synthesised usinng our recently reported method (Faigl, F.; Mátravölgyi, B.; Deák, S.; Holczbauer, T.; Czugler, M.; Balázs, L.; Hermecz, I. *Tetrahedron* 2012, *68*, 4259). Aliphatic and various aromatic N-substituted dibromo-1*H*-pyrroles (**43a-l**) bearing electron withdrawing or electron donating substituents at different positions of the aromatic rings were prepared, in excellent yields. Moreover N-*tert*-butyloxycarbonyl protected derivative (**43m**) was also synthesised (Table 6).

Table 6. Synthesis of 2,5-dibromo-1-substituted-1*H*-pyrroles **43a-m**



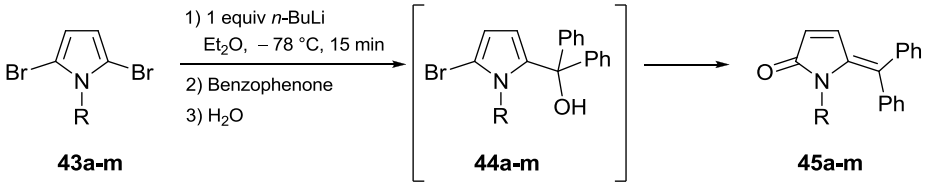
42a-m **43a-m**

Entry	R group	Product	Yield[a] (%)
1	C_6H_5	**43a**	96
2	4-Me-C_6H_4	**43b**	85
3	2-Et-C_6H_4	**43c**	90
4	2-Et-6-Me-C_6H_3	**43d**	91
5[e]	2-biphenyl	**43e**	88
6	1-naphtyl	**43f**	93
7	2-CF_3-C_6H_4	**43g**	98
8	2-Br-C_6H_4	**43h**	94
9	3-Br-C_6H_4	**43i**	97
10	4-Br-C_6H_4	**43j**	94
11	Benzyl	**43k**	97
12	CH_3	**43l**	86
13	BOC	**43m**	56

[a] Isolated yields.

In addition, several α,α',β-tribromo (**44**) and α,α',β,β'-tetrabromo (**45**) derivatives were also prepared using our highly selective bromination method. Our attempts to prepare diphenyl-(pyrrol-2-yl)-methanol derivatives from 1-(2,5-dibromophenyl)-1*H*-pyrrole showed that under acidic conditions water elimination can occur and an undesired compound formed. Therefore, we initiated detailed organometallic studies using benzophenone as electrophile. Selective bromine/lithium exchange reaction of **43a** was performed using 1 equiv of butyllithium at low temperature followed by the addition of the ketone. LC-MS analysis indicated the formation of the desired bromo alcohol (**44a)** as nearly sole product, however, the first attempt to isolate it has failed. After work-up, visible changes took place in the crude material, its colour slowly altered to dark, and purification by flash column chromatography resulted in a more polar compound as it was expected. Characterisation of the obtained material showed that both of the desired transformations, the elimination of water and the formation of 1*H*-pyrrol-2(5*H*)-one unit were realized simultaneously without any specific additives. Moreover, compound **45a** was obtained in excellent yield (Table 7, entry 2). In addition, the exact structure of **45a** was confirmed by single crystal X-ray diffraction measurement.

Table 7. Synthesis of 5-(diphenylmethylene)-1*H*-pyrrol-2(5*H*)-ones **45a-m**



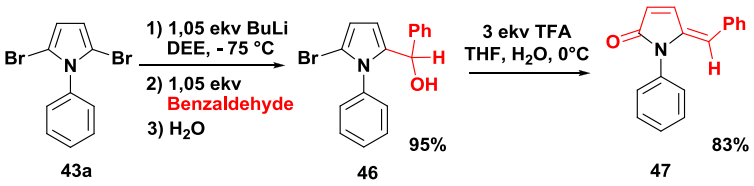
43a-m **44a-m** **45a-m**

Entry	R group	Product	Yield[a] (%)
1[b]	C_6H_5	**44a**	72
2	C_6H_5	**45a**	89
3	4-Me-C_6H_4	**45b**	81
4	2-Et-C_6H_4	**45c**	87
5	2-Et-6-Me-C_6H_3	**45d**	80
6	2-biphenyl	**45e**	82
7	1-naphtyl	**45f**	88
8	2-CF_3-C_6H_4	**45g**	92
9	2-Br-C_6H_4	**45h**	70
10	3-Br-C_6H_4	**45i**	90
11	4-Br-C_6H_4	**45j**	93
12	Benzyl	**45k**	69
13	CH_3	**45**	88
14[c]	BOC → H	**45m**	48

[a] Isolated yields.
[b] The reaction mixture was worked up using basic conditions and **44a** was isolated using preparative RP-HPLC.
[c] Deprotection of *tert*-butyl 2-(diphenylmethylene)-5-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate took place during the transformation, resulting in the deprotected product (**4m**).

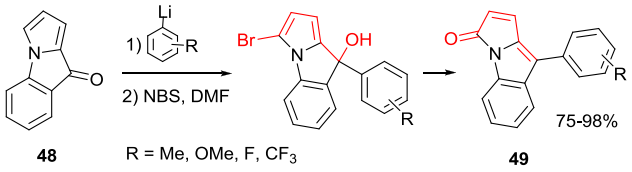
Similar reaction sequences, starting from the tri- and tetrabrominated pyrrole derivatives provided the bromo- and the dibromo derivatives of the corresponding 5-(diphenylmethylene)-1*H*-pyrrol-2(5*H*)-ones.
In order to shed light details of the invented new process, quantumchemical calculations and system chemistry analysis were carried out. Mechanistic study of the reaction mechanism revealed the nature of the process – water elimination followed by hydrolysis of the bromopyrrole unite influenced by acidic condition – and system chemistry analysis suggested that the formation of the conjugated system serves as driving force for the transformation. On the basis of these experimental and mechanistic results this approach could be applied for preparation of highly functionalized diverse conjugated systems.

The new method was extended to the aromatic aldehydes. In these cases the carbinol (eg **46**) was stable enough for isolation and, in a separate step, the carbinol was converted into the corresponding benzylidene arylpyrrolone derivative (**47**, Scheme 21). The reaction was accomplished with 8 substituted benzaldehydes, too.



Scheme 21. Efficient synthesis of a benzylidene arylpyrrolone derivative (**47**)

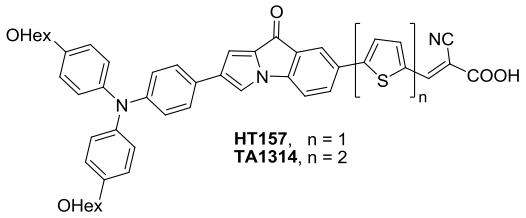
Furhter extension of the new method was the development of novel synthesis of pyrroloindolone derivatives. The starting material in these cases was a sideproduct (**48**) of the preparation of 1-(2-carboxyphenyl)-1*H*-pyrrole which can be formed via an intramolecular ring closure reaction under acidic conditions. Efficient synthesis of this 9*H*-pyrrolo-[1,2-*a*]indol-9-one (**48**, fluorazone) and 18 derivatives was also developed. Compound **48** was reacted with phenyllithium then brominated in the pyrrole α position and the aqueous workup provided the new pyrroloindolone derivatives (3*H*-pyrrolo[1,2-*a*]indol-3-ones, **49**) with good yields (Scheme 22). The prepared new compounds can be useful intermediates of biologically active compounds.



Scheme 22. Novel synthesis of pyrroloindolones (**49**)

4. Snythesis of new sensitizers for D-π-A type photovoltaic cells having 1-phenylpyrrole backbone

Starting from our experience in the preparation of fluorazones (mentioned in point 3), rational synthesis of new, 1-arylpyrrole skeleton containing sensitizers for D-π-A type photovoltaic cells hav been developed (compounds **HT157** and **TA1314**, Sheme 23). The target molecules were designed 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.



Shceme 23. New sensitizers containing fluorazone linker

The designed sensitizers contained one or two tiophene moieties between the novel fluorazone (9*H*-pyrrolo-[1,2-*a*]indol-9-one) linker and the acceptor unit. In addition, the new dyes have been tested in cooperation with an Italian research group. The dyes displayed intense absorption of visible light in dichloromethane solution. Moreover, their spectrum on nanocrystalline TiO_2 was much broader than that in solution, which was promising in view of the utilization of the dyes as DSSC (dye-sensitized solar cell) sensitizers. 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 compounds had energy levels correctly aligned to be used in photovoltaic cell. Small-scale photovoltaic devices fabricated with the new fluorazone dyes displayed moderate in the range 2.09–2.39 %, with

TA1314 giving the best results. The highest efficiency was around 70 % of that recorded with the reference dye (DF15) which is promising for further structure optimization. These results can also serve as the proof of oncept: the planar 1-arylpyrrole derivatives (fluorazones) may serves as new linkers in D-π-A senzitizers containing solar cells.

5. Practical importance of the new scientific results

The developed new synthetic methods could be applied in the preparation of new drug candidates or in the synthesis of practically important organic compounds for fine chemical industry. The new atropisomeric catalyst ligands are suitable for the preparation of a wide range of optically active alcohols, which can serve as chiral building blocks of biologically active compounds. The new D-π-A type sensitizers opened a new perspective of dyes with fluorazone type linkers. In the same time, the invented new synthetic strategy may help other chemists in the preparation of similar senzitiers and such type of compounds could be used in the development of third generation of photovoltaic cells.

6. Dissemination of the new scientific results

Numerous students were involved in the research project. They contribution has been summarized in 6 BSc thesis works, 4 MSc thesis works and 3 PhD thesis works succesfully defended in the 2013-2017 period. The new scientific results were presented in 22 conference presentations/lectures and 12 research articles.

7. Modifications of the budget

The 4 years duration time of the project was extended with a year and the residue of the 4 years budget was used in this additional year, mainly for buying chemicals. A part of the personal costs was also converted into the budget of consumables, according to the permit of the National Research, Development and Innovation Office (NKFIH Office). A PhD student and another undergraduate student was partially supported from the budget, again, with the permit of the NKFIH Office. A researcher, Mr. Ervin Kovács left in the middle of 2017 which was also reported to the NKFIH in time.

Budapest, November 2017

Dr. Ferenc Faigl