Report of published results

I. Synthesis of pyridino-18-crown-6 ethers and their application as chiral selectors (organocatalysts or chiral stationary phases)

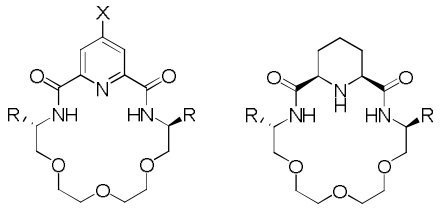
1. Synthesis and determination of pK_a values of new enantiopure pyridino- and piperidino-18-crown-6 ethers[1]

In the beginning of the research, our aim was to prepare new, enantiopure amide-type pyridino-crown ethers as potential organocatalysts.
Six new enantiopure amide type pyridino-crown ethers [(*S,S*)-**1**–(*S,S*)-**6**] and their optically active precursors were synthesized successfully (**Figure 1.**). In the macrocyclization step chiral diamines were transformed to amide type pyridino-crown ethers reacting them with pyridine dicarbonyl dichlorides by high dilution technique.

Hydrogen bonding interactions play a key role in noncovalent organocatalysis, thus determination of pK_a values facilitate the understanding of catalytic activity and catalyst design. Due to this significance of the pK_a values of the organocatalysts, the acidity and basicity of our new crown ether type potential bifunctional organocatalysts were measured. The proton dissociation constants of the amide groups of pyridino-crown ethers (*S,S*)-**1**–(*S,S*)-**6** were determined by UV-spectrophotometric titrations using the D-PAS technique. It was established, that the amide groups are acidic enough (pK_a = ~12–14 in aqueous media) to form strong hydrogen bonds.

Since piperidine is more basic than pyridine, pyridino-crown ethers were reduced to piperidino-crown ethers (*R,S,S,S*)-**7** and (*R,S,S,S*)-**8**. As the piperidino-crown ethers do not have a chromophore unit, the pK_a values were determined by potentiometric titrations. According to our measurements, the piperidino-crown ethers have a more basic nitrogen atom (pK_a ~ 4.4) than that of the pyridino-crown ethers (pK_a ~ 0.5). According to the pK_a measurements these eight new macrocycles are potential organocatalysts (for instance in Michael addition reactions) thanks to their acidic and basic moieties and chiral skeletons, respectively.

In order to increase the yield of crown ethers by more effective separation of the starting materials and the products, preliminary studies were carried out applying the organic solvent nanofiltration (OSN) method. Rejection of pyridino-crown ethers (*S,S*)-**1** and (*S,S*)-**4** was between 97% and 100%, while the rejection of precursors fell between 16% and 33%. These results confirm that nanofiltration can be used for the separation of most of the precursors from the crown ethers.



(*S,S*)-**1**: R=Me, X=H
(*S,S*)-**2**: R=Me, X=Cl
(*S,S*)-**3**: R=Me, X=OMe
(*S,S*)-**4**: R=iBu, X=H
(*S,S*)-**5**: R=iBu, X=Cl
(*S,S*)-**6**: R=iBu, X=OMe

(*R,S,S,S*)-**7**: R=Me
(*R,S,S,S*)-**8**: R=iBu

Figure 1. Structure of new, enantiopure amide type pyridino- and piperidino-crown ethers.

2. Synthesis of enantiopure pyridino-18-crown-6 ethers and their application for the preparation of molecularly imprinted polymers with enantiodiscriminative power[2,3]

Enantiopure pyridino-crown ethers are well-known chiral selectors of bioactive chiral amines. As a result, these macrocycles are suitable for development of synthetic receptors for enantioselective recognition of chiral amines. In our work, three pyridine and two benzene derivatives containing an allyloxy group [(*S,S*)-**9**, **10–13**, see **Figure 2.**] were prepared. Imprinted polymers (IP) were fabricated in the presence of 1-(1-naphthyl)ethylamine hydrogen perchlorate (1-NEA) as template and macrocycles as functional monomer anchors. Parameters such as binding, imprinting factor (IF), enantioseparation factor (EF), and selectivity factor (SF) were used to assess the performance of the polymers. IF is a useful measure of the effect of the presence of a template during polymerization on the performance of the scavengers. EF allows the comparison of chiral discrimination power of different polymers, and shows the ratio of binding of (*R*) and (*S*) enantiomers of template on the polymers.

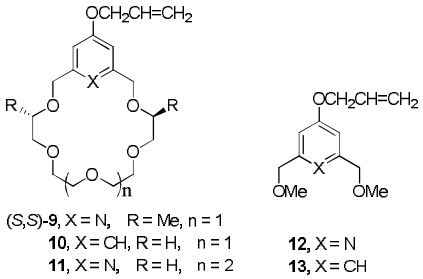


Figure 2. Structure of allyloxy substituted pyridino- and benzo-crown ethers and their precyclization analogues.

Figure 3. demonstrates that macrocyclic units play a key role in the binding of quaternary ammonium salts. IP1 and IP2 derived from enantiopure (*S,S*)-**9** and achiral **10** macrocyclic functional monomers exhibit about 10 times higher binding of (*R*)- 1-NEA than IP4 and IP5 derived from their precyclization analogues **12** and **13**, respectively. This can be explained by the alternating hydrogen bonds and π–π interactions between the IP and the template. In these cases the enantioseparation factor (EF) and imprinting factor (IF) were extremely high (up to EF=21.4, IF=21.6). It was established, that it is not necessary to use enantiopure crown ether for enantioseparation of 1-NEA, while (*R*)-1-NEA is applied as template during the synthesis of IPs (see the comparison of IP2 and CP2 on **Figure 3.**).

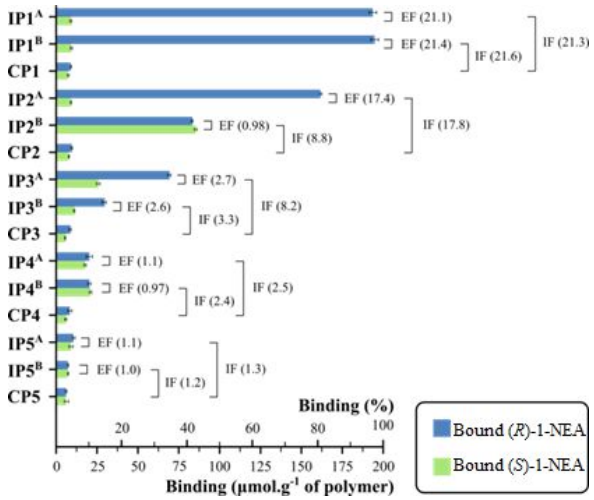


Figure 3. Binding of (*R*) and (*S*) enantiomers of 1-(1-naphthyl)ethylamine hydrogen perchlorate on the imprinted and control polymers. Enantioseparation factors (EF) and imprinting factors (IF) obtained are given for each enantiomer and polymer pairs, respectively. Template used: A: (*R*)-1-NEA; B: *rac*-1-NEA

The selectivity factor (SF) is used to describe the fidelity of the binding sites of the polymers. **Figure 4**. demonstrates that both IP1 and IP2 series have high selectivity toward the (*R*)-1-NEA template over structurally similar protonated primary aralkylamines [2-NEA: 1-(2-naphthyl)ethylamine, Br-PEA: 1-(4-bromophenyl)ethylamine and NO_2-PEA: 1- (4-nitrophenyl)ethylamine]. The highest SF of about 35 was achieved by IP1 series, which is among the highest SFs achieved by IPs in the literature. Hence, these IPs can not only bind the 1-NEA, but have the feature, that they do not have considerable interaction with the structural analogues of the template.

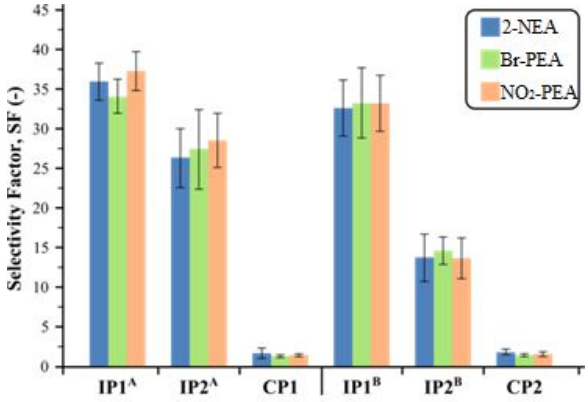


Figure 4. Selectivity factors of the imprinted and control polymers. Protonated primary aralkylamines 2-NEA, Br-PEA and NO_2-PEA were used to probe the selectivity of the polymers over the (*R*)-1-NEA template. Template used: A: (*R*)-1-NEA; B: *rac*-1-NEA

To find a possible application of our IPs, in vitro drug delivery, enantiomeric enrichment and pH-sensitive release were investigated through kinetic models. **Figure 5** shows that the release rate of the template (*R*)-1-NEA enantiomer from the IP1 series and IP2A is highly pH-dependent, while the (*S*)-1-NEA release is nearly instantaneous regardless of pH. This allows the improvement of enantioseparation performance by selective washing of (*S*)-1-NEA under acidic conditions, followed by the selective elution of (*R*)-1-NEA enantiomer. Applications as drug carriers in which release is controlled by a stimulus, such as the varying pH present in the intestinal tract, are envisaged. Kinetic studies revealed the mode of release to be first order and thus the IPs can serve immediate drug release at basic pH. The general concepts described above should be extendable to other classes of macrocycles and enantiomers, and could be applied in chiral resolution of drugs, enantioselective sensors and pH-responsive drug delivery systems.

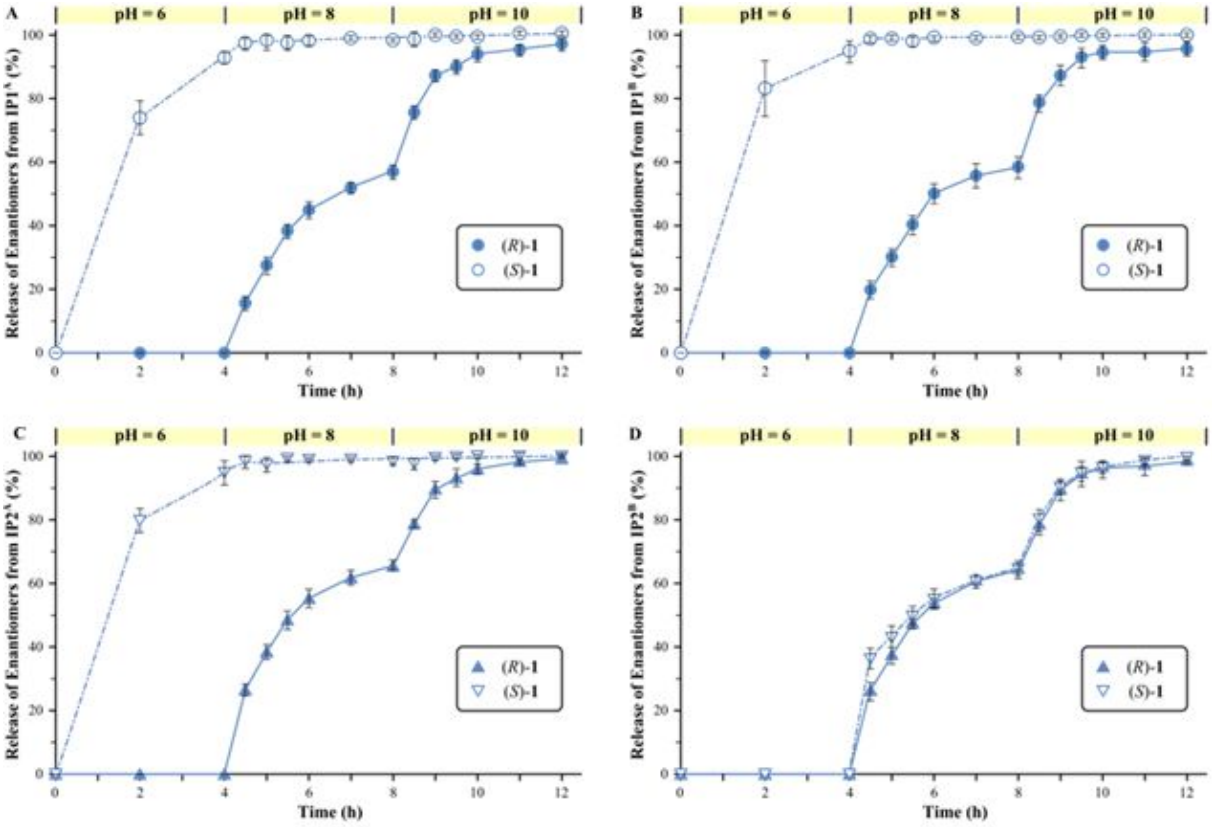


Figure 5. Release kinetic profile of 1-nea enantiomers from IP1 (A, B) and IP2 (C, D) series in response to pH stimuli. The release amount is expressed as the percentage of 1-NEA released towards the total 1-NEA uptake by the polymers. Template used: A: (*R*)-1-NEA; B: *rac*-1-NEA

3. Long-term stability and reusability of molecularly imprinted polymers[4]

As a result of our interesting results achieved using molecular imprinted polymers (MIP), we started to investigate the long-term stability of MIPs. The effect of crosslinker, functional monomer and conditions for template extraction was systematically investigated to reveal the long-term stability and reusability of imprinted polymers. Adsorption–regeneration cycles were carried out 100 times for *L*-phenylalanine methyl ester imprinted polymers. Irrespective of the degree of crosslinking, divinylbenzene-based polymers demonstrated the most robust behaviour compared to methacrylate- and acrylamide-based polymers. These polymers can be reused at least 100 times without loss of affinity towards the template molecule under acidic, basic, and elevated temperature.

4. Application of flow chemistry to macrocyclization of crown ethers[5]

Due to the difficulties of the macrocyclization the synthesis of crown ethers gives only low yields. Our aim was to apply our pyridino-crown ether based MIPs in drug delivery, so the development of their preparation was achieved using flow technique. Macrocyclizations have been performed in a packed-bed flow reactor where deprotonation of a bifunctional primary or a secondary alcohol takes place with potassium hydroxide as a heterogeneous base avoiding the use of stronger and more dangerous one, sodium hydride. Ditosylate derivatives of pyridine as precursors for the macrocyclization used in batch condition were replaced by the appropriate iodides and optimization of the parameters provided higher yields in shorter reaction times. The

setup presented here is suitable for the preparation of different ethers by *Williamson* type syntheses in continuous-flow reactions. (**Figure 6.**)

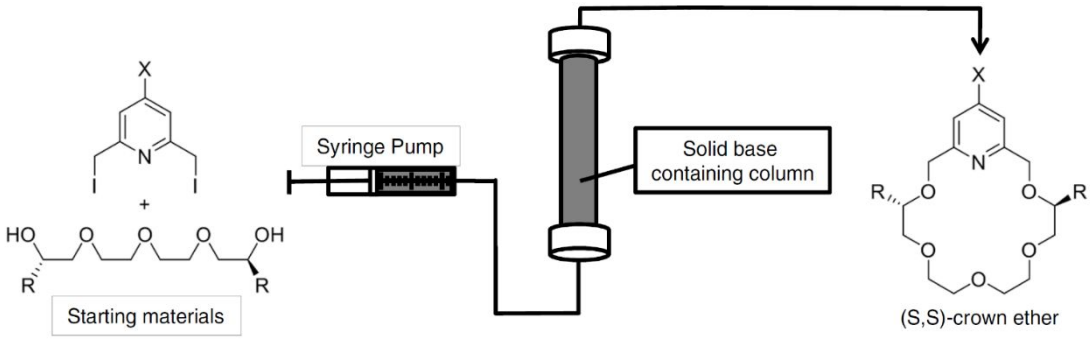


Figure 6. Schematic of the used experimental setup in flow conditions

5. Application of pyridino-crown ether-based chiral stationary phase for the enantioseparation of biogenic chiral amines and amino acid esters by HPLC[6,7]

As it was mentioned in *Detailed research plan* of my OTKA-PD grant, during my PhD work I synthesized three new pyridino-18-crown-6 ether-based chiral stationary phases (CSPs), which were successfully applied for the enantiomeric separation of protonated primary aralkylamines. As a continuation of this research topic, enantiomeric discrimination of a pyridino-crown ether-based [(*S,S*)-CSP-**14**], and an acridino-crown ether-based [(*S,S*)-CSP-**15**] chiral stationary phase were evaluated by HPLC (**Figure 7.**). We used the mixtures of enantiomers of various protonated primary aralkylamines 1-NEA, 2-NEA, Br-PEA, NO_2-PEA, 1-phenylethylamine hydrogen perchlorate (PEA), 2,3-dihydro-1*H*-inden-1-amine, 2,2'-(1,2-diaminoethane-1,2-diyl) diphenol and perchlorate salts of α-amino acid esters (alanine benzyl ester, phenylalanine benzyl ester, phenylalanine methyl ester, phenylglycine methyl ester, glutamic acid dibenzyl ester, and valine benzyl ester). The best enantioseparations were achieved in the case of (*S,S*)-CSP-**14** for PEA, and in case of (*S,S*)-CSP-**15** the best results were found for the separation of the mixtures of enantiomers of Br-PEA. These high enantioselectivities were rationalized by the strong π–π interaction of the extended π system of the aryl-substituted pyridine unit and the three aromatic ring of acridine, respectively.

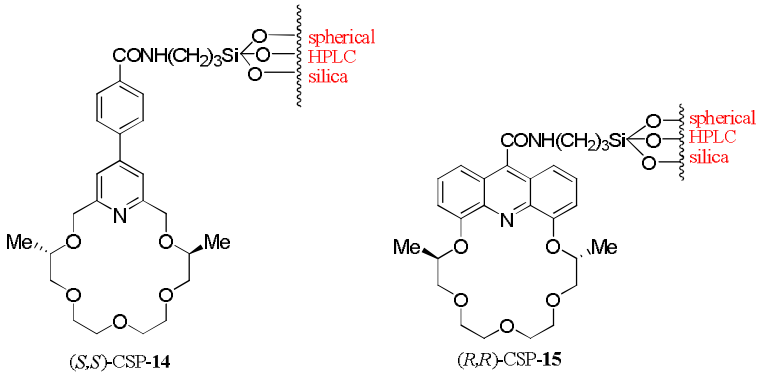


Figure 7. Schematic representation of chiral stationary phases based on enantiopure pyridino- [(*S,S*)-CSP-**14**] and acridino-18-crown-6 ethers [(*S,S*)-CSP-**15**] as selectors.

II. Synthesis of organocatalysts and their application in asymmetric syntheses

6. Organocatalytic *Michael* reaction in a continuous-flow system combined with *in situ* solvent and reagent recycle by nanofiltration[8]

Encouraged by our successful preparations of pyridino-crown ethers in flow system our next aim was to develop a continuous hybrid process for organocatalytic reaction with stable and long-term operation. This requires an efficient catalyst/solvent system. *Michael* addition of nitromethane to *trans*-chalcone was selected as a model reaction (**Scheme 1.**) Amberlyst™ A21, a polymer supported weak anion exchange resin featuring a dialkylbenzylamine base was used as polymer supported organocatalyst, because this is a relatively cheap and commercially available.

Scheme 1. Catalyzed *Michael* addition of nitromethane to *trans*-chalcone

In this work, a nanofiltration unit was coupled to a flow rector for *in situ* solvent and reagent recycle. The nanofiltration unit is straightforward to implement and control. The hybrid process was continuously operated over 6 weeks recycling about 90% of the solvent and the reagent. Consequently, the E–factor and the carbon footprint were reduced by 91% and 19%, respectively. Moreover, the nanofiltration unit concentrated the product 11 times and simultaneously increased the purity from 52.4% to 91.5%.

7. Synthesis of new bifunctional glucose-thiourea organocatalysts and their application in asymmetric *Michael* addition[9]

According to the *Detailed research plan* of my OTKA-PD grant, asymmetric *Michael* addition catalysed by new glucose-thiourea organocatalysts was one of our plans. Three new glucose-based potential asymmetric bifunctional organocatalysts containing a 6-aminopyridyl (**16**) or a 6-methylpyridyl (**17**) or a cinchona unit (**18**) were synthesized (**Figure 8.**).

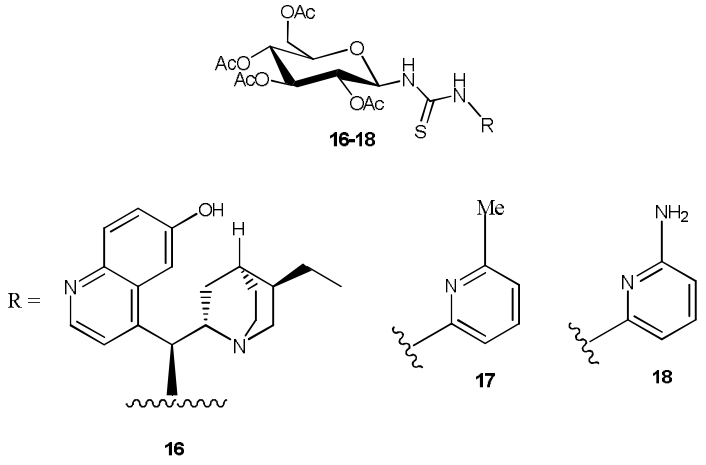
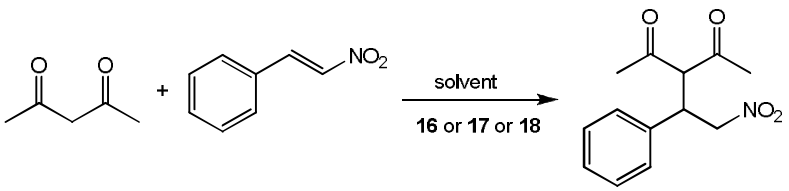


Figure 8. Structures of new, enantiopure glucose-thiourea organocatalysts **16–18.**

Asymmetric *Michael* addition of pentane-2,4-dione to β-nitrostyrene was catalyzed successfully by these catalysts (**Scheme 2.**). In case of the cinchona based glucose-thiourea derivate (**18**) the *S* enantiomer of the corresponding *Michael* adduct was formed with moderate enantiomeric excess (up to 64.1%) in three different solvents.



Scheme 2. Catalyzed *Michael* addition of pentane-2,4-dione to *trans*-β-nitrostyrene

However, using the pyridine based organocatalysts (**17** and **18**) only racemic products were obtained with lower yields. Presumably the high basicity of the quinuclidine unit of cinchona skeleton is needed for the higher yield, and the cinchona skeleton is also necessary for the successful asymmetric induction.

Due to the proved necessity of cinchona unit for successful chiral induction, we turned to the synthesis of new cinchona-based organocatalysts containing thiourea and squaramide units. These results have not been published, but they are prepared for submitting to J. Am. Chem. Soc.

References (published results: 9 papers, overall IF: 27.59, overall independent cit.: 23)

1. Kupai, J.; Kisszékelyi, P.; Rojik, E.; Dargó, G.; Hegedűs, L.; Bezzegh, D.; Maszler, P.; Szabó, L.; Németh, T.; Balogh, Gy. T.; Huszthy, P.: Synthesis and determination of pK_a values of new enantiopure pyridino- and piperidino-18-crown-6 ethers, *Arkivoc* **2016**, *iv*, 130–151. (IF: 1.031)
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8. Fődi, T.; Didaskalou, C.; Kupai, J.; Balogh, G. T.; Huszthy, P.; Szekely, G.: Nanofiltration-enabled in situ solvent and reagent recycle for sustainable continuous-flow synthesis, *ChemSusChem* **2017**, *10*, 3435–3444. (IF: 7.226)
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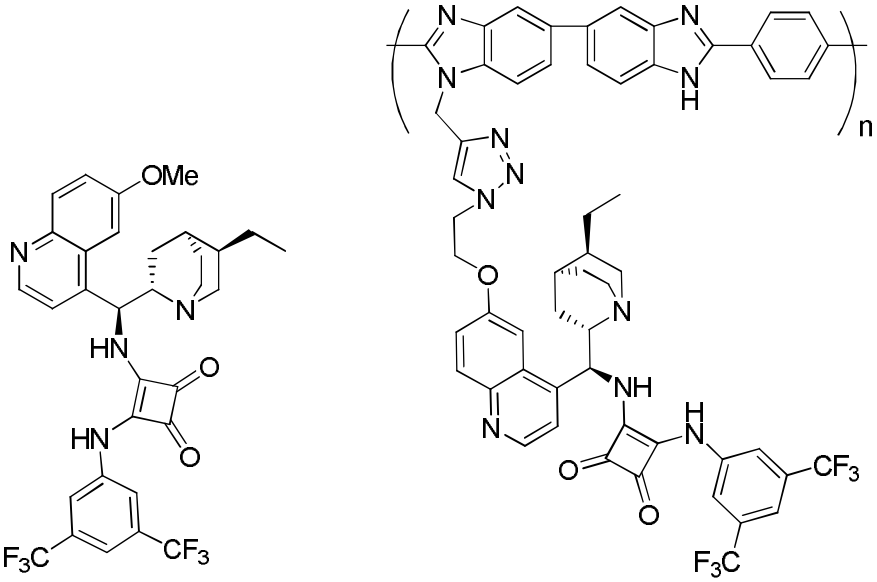
Report of unpublished results

1. Synthesis and application of cinchona-squaramide organocatalysts supported on polybenzimidazole membrane

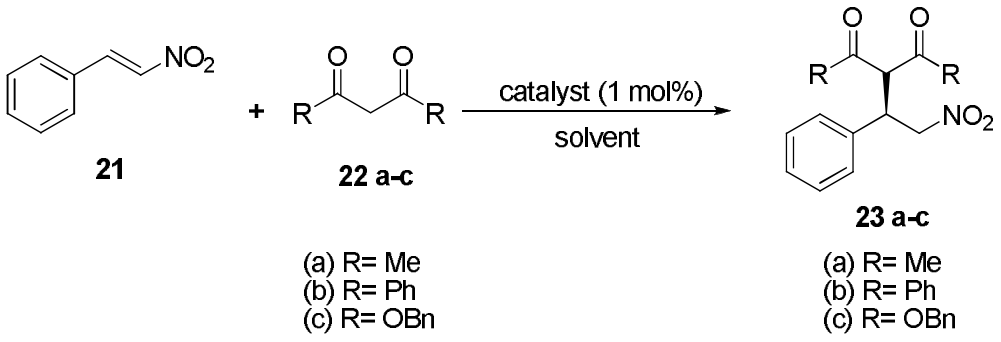
As a consequence of the promising results achieved using cinchona skeleton in asymmetric reactions, we started to prepare new cinchona-based squaramide organocatalysts. Commercially available hydroquinine was converted to cinchona derivative **19** (**Figure 9.**) in a multistep synthesis. This catalyst was tested in different *Michael* reactions. In order to make it recyclable, it was immobilized to a chemical and mechanical stable solid support, the polybenzimidazole (PBI) by a click reaction (**20**).



19 **20**

Figure 9. Structure of cinchona squaramide organocatalyst and the catalyst modified PBI membrane

Organocatalyst **19** was successfully applied in different types of *Michael* reaction. In the conjugated addition of 1,3-dioxo compounds (**22 a-c**, see **Scheme 3.**) to β-nitrostyrene (**21**) the *Michael* adducts **23 a–c** were obtained with excellent yields and high enantiomeric excesses (**Table 1.**).

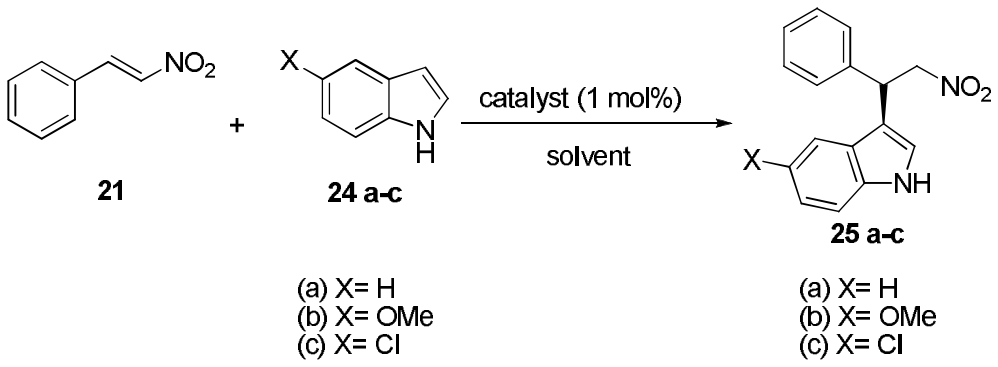


Scheme 3. *Michael* additions of 1,3-dioxo compounds to β-nitrostyrene

Entry	R	Solvent	Yield (%)	e.e. (%)	Configuration*
1	Me	MTBE	90	99.0	(*S*)
2	Me	DCM	31	93.1	(*S*)
3	Me	toluene	92	99.1	(*S*)
4	Me	MeCN	43	18.8	(*S*)
5	Me	EtOAc	42	23.1	(*S*)
6	Ph	MTBE	72	99.1	(*S*)
7	Ph	DCM	87	96.8	(*S*)
8	Ph	toluene	25	99.3	(*S*)
9	Ph	MeCN	50	29.8	(*S*)
10	Ph	EtOAc	65	34.1	(*S*)
11	OBn	MTBE	11	99.2	(*S*)
12	OBn	DCM	27	97.4	(*S*)
13	OBn	toluene	13	99.0	(*S*)
14	OBn	MeCN	19	25.7	(*S*)
15	OBn	EtOAc	4	34.6	(*S*)

Table 1. Results of *Michael* reactions between 1,3-dioxo compounds and β-nitrostyrene (* Absolute configuration was determined by comparison of optical rotatory power with that of the published ones)

The indole framework represents a privileged structural motif of established value in medicinal chemistry and complex target synthesis. C-3 functionalized indole derivatives are known to possess variety of biological activities such as COX-2 inhibitors, serotonin reuptake inhibitor, migrane drugs. Therefore, *Michael* reactions were carried out between β-nitrostyrene (**21**) and different indole derivatives (**24 a–c**, see **Scheme 4.**). *Michael* adducts **25 a–c** were obtained with moderate yields and high enantiomeric excesses (**Table 2.**).

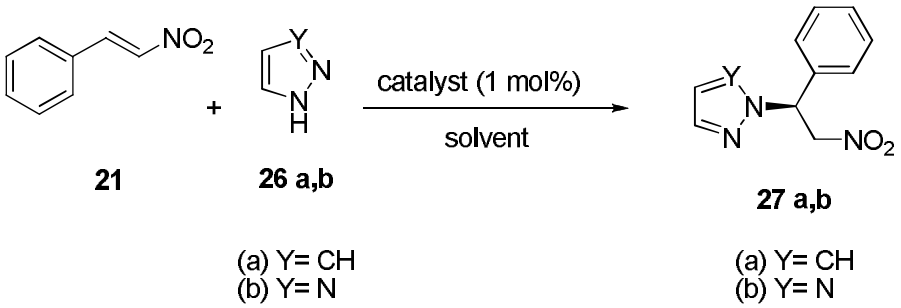


Scheme 4. *Michael* additions of indole derivatives to β-nitrostyrene

Entry	X	Solvent	Yield (%)	e.e. (%)	Configuration*
1	H	MTBE	51	99.1	(*R*)
2	H	DCM	42	96.5	(*R*)
3	H	toluene	81	98.9	(*R*)
4	H	MeCN	54	24.1	(*R*)
5	H	EtOAc	19	29.6	(*R*)
6	OMe	MTBE	51	99.4	(*R*)
7	OMe	DCM	56	96.3	(*R*)
8	OMe	toluene	60	99.6	(*R*)
9	OMe	MeCN	47	22.8	(*R*)
10	OMe	EtOAc	50	18.9	(*R*)
11	Cl	MTBE	28	98.9	(*R*)
12	Cl	DCM	50	93.5	(*R*)
13	Cl	toluene	38	99.1	(*R*)
14	Cl	MeCN	14	24.7	(*R*)
15	Cl	EtOAc	33	20.8	(*R*)

Table 2. Results of *Michael* reactions between indole derivatives and β-nitrostyrene (* Absolute configuration was determined by comparison of optical rotatory power with that of the published ones)

Pyrazole and triazole are versatile lead compound for designing potent bioactive agent, and their derivatives have diverse biological activities. Hence, asymmetric *Michael* addition of pyrazole (**26a**) and triazole (**26b**) to β-nitrostyrene (**21**) was investigated. In these cases we gained *Michael* adducts **27 a–c** (see **Scheme 5.**) with high enantioselectivities, but only with low yields (**Table 3.**).



Scheme 5. *Michael* additions of pyrazole and triazole to β-nitrostyrene

Entry	Y	Solvent	Yield (%)	e.e. (%)	Configuration
1	CH	MTBE	15	99.3	(*S*)
2	CH	DCM	8	95.8	(*S*)
3	CH	toluene	10	99.5	(*S*)
4	CH	MeCN	5	50.6	(*S*)
5	CH	EtOAc	23	43.2	(*S*)
6	N	MTBE	3	98.3	(*S*)
7	N	DCM	8	93.9	(*S*)
8	N	toluene	4	98.7	(*S*)
9	N	MeCN	23	39.0	(*S*)
10	N	EtOAc	11	34.5	(*S*)

Table 3. Results of *Michael* reactions between pyrazole and triazole and β-nitrostyrene (* Absolute configuration was determined by comparison of optical rotatory power with that of the published ones)

The catalyst is a relatively complex system as the cinchona molecule is bound to a polybenzimidazole membrane. Therefore it is important to develop an appropriate model system, which properly describes the protonation and also a sufficiently large part of the membrane is also incorporated.

It is well-known that in the case of the cinchona parent compound, nitrogen atom of the quinuclidine ring deprotonates the acetylacetone substrate, while hydrogen bond is formed with the nitro group of the β-nitrostyrene. Furthermore the oxo groups in the acetylacetone are connected to the amino groups of the squaramide with hydrogen bonds. Thus a similar configuration is also adapted in our model system.

Density Functional Theory calculations were carried out and molecular geometries were optimized using the ωB97X-D functional, including long range and dispersion correction and the 6-31G* basis set.

Our computations showed that the β-nitrostyrene interacts only weakly with the protonated nitrogen of the quinuclidine and instead a π–π stacking with the bis(3,5-trifluoromethyl)phenyl group is expected. Therefore the non-covalent interactions were investigated using the NCI plots.

The results in **Figure 10.** and **Figure 11.** show that the substrates are close enough to each other to make the *Michael* addition feasible and the dispersion interaction between the acetylacetone and the β-nitrostyrene can promote the reaction. In addition there is no substantial interaction between the substrates and the oligomer. Only the quinoline part of the catalyst interacts with the membrane via π–π stacking and no notabe interaction is observed between the membrane and the active part of the catalyst. Thus the non-covalent interactions do not have a direct influence to the reaction.

On the other hand the conformation of the catalyst is different when it is attached to the membrane compared to its free form. The so evolved steric effects can explain the breaking of hydrogen bond between the oxo group of the acetylacetone and the amino group of the squaramide.

From the results we can conclude that the length of the spacer is suitable for the reaction. It is long enough, so the membrane does not interact with the active center of the catalyst, but it is not too long and therefore the substrates can not be incorporated between the membrane and the catalyst. Thus the enantioselectivity of the reaction is preserved.

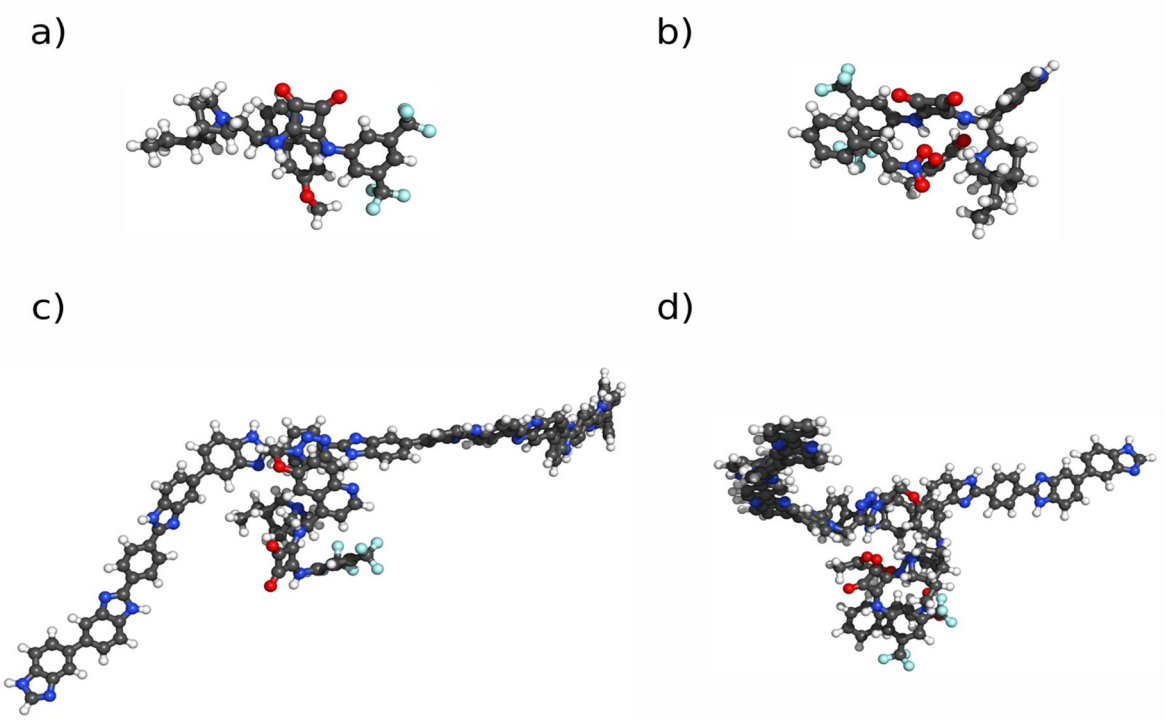


Figure 10. Optimized structures of the cinchona-squaramide organocatalyst (a), the catalyst with the reagents (b) and the model system without (c) and with the reagents (d).

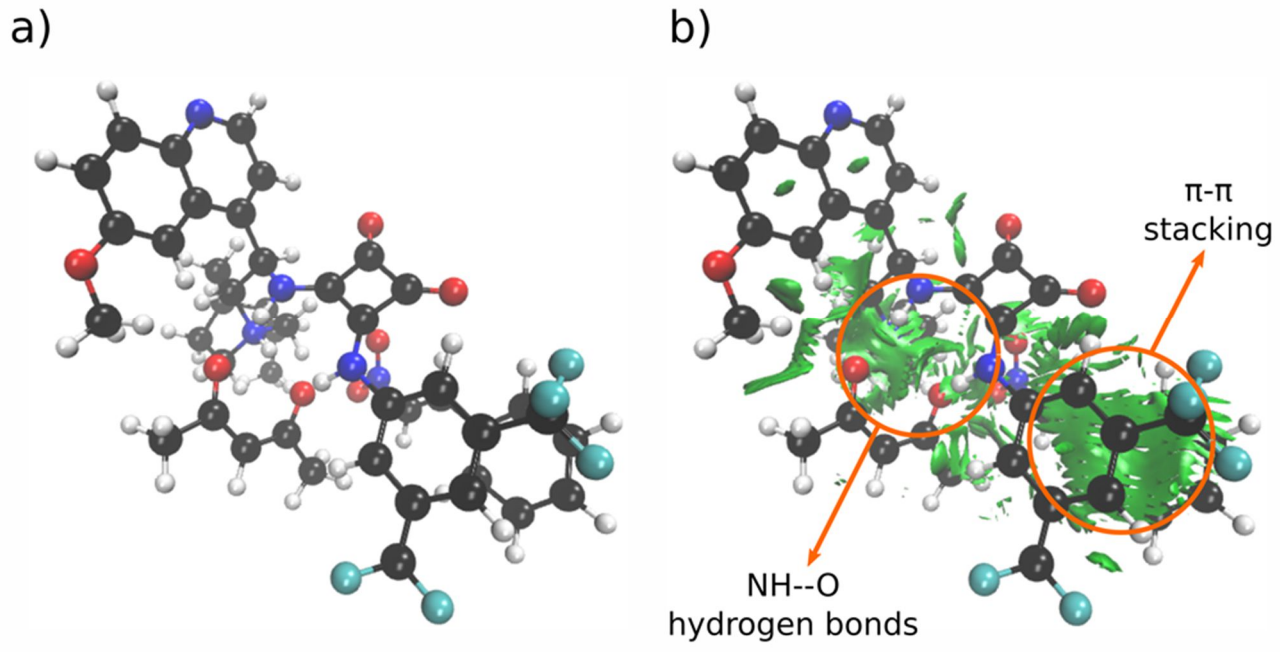


Figure 11. Optimized geometry of the catalyst with substrates system (a) and the noncovalent interactions in this system (b)

The thermodynamics of the substrate adsorption was investigated in different solvents according to the equation ΔGads = G(oligomer+catalyst+reagents) – G(oligomer+catalyst) – G(acetylacetone) – G(beta-nitrostyrene). The results on **Figure 12.** show that the adsorption

free-energy is negative in all cases, indicating that it is a thermodinamically feasible process. It is notable that the adsorption is most feasible in the case of the toluene, which was found to be the most suitable solvent in the experiments.

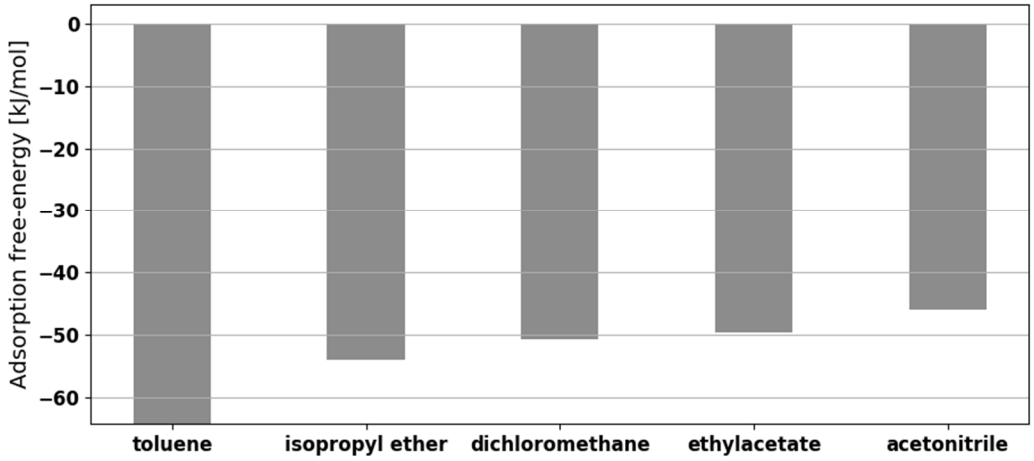
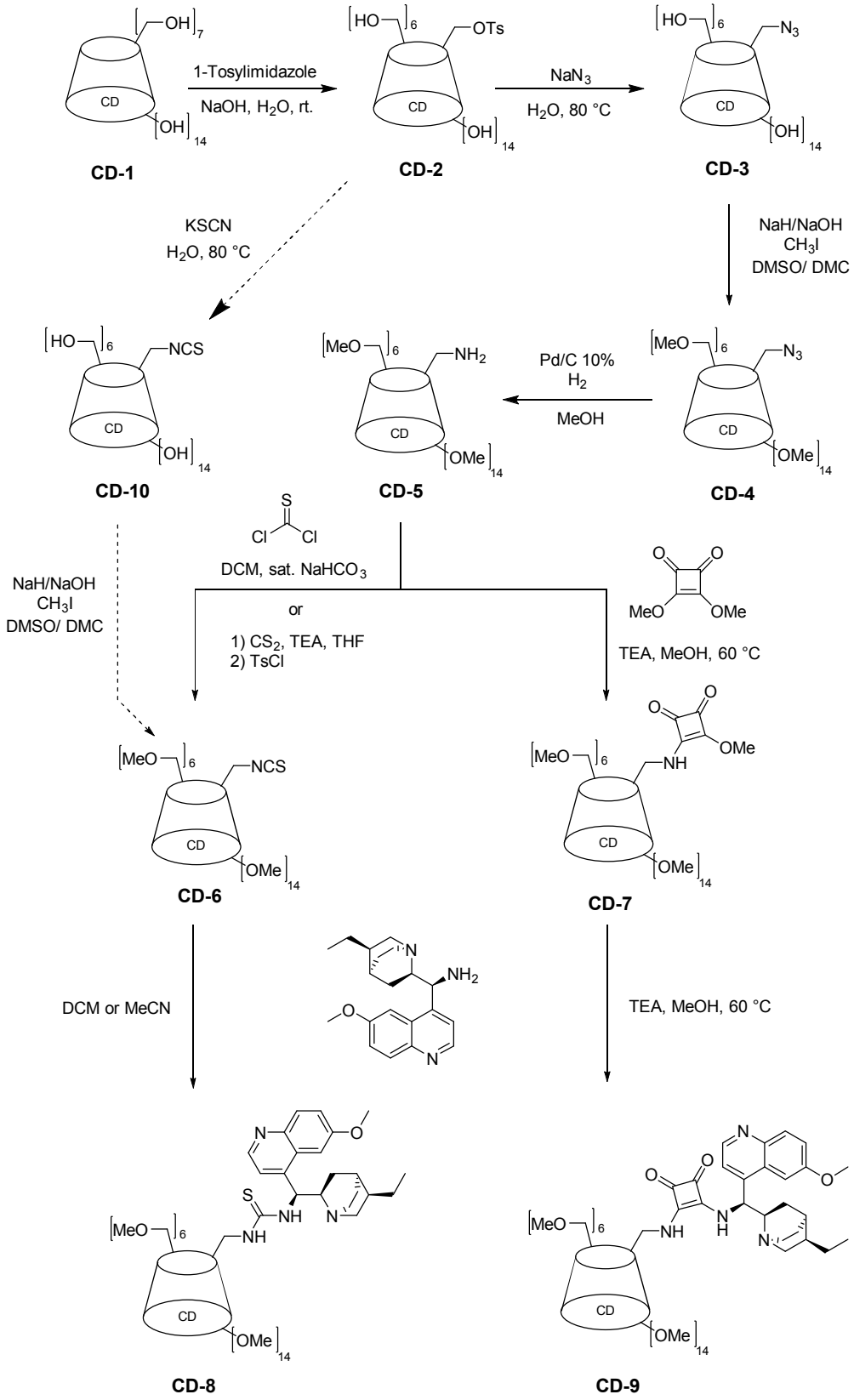


Figure 12. Adsorption free-energies of the substrates calculated in different solvents, calculated with ωB97X-D functional and 6-311G** basis set.

The catalyst modified PBI membrane is planned to be applied in an organic solvent nanofiltration system at *The University of Manchester, School of Chemical Engineering and Analytical Science*. The manuscript can be only submitted to *Journal of American Chemical Society* as soon as these measurements are completed.

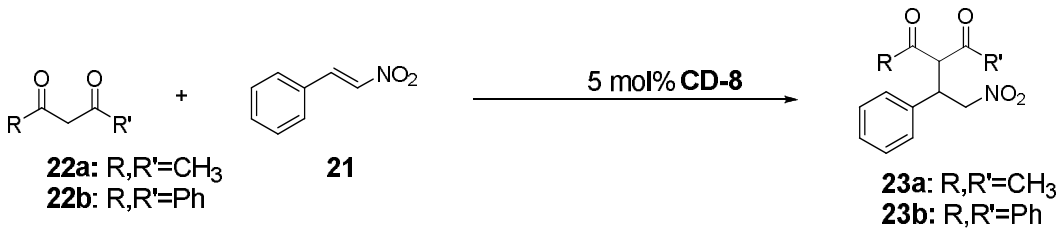
2. Synthesis of cyclodextrin-cinchona thiourea and squaramide and their application as asymmetric organocatalysts in *Michael* reactions

As it was demonstrated above, cinchona-squaramide catalyst gave excellent results in asymmetric *Michael* additions. Our next plan was to attach this valuable catalyst to cyclodextrins (CD), because we can get new catalysts with high molecular weight, which is advantageous in the application of OSN for its recovery. On the other hand, the formation of inclusion complexes between cyclodextrin and the substrates can have benefits in the chiral induction. In order to find the appropriate hydrogen bond donor as the part of catalyst, we planned to prepare thiourea- and squaramide type cyclodextrin-cinchona organocatalysts. The starting material was the cheap and commercially available β-cyclodextrin (**CD-1**). It was successfully converted to CD-cinchona thiourea (**CD-8**) and squaramide (**CD-9**) as it can be seen on **Scheme 6.**. During our work the so-called green synthesis approach was taken into consideration. Only environmentally friendly solvents were used and in some steps (in the synthesis of **CD-2**, **CD-3** and **CD-10**) purification with chromatography was replaced by simple recrystallization.



Scheme 6. Synthesis of CD-cinchona thiourea and squaramide

The test reactions of new organocatalysts **CD-8** and **CD-9** are in progress, but we have already promising preliminary results for the catalysis of *Michael* reaction between 1,3-dioxo compounds (**22a-b**) and β-nitrostyrene (**21**) as it can be seen on **Scheme 7.** and **Table 4.**.



Scheme 7. *Michael* reaction catalyzed by CD-cinchona thiourea

Entry	Dioxo cmpd.	Solvent	Yield (%)	e.e. (%)	Configuration
1	**22a**	MeCN	87	64	(*S*)
2	**22a**	DCM	88	60	(*S*)
3	**22a**	toluene	88	81	(*S*)
4	**22b**	MeCN	95	60	(*S*)
5	**22b**	DCM	43	64	(*S*)
6	**22b**	toluene	95	75	(*S*)

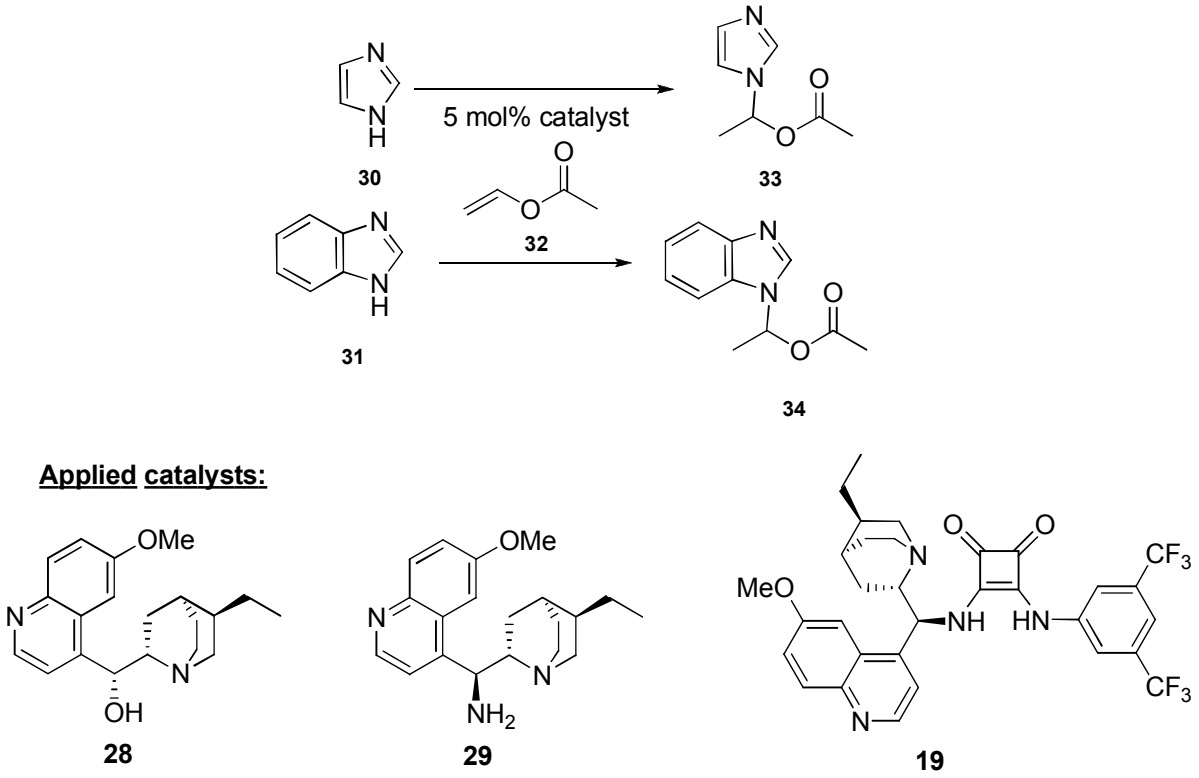
Table 4. Results of *Michael* reactions catalyzed by CD-cinchona thiourea

The catalyst modified CDs are planned to be applied in an organic solvent nanofiltration system at *The University of Manchester, School of Chemical Engineering and Analytical Science*. The manuscript can be only submitted to *Journal of Catalysis* as soon as these measurements are completed.

3. Synthesis of cinchona amine and squaramide derivatives and their application as homogeneous organocatalysts in aza-*Markovnikov* additions

Our aim was not only to synthesize of new type of organocatalyss, but to catalyze new type of important reactions by cinchona alkaloids. Aza-*Markovnikov* additions seemed to be a good reaction type for this purpose. This choice can be explained by the well-known valuable biological activities of the products, the 1-[*N*-(*N*-heterocycle)] alkyl esters that can act as, amongst others, acaricides, antimicrobials, antitumor drugs. Hence, aza-*Markovnikov* addition of *N*-heterocycles to vinyl esters has recently received much attention. Such aza-*Markovnikov* additions were traditionally performed under harsh reaction conditions in which bases, acids and strong heating were usually used to promote the reaction. In order to avoid these disadvantages, application of K_3PO_4 as mild base, ionic liquid as reaction media and catalyst, and acylases as biocatalysts are reported int he literature. In our research work our aim was to develop a new method for efficient synthesis of biological active aza-*Markovnikov* adducts using homogeneous catalysts which can be easily recycle after application. Three cinchona catalysts (**28**, **29** and **19**, see **Scheme 8.**) were tested in aza-*Markovnikov* additions of different *N*-heterocycles [imidazole (**30**), benzimidazole (**31**)] to vinyl acetate (**32**). As a result of the optimization (1.2 eq. vinyl acetate, 50 °C, acetonitrile, 5 mol% **29**, 24 h) imidazole-based aza-

Markovnikov adduct **33** was obtained with 98% yield. The *Sheldon* type E factor, which is defined by the ratio of the mass of waste per mass of product, was reduced in case of adduct **33** from the reported 3.5–7.2 to 1.5, and in case of adduct **34** from the reported 3.6 to 1.8.



Scheme 8. Aza-*Markovnikov* reaction catalyzed by cinchona catalysts

The feasibility of the application of these catalysts was expanded by using OSN technique. PBI membrane was used for separation of molecules. The pore size of membranes was adjusted by their preparation. With the help of OSN technique, organocatalysts **19**, **28** and **29** showed different rejection (**Figure 13.**). So they became recyclable catalysts, furthermore the products of reactions are separable from the reaction mixture.

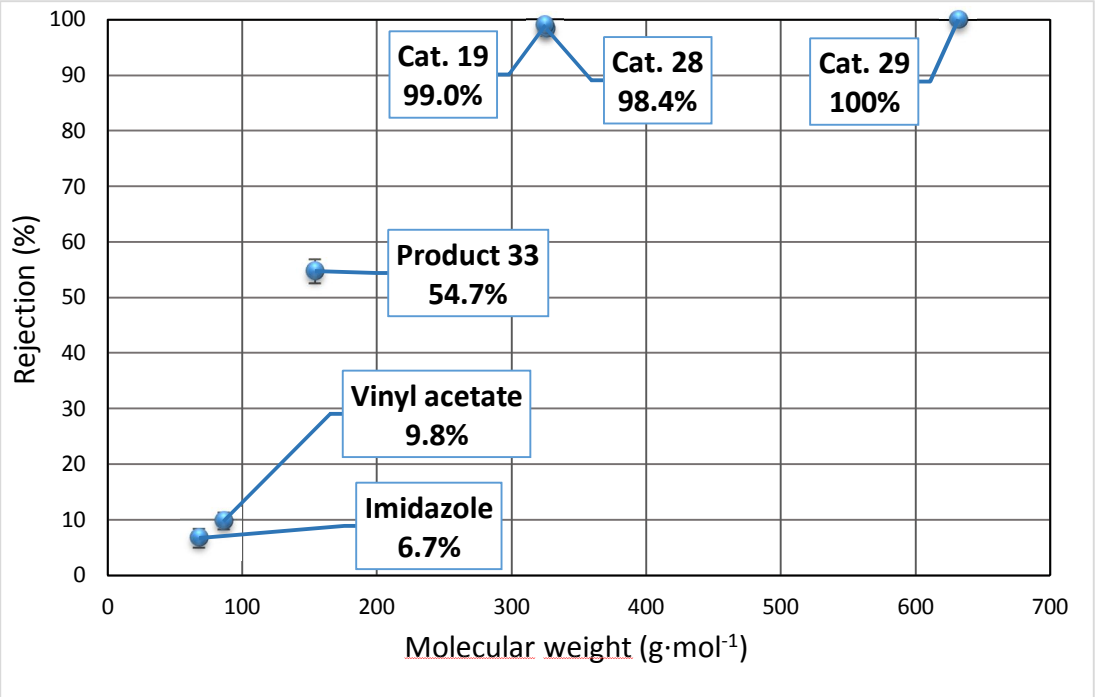
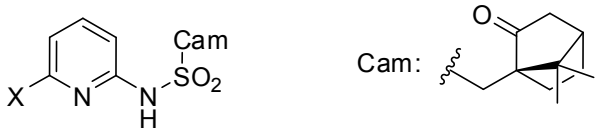


Figure 13. Rejections of product, starting materials and catalysts using OSN technique

Manuscript summarizing the above showed results will be submitted to *RSC Advances* as soon as possible.

4. Synthesis of pyridine- and piperidine camphorsulfonamide derivatives and their application as asymmetric organocatalysts in *Michael* additions

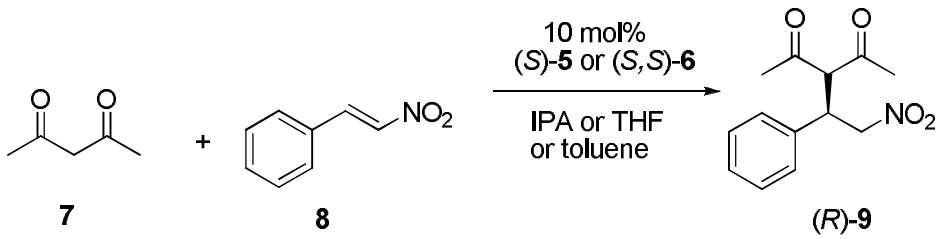
In the beginning of our research we planned to prepare pyridine-based camphorsulfonamide derivatives as it can be read in *Detailed research plan* of my OTKA-PD.
Two new pyridine-based potential asymmetric bifunctional organocatalysts containing one [(*S*)-**35**, see **Figure 14.**] or two camphorsulfonamide units [(*S,S*)-**36**] were synthesized.



(*S*)-**35** (X = CH_3)
or
(*S,S*)-**36** (X = NH_2SO_2Cam)

Figure 14. Structure of pyridine-based camphorsulfonamide derivatives

Asymmetric *Michael* addition of acetylacetone (**22a**) to β-nitrostyrene (**21**) was catalyzed successfully by these catalysts. In case of the monosulfonamide derivate [(*S*)-**35**] the *R* enantiomer of the corresponding *Michael* adduct was formed with appreciable enantiomeric excess in isopropyl alcohol.



Scheme 9. Asymmetric M*ichael* reaction catalyzed by camphorsulfonamides (*S*)-**35** and (*S,S*)-**36**.

Organocatalyst	(*S*)-**35**		(*S,S*)-**36**	
% (mol/mol)	10	10	10	10
Solvent*	THF	IPA	THF	IPA
Yield (%)	36	43	21	27
e.e. [%, (*R*)-**9**]**	racemate	53	racemate	racemate

*: No reaction occurred in toluene.
**: Determined from optical rotations by comparing to the literature value.

Table 5. The results of the preliminary studies using catalyst (*S*)-**35** or (*S,S*)-**36**

Organic solvent nanofiltration was applied successfully for recovery of these organocatalysts. The experimental rejections obtained for catalysts (*S*)-**35** and (*S,S*)-**36** in THF, IPA and toluene (solvents examined in asymmetric *Michael* reactions) at 30 bar using 18PBI and 22PBI (cast from 18 and 22 wt% polybenzimidazole solution) are demonstrated in **Figure 15A.**. The corresponding solvent fluxes are shown in **Figure 15B.**.

In accordance with the expectations, the tighter membranes – cast from 22 wt% PBI solution – have higher catalyst rejection but lower flux values. Due to the larger molecular weight (*S,S*)-**36** has higher rejection compared to (*S*)-**35** in all the tested solvents and membranes. The obtained rejection values also reveal that the rejection difference between the catalysts is smaller for the tighter membranes irrespectively of the solvent. The catalyst rejections vary between 48% and 99%. Efficient catalyst recovery necessitates rejections of virtually 100%. Consequently, both IPA and THF can be used for nanofiltration with 22PBI. Considering the results of the catalyzed asymmetric *Michael* reactions, IPA can be the appropriate solvent for recycling organocatalyst (*S,S*)-**36**.

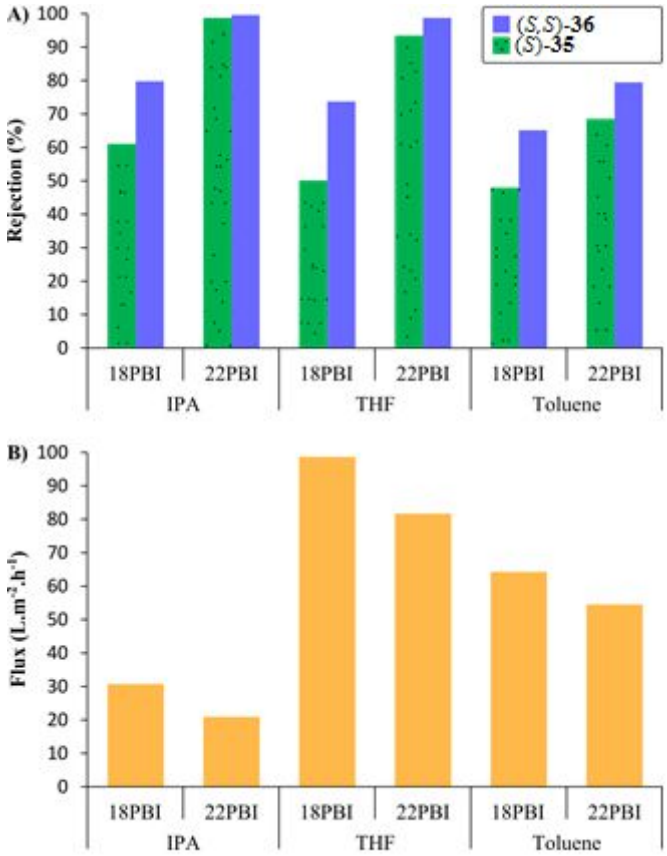
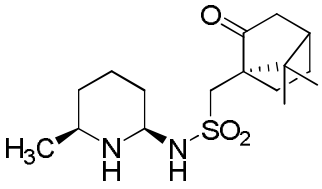


Figure 15. Rejection of organocatalysts on polybenzimidazole membranes at 30 bar (**A**) and the corresponding solvent flux values (**B**).

The above demonstrated results were submitted to *Arkivoc* in 2017, but it was rejected, because one of the referees said that the e.e. values were not enough for publication in this journal. Consequently, we started to reduce pyridine ring of these catalysts to have piperidine based camphorsulfonamides with potentially better catalytic activity. According to our preliminary results, piperidine-camphorsulfonamide (*R,S,S*)-**37** (see **Figure 16.**) is an excellent organocatalyst in the earlier studied (see on **Scheme 9.**) asymmetric *Michael* reaction in different solvents (99.9% e.e. in MTBE, DCM, MeCN, toluene, IPA, cyclohexanol, 94.3% in MeOH, 81.2% in EtOH).



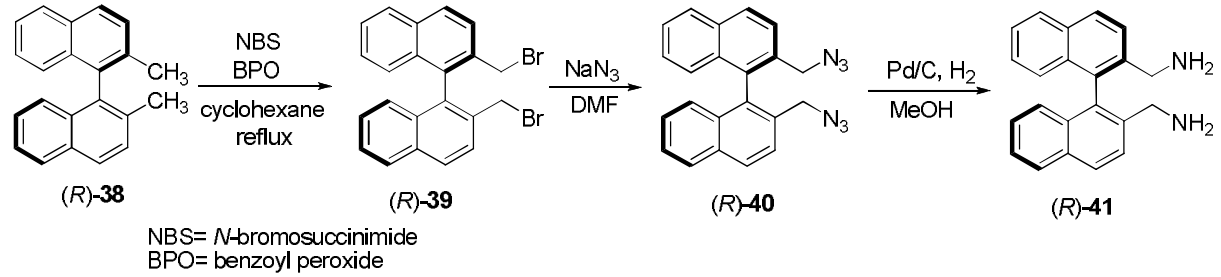
(*R,S,S*)-**37**

Figure 16. Structure of piperidine-based camphorsulfonamide organocatalyst

We plan to recycle piperidine-based camphorsulfonamide organocatalysts using OSN as it was demonstrated in case of pyridine analogues. After successful recovery, we would like to publish our results in *New Journal of Chemistry*.

5. Synthesis of enantiopure, squaramide type organocatalyst containing an axially chiral binaphthyl moiety

We proposed the preparation of a thiourea type organocatalyst containing one or two pyridine rings and a binaphthyl mioety according to the original OTKA-PD plan. As a result of the experiments we collected during our studies on the catalytic activity of thiourea and squaramide derivatives, our new plan was to synthesize a squaramide and binaphthyl containing organocatalyst. Commercially available (*R*)-2,2′-dimethyl-1,1′-binaphthalene [(*R*)-**38**] was brominated. Bisbromomethyl derivative (*R*)-**38** was converted to diazide (*R*)-**39**, that was reduced to diamine (*R*)-**40** (**Scheme 10.**).



Scheme 10. Synthesis of the precursor of binaphthyl-squaramide organocatalysts

The obtained axially chiral diaminomethyl-binaphthyl derivative (*R*)-**40** is the precursor of the potential squaramide type organocatalyst (*R*)-**41** and (*R*)-**42** (**Figure 17.**).

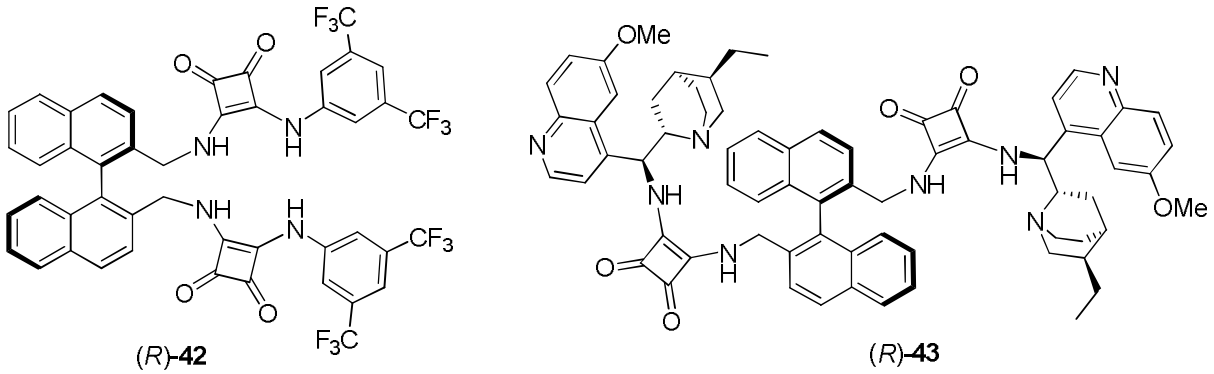


Figure 16. Structure of the planned binaphthyl-squaramide type organocatalysts

After successful preparation organocatalysts will be applied in the earlier showed asymmetric *Michael* reactions.