Report of published results (OTKA-FK138037)

I. Structural modification of cinchona and proline-based organocatalysts

1. 5′-Substituted cinchona catalysts

Following our original research plan, we studied [1] the synthesis of three new asymmetric cinchona-based organocatalysts, with modifications introduced at the underexplored 5'-position of the quinoline ring (**Figure 1.**). Two of the catalysts incorporated squaramide and thiourea H-bond donor groups, while the third combined both an H-bond donor and an enamine moiety to enable dual activation. These catalysts were tested in a pharmaceutically relevant Michael addition reaction leading to a baclofen precursor, as well as in the synthesis of warfarin. The H-bond donor catalysts showed reduced activity compared to established literature examples, with yields ranging from 34%–97% and enantioselectivities of up to 18%, likely due to steric effects and unfavorable spatial positioning. However, the new, bifunctional catalyst demonstrated lower yields (4%–26%) but more promising enantioselectivity (13%–60% ee), suggesting potential for further development. [1]

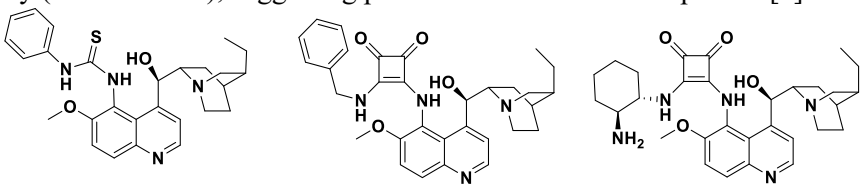


Figure 1.

2. Metal-assisted cinchona hydrogen-bond-donor catalysts

We synthesized cinchona (thio)squaramide and a novel cinchona thiourea organocatalyst functionalized on their C9 positions (**Figure 2.**). These catalysts were employed in pharmaceutically relevant catalytic asymmetric reactions, such as Michael, Friedel–Crafts, and A3 coupling reactions, in combination with Ag(I), Cu(II), and Ni(II) salts. We identified several organocatalyst-metal salt combinations that led to a significant increase in both yield and enantioselectivity. To gain insight into the active catalyst species, we prepared organocatalyst-metal complexes and characterized them using HRMS, NMR spectroscopy, and quantum chemical calculations (B3LYP-D4/def2-TZVP), which allowed us to establish a structure-activity relationship. [2]

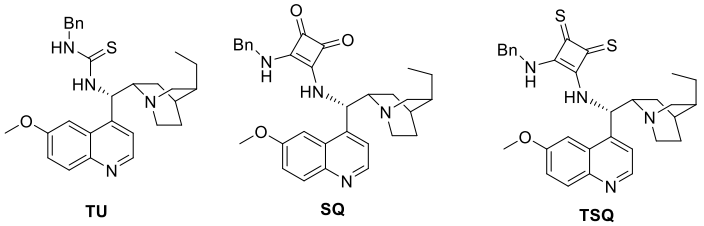


Figure 2.

3. Crown-ether squaramides

We synthesized six new phase-transfer organocatalysts in which the squaramide unit is directly linked to the nitrogen atom of an aza-crown ether (**Figure 3.**). Four chiral skeletons, namely hydroquinine, quinine, cinchonine (cinchonas), and -D-glucopyranoside, were responsible for the asymmetric construction of an all-carbon quaternary stereogenic centre in -alkylation and Michael addition reactions of malonic esters. We investigated the effects of these different chiral units and of crown ethers with different sizes on catalytic activity and enantioselectivity. During extensive parameter investigations, conventional and emerging green solvents were screened, providing valuable-disubstituted malonic ester derivatives with excellent yields (up to 98%). [3]

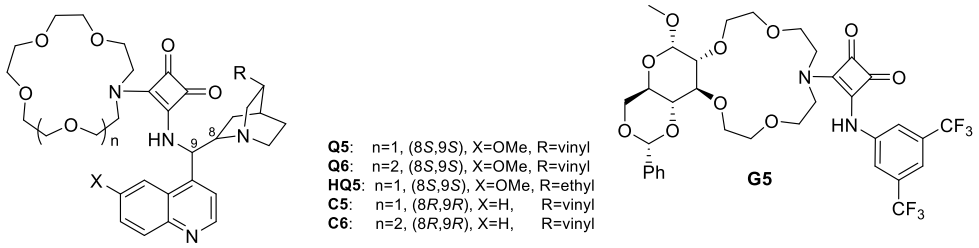


Figure 3.

4. Biological activity of cinchona-derived H-bond-donor catalysts

As part of our research programme on cinchona-derived organocatalysts, we also investigated their biological activity. We supposed that as natural quinine can be applied as an anti-malarial drug and cinchona alkaloids and their derivatives have been exhaustively studied for their biological activity, the investigation of their anticancer activity would result in an interesting and useful study. Therefore, we tested 13 cinchona alkaloid organocatalysts synthesised from quinine. These derivatives were screened against MES-SA and Dx5 uterine sarcoma cell lines for in vitro anticancer activity and to investigate their potential to overcome P-glycoprotein (P-gp) mediated multidrug resistance (MDR). Based on the results, cinchona derivatives are good anticancer candidates for further drug development. [4]

5. Proline-derived (thio)squaramides

We prepared chiral proline-derived squaramide and thiosquaramide organocatalysts, which are capable of dual activation in asymmetric reactions (**Figure 4.**). The (thio)squaramide moiety can form hydrogen bonds to activate the substrates and stereocontrol the reaction, while the pyrrolidine unit can form enamines to activate carbonyl compounds via aminocatalysis. Comparing the performance of thiosquaramide to squaramide, the Diels–Alder reaction of (anthracene-9 yl)acetaldehyde and trans-β-nitrostyrene was examined, which has been investigated in the literature using quantum chemical calculations. Both squaramide and thiosquaramide gave excellent yields (up to 99%) and enantiomeric excess values (up to 98%). Moreover, their catalytic performance was compared in conjugate addition of lawsone to β,γ-unsaturated α-keto ester. [5]

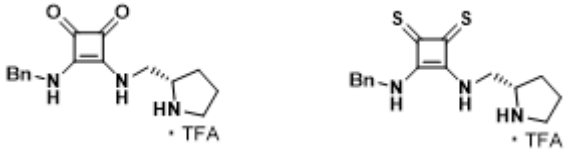


Figure 4.

II. Making organocatalytic reactions more sustainable

1. Recycling of lipophilic organocatalyst by solvent exchange

Following the research plan of our grant, we demonstrated the synthesis, application, and recycling of a new lipophilic cinchona squaramide organocatalyst. The synthesized lipophilic organocatalyst (**Figure 5.**) was applied in Michael additions. The catalyst was utilized to promote the Michael addition of cyclohexyl Meldrum's acid to 4-chloro-trans-β-nitrostyrene (quantitative yield, up to 96% ee). Moreover, 1 mol% of the catalyst was feasible to conduct the gram-scale preparation of baclofen precursor (89% yield, 96% ee). Finally, thanks to the lipophilic character of the catalyst, it was easily recycled after the reaction by replacing the non-polar reaction solvent with a polar solvent, acetonitrile, with 91–100% efficiency, and the catalyst was reused in five reaction cycles without the loss of activity and selectivity. [6]

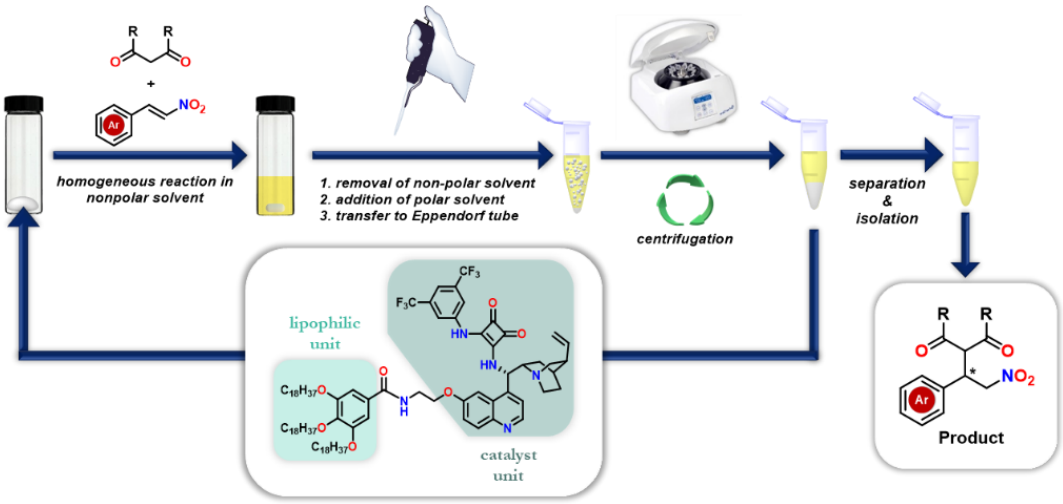


Figure 5.

2. MeSesamol: a bio-based polar aprotic solvent

Applications of polar aprotic solvents are inevitable in the chemical industry, but few non-hazardous alternatives are available. We developed methyl sesamol (MeSesamol) as a promising new bio-based alternative for polar aprotic solvents and demonstrated its versatile applications. MeSesamol was derived from natural resources using environmentally friendly and facile procedures, such as methylation using dimethyl carbonate. MeSesamol has a distinctive smell and demonstrates excellent properties as a green solvent candidate: high boiling and open-cup flash points, immiscibility with water but miscibility with common organic solvents, high stability, and resistance to several acids and bases. MeSesamol was an effective solvent in nine C–C coupling reactions, including the Suzuki and Sonogashira reactions and asymmetric Michael addition. MeSesamol lies close to dichloromethane (DCM) in Hansen space and achieves a similar or higher yield and enantiomeric excess (up to 97% and 99%, respectively) in the asymmetric Michael reactions compared to DCM. MeSesamol proved to be an excellent recyclable solvent in the depolymerizations of BPA–PC and PET (**Figure 6.**). MeSesamol was recycled in five reaction cycles with excellent efficiency (92%–100%) and outstanding cumulative monomer yields (92% bisphenol-A from BPA–PC and 92% terephthalic acid from PET). [7]

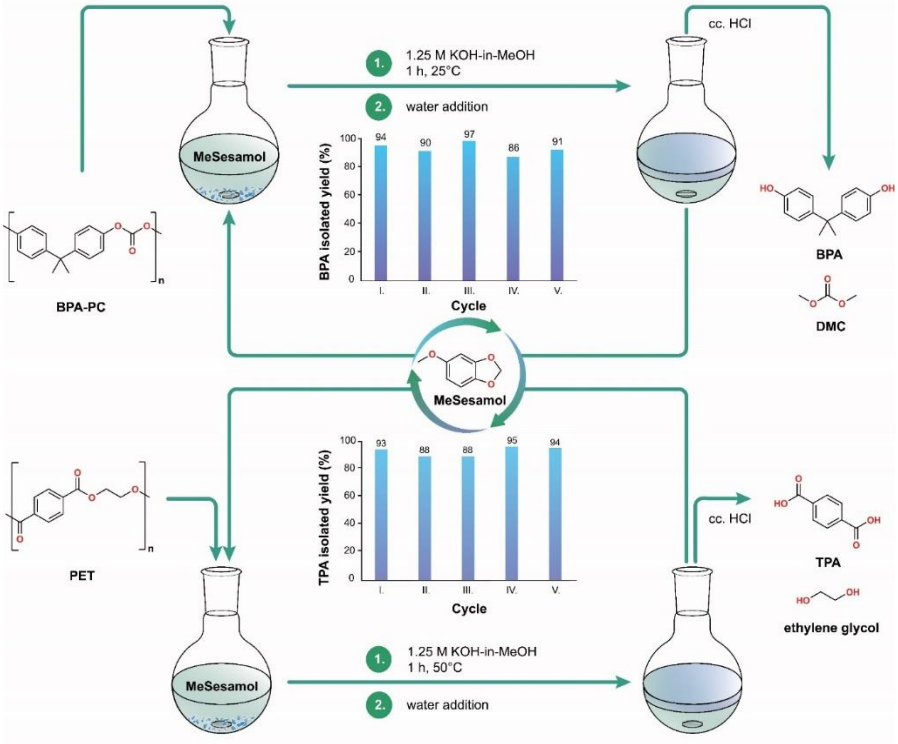


Figure 6.

III. Recyclable heterogeneous organocatalysts for polymer depolymerization

1. PET glycolysis using silica-supported organocatalysts

In our original research plan, we aimed to modify cellulose with different organocatalysts and apply them in asymmetric aldol reactions. Therefore we oxidized the hydroxymethyl groups of cellulose to carboxy groups, and L-prolinamine was immobilized on the surface. Furthermore, we got a similarly modified cellulose catalyst with a three-carbon atom containing a linker: L-prolinamine was reacted with 3-chloropropanoic acid modified cellulose in a coupling reaction. Both catalysts were applied in aldol reactions, however, only racemic products formed. Therefore we tried another commercially available solid support for organocatalyst functionalization, the silica gel, and later we aimed to apply the modified silicas for catalytic glycolytic reactions. We tested four organocatalyst-modified silica gels (**Figure 7.**) in the glycolysis of PET. The applied heterogeneous modified silica gels were recovered easily by filtration. Si-TEA catalyst was chosen for reaction optimisation because it has the highest thermal stability and good catalytic activity. The PET glycolysis process was optimised by fractional factorial experimental design and response surface methodology. Under optimal reaction conditions, 88.5% non-isolated bis(2-hydroxyethyl) terephthalate (BHET) monomer yield was obtained. Si-TEA and Si-TBD catalysts were recycled in five reaction cycles, and with both catalysts, high cumulative BHET yields (89 and 88%, respectively) were achieved. Additionally, environmental energy impacts were calculated for the two catalysts and were compared favourably with other organocatalysts in the literature. A process scale-up was also implemented. Finally, it has been verified that modified silica gels have much higher catalytic activities than native silica gel, as solvolytic reactions using the former catalysts took a significantly shorter time. , the stabilities of Si-TEA and Si-TBD catalysts were further investigated by HS-GC-MS, and only a small amount of amines were detected as decomposition products in the case of Si-TEA. After a 4-hour glycolysis reaction under optimized conditions, we detected a very low amount of different amines (triethylamine, diethylmethylamine, diethylamine) compared to a triethylamine reference, which contained 5% of the TEA amount grafted on the silica gel. [8]

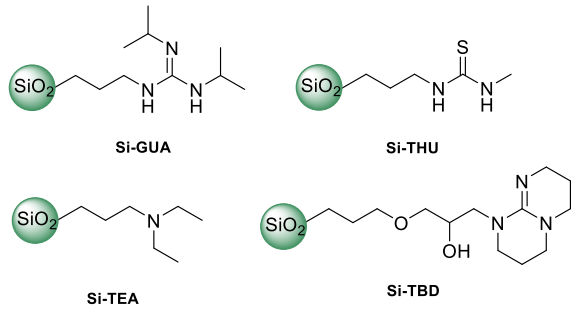


Figure 7.

2. Polycarbonate methanolysis under mild conditions

As a continuation of our work on modified silica gels for PET glycolysis and catalyst recovery, we extended the approach to the depolymerization of another polymer. The study focused on the depolymerization of poly(bisphenol A carbonate) (BPA-PC), an engineering plastic with the monomer bisphenol A (BPA), a known xenoestrogen. Improving BPA-PC recycling is crucial to prevent the release of BPA into the environment. Our investigation centred on three commercially available organocatalyst-modified silica gels in polycarbonate (PC) methanolysis, alongside one functionalized with TBD, previously reported for PET glycolysis. The latter Si-TBD, among these catalysts, exhibits superior catalytic activity in PC methanolysis. The PC methanolysis process was optimised economically by experimental design. Under optimal reaction conditions (PC: 2.00 g, methanol (n(MeOH):n(PC) = 13:1), Si-TBD: 5 mol%, 65 °C, 2 h), 96% non-isolated BPA monomer yield was obtained. The kinetics of the reaction reveals that the Si-TBD-catalysed PC methanolysis is a pseudo-first-order reaction with an exceptionally low activation energy of 44.19 kJ mol−1, the lowest reported to date. Si-TBD was recycled in ten reaction cycles after regeneration, (**Figure 8.**) and even though the regenerated catalyst has slightly lower activity than the native catalyst, good BPA yields (72 ± 4%) were achieved consistently. Investigations into the necessity of an inert atmosphere during catalyst recycling indicate that it is not required. Impressively, Si-TBD demonstrates the ability to depolymerize PC even at room temperature,

without stirring, in 2 days, with an excellent BPA yield (94%). Notably, this catalyst offers similar performance at lower temperature than others reported in the literature for PC methanolysis [9].

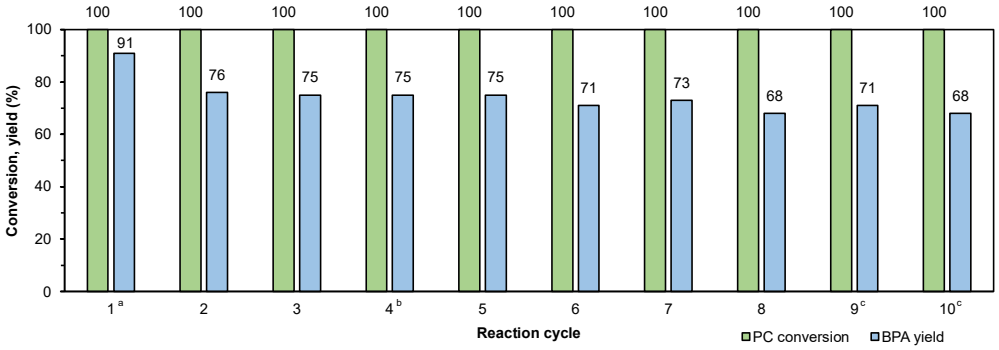


Figure 8.

Building on the experience gained in functionalizing solid supports with organocatalysts, we also prepared a review of the key parameters governing the performance of immobilized organocatalysts. The review addressed the influence of support type, immobilization strategy, and support–catalyst interactions on catalytic activity, selectivity, and recyclability, providing guidelines for the design and optimization of heterogeneous organocatalytic systems for practical applications. [10]

3. Electrosynthesis of FDCA and PEF depolymerization

We extended the project towards the valorization of bio-based platform molecules by developing an electrochemical route from 5-hydroxymethylfurfural (HMF) to 2,5-furandicarboxylic acid (FDCA). In our study, we derived 2,5-Furandicarboxylic acid (FDCA) that is a promising platform molecule from 5-hydroxymethyl furfural (HMF) via sustainable electrochemical oxidation. We demonstrated TEMPO-mediated electrooxidation of HMF to FDCA in ElectraSyn 2.0 using inexpensive commercially available electrodes: graphite anode and stainless-steel cathode, thereby avoiding the often cumbersome electrode preparation. Key parameters such as concentration of HMF, KOH, and catalyst loading were optimized by experimental design. Under the optimized conditions, using only a low amount of TEMPO (5 mol%), high yield and Faradaic efficiency of 96% were achieved within 2.5 hours. Moreover, since FDCA is a monomer of the bio-based poly(ethylene furanoate), PEF, we aimed to investigate its recovery by depolymerization, which could be of paramount importance in the circular economy of the FDCA. For this, our new polar aprotic solvent, (MeSesamol, was also used, allowing the facile depolymerization of PEF at room temperature with high monomer yields (up 0to 85%), while the cosolvent MeSesamol was recycled with high efficiency (95–100%) over five reaction cycles (**Figure 9.**). [11]

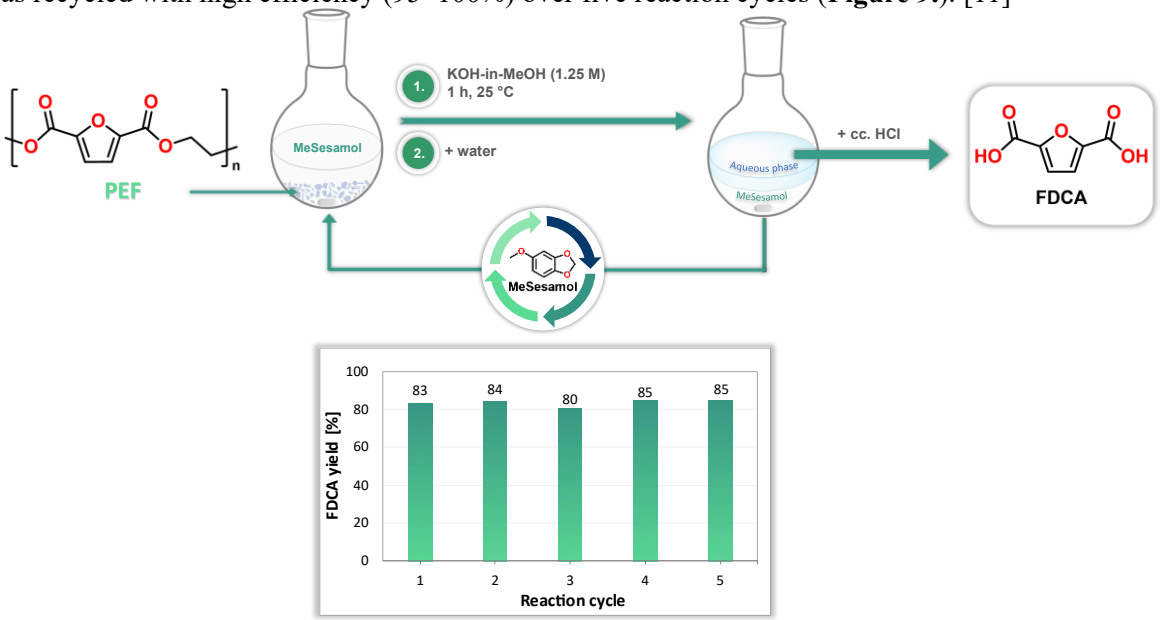


Figure 9.

IV. Development of a photocatalytic C-alkylation in a 3D-printed photoreactor

We investigated the use of the metal-free photocatalyst 4CzIPN for visible-light-mediated carbon–carbon bond formation between CH-acidic substrates and alkenes under mild and sustainable conditions (**Figure 10.**). A custom 3D-printed photoreactor was employed to ensure reproducibility and allow systematic optimization using design of experiments (DoE). Methyl cyanoacetate was chosen as a model substrate, and optimization revealed temperature and substrate ratio as the most influential factors, achieving a 91% yield under mild deoxygenation with argon. While the optimized conditions applied less effectively to other substrates, the method was successfully adapted to continuous flow, offering a pathway to scalable synthesis. To assess sustainability, we introduced a new energy economy factor, εphoto, which accounts for cooling requirements and enables more meaningful comparisons of photochemical efficiency on different systems. [12]

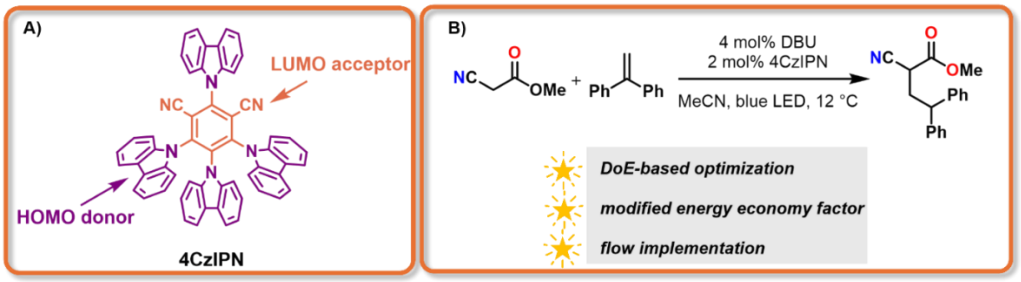


Figure 10.

V. Development and applications of carbohydrate-based macrocycles

Previously, it was proved that the carbohydrate moiety affects the catalytic activity of sugar-based macrocycles. To get more information about the effect of the sugar unit, a rare monosaccharide, D-idose was incorporated into the crown structure. Using methyl 4,6-*O*-benzylidene-α- and -β-D-idopyranoside, which were synthesized from D-galactose, five novel crown compounds were prepared (**Figure 11**.). The efficiency of these idopyranoside-based macrocycles was investigated in asymmetric phase transfer reactions. In liquid-liquid biphasic reactions (Darzens condensation and epoxidation) the highest enantioselectivity was 81% ee, while in solid-liquid phase systems (Michael addition and Michael initiated ring closure) the highest asymmetric induction was 67% ee. It was observed that the enantiodiscrimination was strongly dependent on the configuration of the anomeric center, on the side arm of the nitrogen, and on the structure of the substrate. [13]

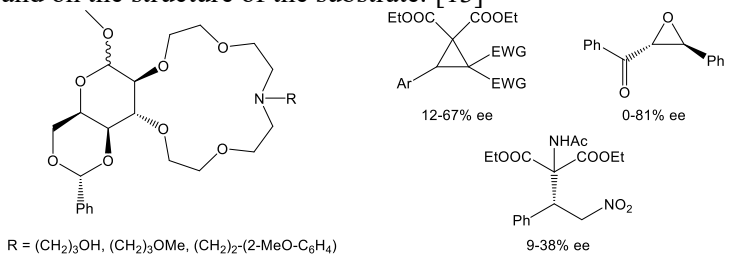


Figure 11.

Using D-glucopyranosides, containing a propargyloxy group attached to the anomeric center or a 4-(propargyloxy)benzylidene protecting group, different monoaza-15-crown-5 ethers were prepared. In addition, a glucose-based crown catalyst was modified on the side chain of the nitrogen, and a propargyl group was introduced. The triple bond was used to bind these catalysts to a stationary phase (PVC modified with azide functions, **Figure 12.**). The immobilized crown ethers were tested in asymmetric reactions. It was found that glucose-based crown ether bearing the propargyl group on the benzylidene unit and grafted to PVC in 4% has the highest activity regarding the enantioselectivity (77% ee). The catalyst was recoverable in the Michael addition of diethyl acetamidomalonate to nitrostyrene and it could be reused five times without the loss of enantioselectivity. [14]

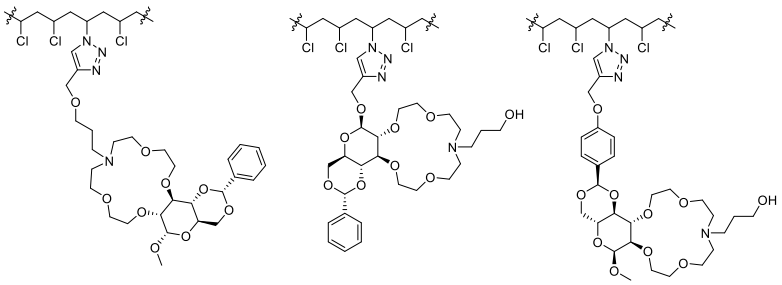


Figure 12.

Macrocycles derived from threitol and tartaric acid were synthesized with similar structure, and their catalytic activity and reusability were tested and compared in different model reactions along with some previously prepared compounds (**Figure 13.**). None of the crown ethers contained acid-sensitive protecting group, thus, the recovery was performed via formation of hydrochloric acid salt. The enantiomeric excess varied widely when the catalysts were tested in asymmetric phase-transfer model reactions. We showed that the recoverability of the examined crown ethers and the enantiomeric excess generated tends to decrease along with the amount of recovered catalyst. [15]

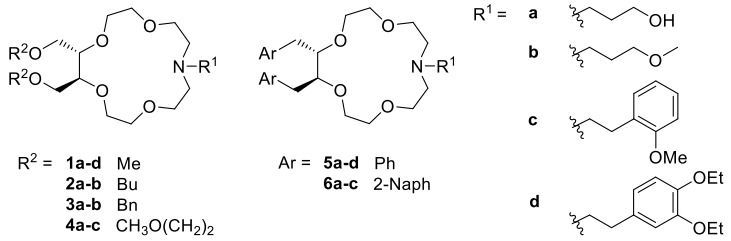


Figure 13.

D-Mannose was previously incorporated into the crown structure. Their catalytic activity was tested mainly in Darzens condensation and epoxidation of chalcone. A few novel monoaza-15-crown-5 ethers have been synthesized with an α-D-mannopyranoside backbone and with different heteroaromatic side chains, which have never been incorporated in sugar-based crown ethers before (**Figure 14.**). The novel crown compounds and a few previously synthesized mannose-based lariat ethers were tested in four asymmetric phase-transfer cyclopropanations. The reactions proceeded mainly with excellent yields (up to 99%), while enantiomeric excesses varied between 1–44%, showing that the mannose-based lariat ethers are moderate enantioselective catalysts in these reactions. [16]

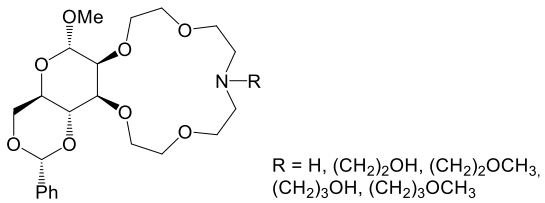


Figure 14.

Carbohydrate-based crown ethers were tested in Michael additions of P-H acidic compounds. The products formed in these reactions may have biological activity. At most, low enantioselectivity could be reached in the presence of chiral crown compounds. The asymmetric induction appeared to be independent of catalyst, solvent, base, and temperature. While the literature was studied to obtain information on the possible explanations for the ineffectiveness, a review was written on this topic. [17]

Finally, enantioenriched, highly functionalized cyclopropane derivatives were prepared using monosaccharide-based chiral crown ethers as phase transfer catalysts. The Michael-initiated ring closure (MIRC) reactions of diethyl bromomalonate with 2-cyano-3-phenylacrylate took place with complete diastereoselectivity in the presence of chiral lariat ethers derived from carbohydrates and enantioselectivity up to 87 % ee was achieved. In the reactions of analogous 2-cyano-3-arylacrylates, enantioselectivity was in the range of 8–91 % ee. [18]

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6) Kis, D.; Dargó, G.; Székely, G.; Kupai, J.: Development and application of a new, bio-based solvent, 10th European Young Engineers Conference, online, Varsó, Lengyelország, 2022. április 4–6., oral presentation
7) Kiss, J.; Fehér, Z.; Kisszékelyi, P.; Nagy, S.; Kárpáti, L.; Huszthy, P.; Kupai, J.: Optimization of PET chemical recycling, 10th European Young Engineers Conference, online, Varsó, Lengyelország, 2022. április 4–6., poster presentation
8) Németh, R.; Richter, D.; Nagy, S.; Dargó, G.; Huszthy, P.; Bagi, P.; Kupai, J.: Synthesis of cinchona-thiourea or (thio)squaramide organocatalysts and their application in A reactions combined with transition metals, 10th European Young Engineers Conference, online, Varsó, Lengyelország, 2022. április 4–6., oral presentation
9) Richter, D.; Németh, R.; Nagy, S.; Dargó, G.; Huszthy, P.; Bagi, P.; Kupai, J.: Application of transition metals combined with cinchona organocatalysts, 10th European Young Engineers Conference, online, Varsó, Lengyelország, 2022. április 4–6., oral presentation
10) Erdélyi, D.; Dargó, G.; Molnár, B.; Bagi, P.; Kisszékelyi, P.; Fehér, Z.; Huszthy, P.; Kupai, J.: Lipofil organokatalizátorok alkalmazásának és visszaforgatásának vizsgálata aszimmetrikus szintézisekben, XV. Szent-Györgyi Albert Konferencia, Budapest, 2022. április 29–30., oral presentation
11) Fehér, Z.; Kiss, J.; Kisszékelyi, P.; Kárpáti, L.; Huszthy, P.; Kupai, J.: PET lebontása szilikagélhez rögzített organokatalizátorokkal, XV. Szent-Györgyi Albert Konferencia, Budapest, 2022. április 29–30., oral presentation
12) Kis, D.; Dargó, G.; Székely, G.; Kupai, J.: Metilszezamol: egy új természetes alapú oldószer fejlesztése és alkalmazása, Szent-Györgyi Albert Konferencia, Budapest, 2022. április 29–30., oral presentation
13) Kiss, J.; Fehér, Z.; Kisszékelyi, P.; Nagy, S.; Kárpáti, L.; Huszthy, P.; Kupai, J.: Poli(etilén-tereftalát) glikolízisének optimalizálása, Szent-Györgyi Albert Konferencia, Budapest, 2022. április 29–30., poster presentation
14) Richter, D.; Dargó, G.; Németh, R.; Huszthy, P.; Nagy, S.; Kupai, J.: Cinkona-alkaloid-alapú organokatalizátorok és átmeneti fémsók kombinált alkalmazása aszimmetrikus reakciókban, XV. Szent-Györgyi Albert Konferencia, Budapest, 2022. április 29–30., oral presentation
15) Dargó, G.; Molnár, B.; Erdélyi, D.; Bagi, P.; Kisszékelyi, P.; Huszthy, P.; Kupai, J.: Lipofil cinkona organokatalizátor szintézise, alkalmazása és visszaforgatása XXV. Tavaszi Szél Konferencia, Pécs, 2022. május 6–8., oral presentation
16) Fehér, Z.; Kiss, J.; Kisszékelyi, P.; Kárpáti, L.; Huszthy, P.; Kupai, J.: Heterogén organokatalizátorok alkalmazása PET glikolitikus lebontásában, XXV. Tavaszi Szél Konferencia, Pécs, 2022. május 6–8., oral presentation
17) Kiss, J.; Fehér, Z.; Kárpáti, L.; Kisszékelyi, P.; Huszthy, P.; Kupai, J.: Poli(etilén-tereftalát) fenntartható lebontása szilikagélhez rögzített organokatalizátorok segítségével, Heterociklusos és Elemorganikus Kémiai Munkabizottság ülése, Balatonszemes, 2022. május 23–25., oral presentation

18) Kupai, J.; Dargó, G.; Erdélyi, D.; Molnár, B.; Bagi, P.; Huszthy, P.; Kisszékelyi, P.: Cinkona organokatalizátor alkalmazása és visszaforgatása lipofil oldallánc beépítésének segítségével Heterociklusos és Elemorganikus Kémiai Munkabizottság ülése, Balatonszemes, 2022. május 23–25. (oral presentation)
19) Kupai, J.; Feher, Z.; Nagy, S.: Synthesis and application of a cinchona squaramide organocatalyst immobilized on poly(glycidyl methacrylate), XIII Young Investigator Workshop, EuChemS Division of Organic Chemistry, Lisszabon, Portugália, 2022. szeptember 3. (oral presentation, meghívott előadó)
20) Rapi, Zs.: Carbohydrate-based crown ethers, 3rd Global Virtual Summit on Catalysis & Chemical Engineering, 2022.09.13, online.
21) Kis, D.; Dargó, G.; Székely, G.; Kupai, J.: Egy új, természetes alapú oldószer fejlesztése és alkalmazása, XLV. Kémiai Előadói Napok, Szeged, 2022. október 25–27., oral presentation
22) Németh, R.; Fehér, Z.; Kiss, J.; Kupai, J.; Polikarbonát bontása szilikagélhez rögzített organokatalizátorral, XLV. Kémiai Előadói Napok, Szeged, 2022. október 25–27., oral presentation
23) Richter, D.; Dargó, G.; Németh, R.; Huszthy, P.; Nagy, S.; Kupai, J.: Cinkonaalkaloid organokatalizátorok és átmenetifémek in situ képzett komplexeinek alkalmazása aszimmetrikus reakciókban, XLV. Kémiai Előadói Napok, Szeged, 2022. október 25–27., oral presentation
24) Orbán, I., Bakó, P., Rapi, Zs.: D-Idopiranozid-alapú lariát koronaéterek előállítása és alkalmazásuk enantioszelektív reakciókban, Kémiai Előadói Napok, 2022.10.26., Szeged.
25) Dargó, G.; Erdélyi, D.; Molnár, B.; Garádi, Z.; Huszthy, P.; Kisszékelyi, P.; Bagi, P.; Kupai, J.: Synthesis, application, and recycling of lipophilic chiral organocatalyst, XXVIII. Nemzetközi Vegyészkonferencia, Nagyvárad, Románia, 2022. október 27–29., oral presentation
26) Kiss, J.; Fehér, Z.; Kisszékelyi, P.; Kárpáti, L.; Kupai, J.: A PET glikolízisének optimalizálása, XXVIII. Nemzetközi Vegyészkonferencia, Nagyvárad, Románia, 2022. október 27–29., poster presentation
27) Németh, R.; Fehér, Z.; Kiss, J.; Kupai, J.: Polikarbonát bontása szilikagélhez rögzített organokatalizátorral, XXVIII. Nemzetközi Vegyészkonferencia, Nagyvárad, Románia, 2022. október 27–29., poster presentation
28) Richter, D.; Németh, R.; Dargó, G.; Nagy, S.; Huszthy, P.; Mátravölgyi, B.; Kupai, J.: Fémmel kombinált cinkona organokatalizátorok szintézise és alkalmazása aszimmetrikus reakciókban, XXVIII. Nemzetközi Vegyészkonferencia, Nagyvárad, Románia, 2022. október 27–29., oral presentation
29) Kis, D., Dargó, Gy., Kupai, J., Székely, Gy.: Development and application of a new, bio-based solvent, 11th European Young Engineers Conference, Varsó, 2023. április 17-19.
30) Erdélyi, D., Dargó, Gy., Molnár, B., Bagi, P., Huszthy, P., Kisszékelyi, P., Garádi, Z., Kupai, J.: *Investigation of application and recycling of lipophilic organocatalyst in asymmetric syntheses, 11th European Young Engineers Conference, Varsó, 2023. április 17-19.
31) Kiss, J., Fehér, Zs., Kisszékelyi, P., Kárpáti, L., Kupai, J.: Scale-up of PET glycolysis process applying recyclable catalysts, 11th European Young Engineers Conference, Varsó, 2023. április 17-19.
32) Németh, R., Fehér, Zs., Kiss, J., Kupai, J.: Optimization for polycarbonate methanolysis applying a recyclable heterogeneous organocatalyst, 11th European Young Engineers Conference, Varsó, 2023. április 17-19.
33) Kis, D., Dargó, Gy., Kupai, J., Székely, Gy.; Egy új, alternatív oldószer szintézise és alkalmazása, XVI. Szent-Györgyi Albert Konferencia, Budapest, 2023. április 21-22.
34) Kiss, J., Fehér, Zs., Kupai, J.: Poli(etilén-tereftalát) visszaforgatható organokatalizátorokkal történő glikolízisének méretnövelése, XVI. Szent-Györgyi Albert Konferencia, Budapest, 2023. április 21-22.
35) Németh, R., Fehér, Zs., Kiss, J., Dr. Kupai, J. Polikarbonát metanolízise visszaforgatható katalizátorral és annak optimalizálása, XVI. Szent-Györgyi Albert Konferencia, Budapest, 2023. április 21-22.
36) Erdélyi, D., Dargó, Gy., Molnár, B., Bagi, P., Kisszékelyi, P., Kupai, J.: Lipofil cinkona-négyzetamid organokatalizátor visszaforgatása és felhasználása a baklofen királis intermedierjének előállítására, XVI. Szent-Györgyi Albert Konferencia, Budapest, 2023. április 21-22.
37) Dargó, Gy., Kis, D., Székely, Gy., Kupai, J. Egy új természetes alapú oldószer szintézise és alkalmazása, XXVI. Tavaszi Szél Konferencia, Miskolc, 2023. május 5–7.
38) Fehér, Z.; Németh, R.; Kiss, J.; Kupai, J.: Polikarbonát depolimerizációjának optimalizálása szilikagélhez rögzített organokatalizátorral, XXVI. Tavaszi Szél Konferencia, Miskolc, 2023. május 5–7.

39) Fehér, Z.; Kiss, J.; Németh, R.; Kupai, J.: Poli(etilén-tereftalát) és polikarbonát szolvolitikus depolimerizációja heterogén katalizátorok alkalmazásával, MTA Heterociklusos és Elemorganikus Kémiai Munkabizottság ülése, Balatonszemes, 2023. május 31.–június 2.
40) Kupai, J., Dargó, Gy., Kis, D., Székely, Gy.: Egy új, biomassza-alapú poláris aprotikus oldószer kifejlesztése, MTA Heterociklusos és Elemorganikus Kémiai Munkabizottság ülése, Balatonszemes, 2023. május 31.–június 2.
41) Dargó, Gy.: Lipofil cinkona-négyzetamid organokatalizátor előállítása, alkalmazása és visszaforgatása a baklofen szintézisében, BME Szerves és Gyógyszerkémiai Nap, Budapest, 2023. június 30.
42) Dargó, Gy., Erdélyi, D., Molnár, B., Bagi, P., Kisszékelyi, P., Kupai, J.: Lipofil, cinkonaalapú organokatalizátor alkalmazása és visszaforgatása a baklofen szintézisében, 4. MKE Nemzeti Konferencia, Eger, 2023. július 10–12., poster presentation
43) Varga, B., Rapi, Zs.: Ciklopropanálási reakciók vizsgálata aszimmetrikus fázistranszfer katalitikus körülmények között – poster presentation, MKE 4. Nemzeti Konferencia, 2023. július 10-12., Eger.
44) Dargó, Gy., Kis, D., Martin Gede, Székely, Gy., Kupai, J.: MeSesamol, a new, bio-based polar aprotic solvent with versatile applications, International Symposium on Synthesis and Catalysis, Évora, Portugal, 2023. szeptember 5–8.
45) Fehér, Z.; Németh, R.; Kiss, J.; Kupai, J.: Depolymerisation of polycarbonate applying silica gel-supported organocatalysts, International Symposium on Synthesis and Catalysis, Évora, Portugália, 2023. szeptember 5–8.
46) Gémes, G.; Richter, D.; Kisszékelyi, P.; Kupai, J.; Fotokatalitikus rendszerek fejlesztése szén-szén kapcsolások kivitelezésére, XLVI. Kémiai Előadói Napok, 2023. október 19., oral presentation
47) Dargó, Gy.: Természetes alapú vegyületek sokszínű alkalmazása katalízisben, Kajtár–Hollósi Alapítvány Emlékülés, 2023. november 24.
48) Fehér, Zs. A PET glikolízisének optimalizálása visszaforgatható heterogén organokatalizátorok alkalmazásával Kisfaludy Lajos Alapítvány előadóülése Richter Gedeon Nyrt. 2023. november 28.
49) Kupai, J. Organokatalizátorok fenntartható alkalmazása, Zemplén Géza Díj előadóülés, 2023. december 6.
50) Dargó, Gy. Egy új, természetes alapú oldószer szintézise és alkalmazása Patonay Tamás előadóülés, 2023. december 8.
51) Gémes, G.; Richter, D.; Kisszékelyi, P.; Kupai, J.; Development of photocatalytic systems for C-C bond formation reactions, 12th European Young Engineers Conference, Varsó, 2024. április 7–9., oral presentation
52) Kis, D., Dargó, Gy., Kupai, J. Sonogashira reactions in MeSesamol, a new bio-based solvent 12th European Young Engineers Conference, Varsó, 2024. április 7–9., oral presentation
53) Erdélyi, D., Dargó, Gy., Richter, D., Kupai, J., Synthesis and application of cinchona-based organocatalyst 12th European Young Engineers Conference, Varsó, 2024. április 7–9., oral presentation
54) Rapi, Zs.: Carbohydrate-based crown ethers in asymmetric syntheses, European Journal of Organic Chemistry Society Award 2023 Virtual Event, 2024.04.10, online.
55) Gémes, G.; Richter, D.; Kisszékelyi, P.; Kupai, J.; Fotokatalitikus rendszerek fejlesztése és alkalmazása C-alkilezési reakciókban, XVII. Szent-Györgyi Albert Konferencia, Budapest 2024. április 26–27. oral presentation
56) Varga, B., Rapi, Zs.: Visszaforgatható szénhidrátalapú koronaéterek vizsgálata enantioszelektív katalizátorként – oral presentation, MKE Vegyészkonferencia, 2024. június 10-12., Eger.
57) Orbán, I., Ujj, D., Rapi, Zs.: D-Mannózalapú királis koronaéterek szintézise és katalizátorként való alkalmazása, MKE Vegyészkonferencia, 2024.06.10-12., Eger.
58) Dargó, Gy., Kis, D., Ráduly, A., Kupai, J. FDCA körkörös gazdasága: elektroszintézis és polietilén-furanoát depolimerizációja, Heterociklusos és Elemorganikus Kémiai Munkabizottság ülése, Balatonszemes, 2024. június 12 – 14.
59) Kupai, J., Fehér, Zs., Kiss, J., Németh, R. Polikarbonát szolvolitikus depolimerizációja heterogén katalizátorok alkalmazásával Heterociklusos és Elemorganikus Kémiai Munkabizottság ülése, Balatonszemes, 2024. június 12–14.
60) Gémes, G.; Richter, D.; Kisszékelyi, P.; Kupai, J.; Fotokatalitikus rendszerek fejlesztése és optimalizálása szén–szén kapcsolási reakciókban, XXX. Vegyészkonferencia, Kolozsvár, 2024. október 24–26. oral presentation

61) Richter, D.; Erdélyi, D.; Dargó, Gy.; Hegedűs, L.; Kupai, J. The modification of the cinchona frame at a new position for the development of organocatalysts, 30th International Conference on Chemistry, Cluj-Napoca, Románia, 2024. 10. 23-26., oral presentation
62) Gémes, G.; Richter, D.; Kisszékelyi, P.; Kupai, J.; Organo-fotokatalitikus rendszerek alkalmazása C-alkilezési reakciók fejlesztésére, XLVII. Kémiai Előadói Napok, Szeged 2024. október 29–31. oral presentation
63) Richter, D.; Gémes, G.; Hangya, K.I.; Kisszékelyi, P.; Kupai, J. Organo-fotokatalitikus C-alkilezési reakciók fejlesztése, Antus Sándor Emlékülés, Debrecen, 2025.01.24., oral presentation
64) Richter, D.; Gémes, G.; Hangya, K.I.; Kisszékelyi, P.; Kupai, J. Optimization of a photocatalytic C-alkylation reaction in a 3D printed photoreactor, 13th European Young Engineers Conference, Varsó, Lengyelország, 2025.04.07–09., oral presentation
65) Hangya, K. I.; Gémes, G.; Richter, D.; Kisszékelyi, P.; Kupai, J.: Synthesis of a metal-free photocatalyst and its applications in C-C bond formation reactions, 13th European Young Engineers Conference, Varsó, 2025. április 07-09., oral presentation (poster presentation)
66) Boda-Papp, B.; Kis, D.; Dargó, G.; Hegedűs, L.; Kupai, J.: A metilszezamol alternatív oldószer előállításának optimalizálása, illetve alkalmazása C-C kapcsolási reakciókban XVIII. Szent-Györgyi Albert Konferencia, Budapest, 2025. május 9–10., oral presentation
67) Hangya, K. I.; Gémes, G.; Richter, D.; Kisszékelyi, P.; Kupai, J.: Egy fotokatalizált C–C kapcsolási reakció kiterjesztése, XVIII. Szent-Györgyi Albert Konferencia, Budapest, 2025. május 9-10., oral presentation
68) Ráduly A.; Kiss J.; Fehér Zs.; Kupai J.: Poli(etilén-tereftalát) fenntartható depolimerizációja természetes alapú heterogén katalizátorokkal, XVIII. Szent-Györgyi Albert konferencia, Budapest, 2025.05.10. oral presentation
69) Varga, B., Ujj, D., Mireisz, T., Rapi, Zs.: Electrostatic immobilization of cyclodextrins containing permanent positive charges – wastewater monitoring in focus - 5th Young Researchers' International Conference on Chemistry and Chemical Engineering (YRICCCE V), 2025.05.09., Kolozsvár.
70) Kupai, J.: Sustainable application and recycling of organocatalysts, Young Researchers' International Conference on Chemistry and Chemical Engineering (YRICCCE V), Kolozsvár, Románia, 2025. május 9. (oral presentation, plenáris előadó)
71) Kupai, J.: MeSesamol, a new, bio-based alternative solvent with versatile applications, XVI. Young Investigator Workshop, EuChemS Division of Organic Chemistry, Koppenhága, Dánia, 2025. június 27–28. (oral presentation, meghívott előadó)
72) Varga, B., Ujj, D., Mireisz, T., Rapi, Zs.: Development of novel SPE packings for wastewater monitoring via electrostatic immobilization of cationic cyclodextrins - 8th European Cyclodextrin Conference (EuroCD 2025), 2025.szeptember 9-12., Milánó.
73) Gémes, G.; Hangya, K. I.; Richter, D.; Lakné Komka, K.; Kisszékelyi, P.; Kupai, J.: 3D-nyomtatott fotoreaktorban végzett C-alkilezési reakció kísérlettervezésen alapuló optimalizálása, XLVIII. Kémiai Előadói Napok, Szeged, 2025. október 27–29. oral presentation
74) Ráduly, A.; Kupai, J.: Homok, mint heterogén katalizátor a poli(etilén-tereftalát) gazdaságos depolimerizációjában XLVIII. Kémiai Előadói Napok, Szeged, 2025.10.27. oral presentation
75) Kupai, J.: Poli(etilén-tereftalát) és polikarbonát szolvolitikus depolimerizációja heterogén katalizátorok alkalmazásával, Simkon szakmai nap, Budapest, 2025. november 13.
76) Richter, D.; Gémes, G.; Hangya, K. I.; Komka, K.; Kisszékelyi, P.; Kupai, J. Optimization of a photocatalytic C–C bond formation reaction using design of experiments, CEMS International Symposium on Supramolecular Chemistry and Functional Materials, Tokyo, Japan, 2026. január 15-16., poster presentation
77) Gémes, G.; Hangya, K. I.; Richter, D.; Lakné Komka, K.; Kisszékelyi, P.; Kupai, J.; Optimization of a photocatalytic C–C bond formation reaction using design of experiments, 14th European Young Engineers Conference, Varsó, 2026. április 14., oral presentation
78) Hangya, K. I.; Gémes, G.; Richter, D.; Kisszékelyi, P.; Kupai, J.: Comparison of batch and flow chemistry in a photocatalytic C-alkylation reaction, 14th European Young Engineers Conference, Varsó, 2026. április 13-15., oral presentation
79) Ráduly, A; Kupai, J.: Sand as a heterogeneous catalyst in the economical depolymerization of polyethylene terephthalate 14th European Young Engineers Conference (EYEC), Varsó, Lengyelország, 2026.04.14., oral presentation

80) Varga, B., Ujj, D., Mireisz, T., Rapi, Zs.: Új SPE töltetek fejlesztése szennyvíz-monitorozáshoz kationos ciklodextrinek elektrosztatikus immobilizálásával, Műszaki Kémiai Napok 2026, 2026. április 22., Veszprém
81) Szabó, E., Varga, B., Rapi, Zs.: Ciklodextrinalapú karbamidok in-situ előállítása, Műszaki Kémiai Napok 2026, 2026.04.22., Veszprém
82) Miklós, B., Varga, B., Rapi, Zs.: Királis ciklopropán-származékok Krapcho-dekarboxilezésének vizsgálata, Műszaki Kémiai Napok 2026, 2026.04.22., Veszprém
83) Boda-Papp, B.; Kis, D.; Dargó, G.; Richer, D.; Hegedűs, L.; Kupai, J.: A metilszezamol hatékony szintézise és oldószerként történő alkalmazása szerves kémiai reakciókban XIX. Szent-Györgyi Albert Konferencia, Budapest, 2026. május 15–16., oral presentation
84) Hangya, K. I.; Gémes, G.; Richter, D.; Kisszékelyi, P.; Kupai, J.: Fotokatalitikus szén-szén kapcsolási reakció optimalizálása kísérlettervezéssel, XIX. Szent-Györgyi Albert Konferencia, Budapest, 2026. május 15-17., oral presentation
85) Vásárhelyi, I., P.; Ráduly, A.; Kupai, J.: Homok alkalmazása PET depolimerizációjának katalízisére, XIX. Szent-Györgyi Albert Konferencia, Budapest, 2026. május 15-16., oral presentation
86) Szabó, E., Varga, B., Rapi, Zs.: Ciklodextrinalapú karbamidok in-situ előállítása, XIX. Szent-Györgyi Albert Konferencia, 2026.05.15-16., Budapest.
87) Miklós, B., Varga, B., Rapi, Zs.: Királis ciklopropán-származékok Krapcho-dekarboxilezésének vizsgálata, Műszaki Kémiai Napok 2026, 2026.04.22., Veszprém, XIX. Szent-Györgyi Albert Konferencia, 2026.05.15-16., Budapest.
88) Gémes, G.; Hangya, K. I.; Richter, D.; Lakné Komka, K.; Kisszékelyi, P.; Kupai, J.; Fotokatalitikus C-alkilezési reakciók optimalizálása és áramlásos kémiai megvalósítása, Heterociklusos és Elemorganikus Munkabizottság ülése, Balatonszemes, 2026. június. 01., oral presentation
89) Ráduly, A; Gémes, G.; Richter, D.; Vásárhelyi P.; Kupai, J.: A poli(etilén-tereftalát) glikolízise homok katalizátor jelenlétében MTA Heterociklusos és Elemorganikus Kémiai Munkabizottság előadóülése, Balatonszemes, 2026.06.01., oral presentation
90) Boda-Papp, B.; Kis, D.; Dargó, G.; Richer, D.; Hegedűs, L.; Kupai, J.: A metilszezamol hatékony szintézise és oldószerként történő alkalmazása szerves kémiai reakciókban Szerves- és Gyógyszervegyész Konferencia, Esztergom, 2026. június 8–10., oral presentation
91) Ráduly, A., Vásárhelyi, I. P., Gémes, G., Kupai, J. Homok mint heterogén katalizátor a poli(etilén-tereftalát) gazdaságos depolimerizációjában Szerves- és Gyógyszervegyész Konferencia, Esztergom, 2026. június 8–10., oral presentation

Report of unpublished results (OTKA-FK138037)

1. Alternative Catalysis for a Circular Economy: Natural Sands in the Depolymerization of Poly(ethylene terephthalate)

As a continuation of the PET depolymerization project, natural sands were investigated as alternative materials for the degradation of PET to BHET (**Figure 15.**). To assess the influence of the intrinsic properties of sand on its performance, 14 samples collected from different locations were systematically investigated. The sands were characterised using X-ray diffraction (XRD), scanning electron microscopy (SEM), atomic absorption spectroscopy coupled with inductively coupled plasma optical emission spectroscopy (AAS/ICP-OES), and X-ray photoelectron spectroscopy (XPS), providing information on their mineralogical composition, morphology, elemental composition, and surface chemistry. The characterisation data were evaluated together with the PET depolymerisation performance of the individual sand samples to explore possible relationships between their physicochemical properties and activity. The results revealed substantial differences in the performance of the investigated sands, demonstrating that naturally occurring sands are not equivalent in their ability to promote PET depolymerisation. Although no single compositional parameter could be identified as solely responsible for the observed activity, the combined characterisation provides insights into the complex factors governing the performance of natural sands. We extended the method to the degradation of industrial PET waste, that is, the friction dust generated during the crystallization step of the polymer. we investigated the effect of reaction parameters on yield and energy consumption using a 2^{4-1} factorial design, then optimized the reaction conditions. Under the determined optimal conditions, we verified the recyclability of the catalyst over multiple cycles. Overall, this study provides a systematic investigation of natural sands in PET depolymerisation and contributes to a better understanding of the role of naturally occurring mineral materials in circular plastics recycling. A manuscript based on this work is going to be submitted in February 2027.

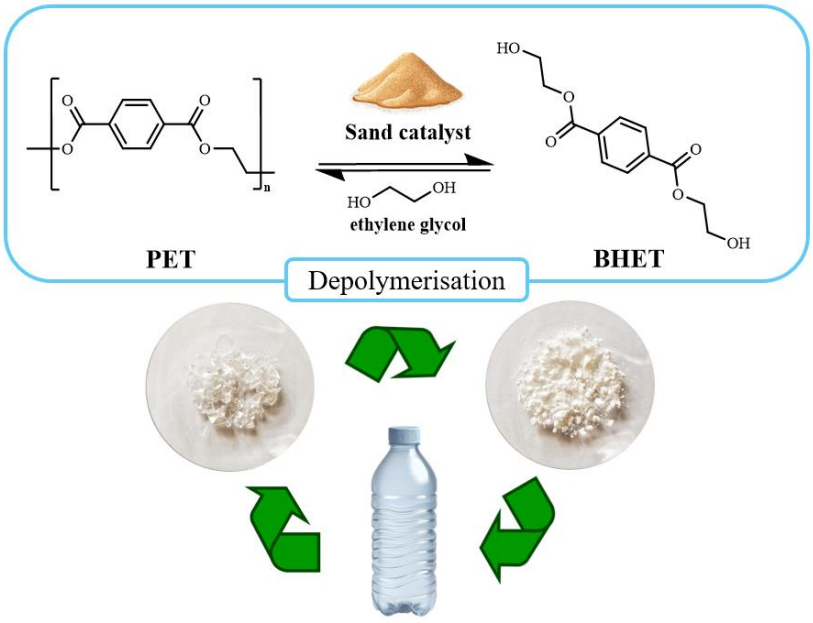


Figure 15: Chemical degradation of PET with sand catalyst

2. Application of MeSesamol as a solvent in various organic reactions

MeSesamol was synthesized by methylation of sesamol with dimethyl carbonate in the presence of DBU. In this reaction, dimethyl carbonate serves both as the methylating agent and as the solvent, while DBU acts as a base and catalyst. During the course of our research, we optimized the synthesis of MeSesamol. The methylation reaction was carried out under elevated pressure in an autoclave. The

amount of DBU used previously was significantly reduced while maintaining a good yield and a short reaction time. The reaction was also performed using another base, DABCO, and an attempt was made to carry out the reaction in the absence of a base.

Our aim was to investigate the applicability of MeSesamol as a solvent (**Figure 16.**) in reactions such as the **Sonogashira** coupling, which can be used for the synthesis of aromatic acetylene derivatives relevant to pharmaceutical synthesis, as well as the **Cacchi cyclization**, which is applicable to the synthesis of benzofuran- and indole-based compounds.

To identify the optimal reaction conditions, we performed a systematic parameter study, investigating the effects of the base used, reaction time, and temperature on the achievable yield. In addition, we examined how the type of halogen atom present in the aryl halide affects the reaction yield. Another objective was to compare the yields obtained using MeSesamol with those reported in the literature for the same reactions performed in other solvents.

MeSesamol was investigated as a solvent for the **Heck** reaction. In the literature, the Heck reaction has been performed in polar aprotic solvents, such as dimethyl sulfoxide and dimethylformamide, as well as in another alternative solvent, Cyrene. Reactions involving aryl iodides and substituted styrenes were studied. Subsequently, a parameter study was conducted. Using the reaction of iodobenzene with styrene as a model reaction, the effects of the type and amount of base, the substrate ratio, and the reaction temperature on the yield were investigated.

MeSesamol was also investigated as a solvent for the **Wittig** reaction. Reactions between 4-(dialkylamino)benzaldehydes and methyltriphenylphosphonium bromide were studied. In the literature, this reaction has been performed in tetrahydrofuran.

Finally, MeSesamol was investigated as a solvent for the **Bischler–Napieralski** reaction. The cyclization of *N*-acetyltryptamine was studied, affording 1-methyl-3,4-dihydro-β-carboline as the product. Literature examples of solvents for this reaction include xylene and a toluene–acetonitrile solvent mixture. A manuscript based on this work is going to be submitted in December 2026.

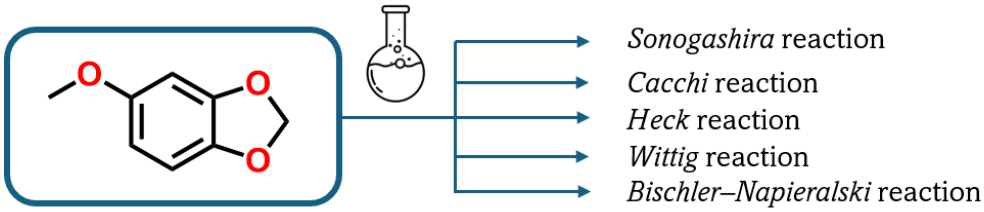
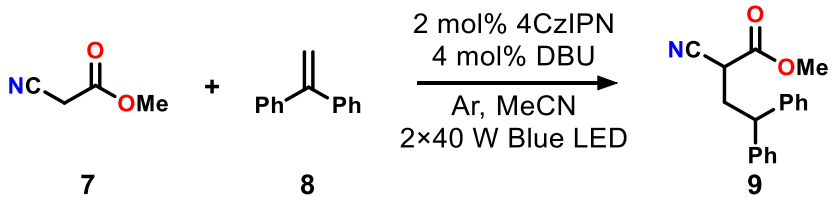


Figure 16: Application of MeSesamol as solvent in various organic reactions

3. A flat-spiral flow reactor for efficient photocatalytic C-alkylation

A simple, easy-to-construct flat-spiral flow photoreactor was developed for photocatalytic C-alkylation using high-power LED light sources. The reactor is based on commercially available PFA tubing arranged in a flat-spiral geometry enabling efficient use of planar light sources and double-sided irradiation. To maximize light harvesting, the high volume to surface area ratio provides good temperature control, and light penetration. The performance of the reactor was evaluated using the C-alkylation of CH-acidic substrates with 1,1-diphenylethylene (**8**) compared with a coiled-tube flow configuration (**Scheme 1.**).



Scheme 1*:* The C-alkylation reaction used for testing the different flow setups

The flat-spiral design provided higher yields at all investigated residence times and enabled shorter residence times and higher reaction concentrations while maintaining high product yields. Optimization afforded a 93% yield at a reaction concentration of 0.27 M and a residence time of 2 h, while the use of

1/16-inch PFA tubing (**Figure 17.**) enabled almost quantitative yields. The new setup was applied to several additional CH-acidic substrates, providing space time yields up to 98 mmol h^{-1} L^{-1}, while the residence time was reduced from 5 to 1 h, which led to substantially higher productivity than the corresponding batch processes. A power-normalized modification of the energy economy factor was also introduced, highlighting the influence of irradiation power and temperature control on the calculated process efficiency. Finally, controlled oxygenation experiments showed that oxygen promotes benzophenone formation from 1,1-diphenylethylene, which can suppress the desired C-alkylation. A manuscript based on this work has been submitted to *Beilstein Journal of Organic Chemistry* in November 2026.

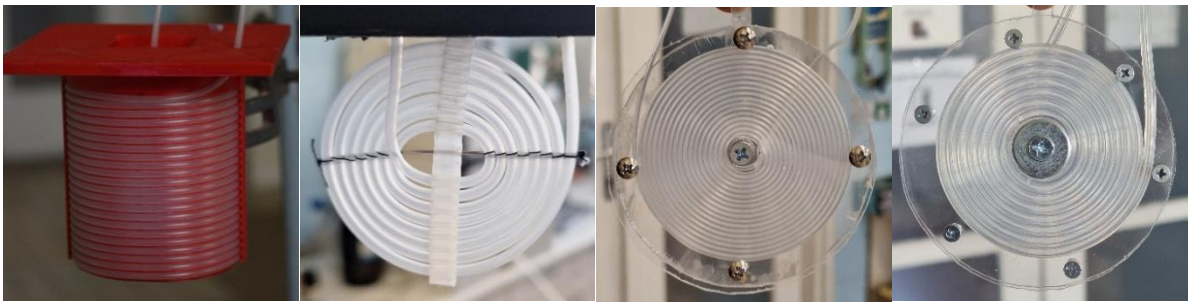


***Figure 17**:* From left to right: The original flow insert, the prototype for the flat spiral reactor (1/8" ID PP tubing), flat spiral with 1/16" PFA tubing, and flat spiral with 1/8" PFA tubing

4. Carbohydrate-based macrocycles

It was proven that the side chain of the sugar-based crown ethers influences the generated enantioselectivity. A series of primary amines were synthesized, which contain different type of amides, which unit were not incorporated in side chains before. Using these compounds, glucose-based crown ethers were synthesized, and they have been investigated in asymmetric phase-transfer reactions. The results showed that these types of crown ethers are less stable (slow decomposition occurs when not stored under inert atmosphere) and can generate low to moderate enantiomeric excess in the model reactions investigated.

Glucose-based crown ethers suitable for immobilization on a solid support were synthesized, two of these macrocycles were linked to β-cyclodextrin. By employing the resulting cyclodextrin–crown ether conjugate as a phase-transfer catalyst, we successfully induced enantioselectivity. However, we observed a significant increase in reaction time, and we have not yet been able to efficiently recover the catalyst from the reaction mixture. In addition to cyclodextrin, we also immobilized crown ethers onto Merrifield resin; an increase in reaction time was observed in this case as well. Recycling studies have not yet commenced.

Starting from glucose and galactose, we synthesized crown ether precursors containing a 4-bromophenyloxy group at the anomeric center. We found that these carbohydrate derivatives undergo decomposition under the conditions used for the formation of the crown ring.

Compounds containing quaternary ammonium units derived from beta-cyclodextrin were synthesized and their applicability as phase-transfer catalysts was investigated. We observed that, although they were capable of phase-transfer catalysis, the asymmetric induction achieved in the reactions studied was low.

We investigated additional acceptors (e.g., 2-cyanoiminochromene, *N*-benzylidenetosylamide), Michael donors (e.g., 3-phenylphthalide), and halogenated compounds (e.g., ethyl 3-bromoacetoacetate, 3-bromopentane-2,4-dione) in Michael addition and MIRC reactions. Although products were formed in some cases, we did not observe asymmetric induction in the presence of chiral crown ethers. Attempts to synthesize isoxazoline derivatives were not enantioselective—yielding racemic products in every case—whereas attempts to prepare pyrazoline derivatives were unsuccessful, resulting in no product formation.

The decarboxylation of several cyclopropane-tricarboxylic acid triesters under Krapcho conditions were investigated. We found that, with appropriately chosen conditions, the decarboxylation

can selectively yield mono- or di-decarboxylated cyclopropane derivatives. We also performed the decarboxylation using chiral samples; the stereochemical consequences are currently being analyzed via chiral HPLC. The resulting compounds have undergone further transformation, and only one step remains to obtain non-natural amino acids. A student research project (TDK) thesis and a manuscript based on this work are currently in preparation.

In our work with cyclodextrins, we prepared CD-based urea derivatives via a one-pot synthesis starting from mono-6-*O*-tosyl-β-cyclodextrin, using sodium cyanate and various amines. By further developing the method, we successfully synthesized these urea derivatives directly from β-CD, thereby reducing the number of required steps. The method is unknown in the literature. A student research project (TDK) thesis and a manuscript based on this work are currently in preparation.

Macrocycles derived from methyl-4,6-di-*O*-alkyl-glucopyranosides were synthesized with similar structure, and their catalytic activity and reusability were tested in different model reactions. The recovery was performed via formation of hydrochloric acid salt. The enantiomeric excess varied widely (0-75% ee) when the catalysts were tested in asymmetric phase-transfer model reactions. We showed that the recoverability of the examined crown ethers and the enantiomeric excess generated seems to be unchanged for three cycles. A manuscript based on this work is going to be submitted in October 2026.

Overall Scientific Achievements and Conclusions

The research carried out within the project has resulted in substantial advances in the development of sustainable organocatalytic methodologies and their application to asymmetric synthesis, catalyst recycling, and chemical recycling of polymers. Although the individual research directions addressed different catalytic systems and chemical transformations, they were connected by a common objective: to develop efficient catalytic processes that combine high activity and selectivity with improved sustainability, recyclability, and practical applicability.

A major scientific outcome of the project was the systematic development and investigation of new hydrogen-bond-donor organocatalysts. Several cinchona- and proline-derived squaramide, thiosquaramide, and thiourea catalysts were prepared and evaluated in asymmetric transformations. The studies provided valuable structure–activity relationships and demonstrated how the position and nature of the hydrogen-bond-donor functionality, the chiral scaffold, and the possibility of dual activation influence catalytic performance. In particular, the development of proline-derived (thio)squaramides demonstrated the potential of combining hydrogen-bond activation with enamine catalysis in a single catalyst. These catalysts provided excellent yields and enantioselectivities in selected asymmetric Diels–Alder and conjugate addition reactions.

The project also demonstrated that the catalytic performance of cinchona-derived hydrogen-bond-donor systems can be substantially modified through metal coordination. The preparation and structural investigation of cinchona-based organocatalyst–metal complexes provided insight into the nature of the active catalytic species and established relationships between catalyst structure, metal coordination, and catalytic activity. These results extended the concept of hydrogen-bond-donor organocatalysis towards metal-assisted catalytic systems and demonstrated that appropriate combinations of organocatalysts and metal salts can significantly improve both conversion and stereoselectivity.

An important achievement was the development of approaches for making organocatalytic processes more sustainable through catalyst recovery and reuse. A lipophilic cinchona squaramide was successfully applied in asymmetric Michael additions and recovered by a simple solvent-exchange procedure. The catalyst could be reused repeatedly without significant loss of activity or stereoselectivity, and its application to the gram-scale synthesis of a baclofen precursor demonstrated the practical relevance of the approach. These results showed that catalyst recovery can be incorporated into asymmetric organocatalytic processes without compromising catalytic performance.

The project subsequently extended the concept of catalyst recycling to heterogeneous organocatalysis and polymer chemical recycling. Silica-supported organocatalysts were developed and successfully applied to the glycolytic depolymerization of PET. Experimental-design-based optimization enabled the identification of efficient reaction conditions, while the heterogeneous catalysts could be readily separated from the reaction mixture and reused in multiple cycles. The approach was subsequently extended to the methanolysis of poly(bisphenol A carbonate), where Si-TBD enabled efficient depolymerization under comparatively mild and economically favourable conditions. These studies

demonstrated that immobilized organocatalysts can provide an effective link between organocatalysis and circular plastics recycling.

A further significant outcome was the development of MeSesamol as a bio-based polar aprotic solvent. The project established its synthesis from a renewable feedstock and demonstrated its applicability in a broad range of organic transformations. Importantly, MeSesamol was not investigated merely as a replacement solvent for individual reactions, but as a multifunctional component of more sustainable chemical processes. Its favourable physical and chemical properties, broad solvent compatibility, and recyclability enabled its application both in organic synthesis and in depolymerization. The successful recovery of MeSesamol during the depolymerization of BPA–PC and PET demonstrated the potential of combining a bio-based solvent with recyclable catalytic systems.

The project also established a connection between organocatalysis, renewable feedstocks, and electrochemical synthesis. Sustainable electrooxidation of 5-hydroxymethylfurfural to 2,5-furandicarboxylic acid was developed using a TEMPO-mediated process and commercially available electrodes. The optimization of the electrochemical transformation by experimental design resulted in high FDCA yields and demonstrated the feasibility of avoiding more elaborate electrode preparation. In addition, the recovery of FDCA from PEF by depolymerization using MeSesamol provided a complementary approach to the chemical recycling of bio-based polymers. Together, these studies demonstrate how renewable platform molecules can be incorporated into a circular materials framework.

Another important achievement of the project was the extension of the research programme towards visible-light photocatalysis and flow chemistry. A 3D-printed photoreactor was developed as a reproducible platform for the systematic optimization of photocatalytic C–C bond-forming reactions. The use of design of experiments allowed the most influential reaction parameters to be identified and led to substantial improvements in product yield. The subsequent development of a simple flat-spiral flow photoreactor further demonstrated the potential for increasing productivity while maintaining high reaction efficiency. These studies broadened the methodological scope of the project from organocatalysis towards modern sustainable photochemical and continuous-flow technologies.

The project also generated several results beyond the originally investigated catalyst systems. In particular, the research on carbohydrate-based macrocycles provided new information on the relationship between macrocycle structure, chiral environment, catalyst recovery, and asymmetric induction. Although not all investigated systems provided the desired catalytic performance, these studies identified structural limitations and favourable design elements that can guide the development of future recyclable phase-transfer catalysts. Such results are scientifically relevant because they help define the structural requirements for successful asymmetric catalysis using complex chiral macrocycles.

Overall, the project has established a coherent research platform centred on **sustainable catalysis, asymmetric synthesis, catalyst recyclability, and circular chemical processes**. The results demonstrate that sustainability can be addressed at several interconnected levels: through the molecular design of efficient organocatalysts, through catalyst immobilization and recovery, through the replacement of conventional solvents with bio-based alternatives, through the use of renewable feedstocks, and through the development of chemical recycling strategies for both fossil-based and bio-based polymers.

The scientific output of the project includes numerous peer-reviewed publications covering organocatalyst design, asymmetric catalysis, recyclable heterogeneous catalysis, sustainable solvents, polymer depolymerization, electrochemical synthesis, and photocatalytic flow chemistry. Several additional results obtained during the project remain unpublished and are currently being prepared for publication, including the systematic investigation of natural sands as catalysts for PET depolymerization, further applications of MeSesamol in organic synthesis, the flat-spiral flow photoreactor, and new carbohydrate-based macrocycles.

In conclusion, the project successfully fulfilled its central scientific objectives while also generating new research directions that emerged naturally from the results obtained during the project. The work provided new catalysts and catalytic concepts, established structure–activity relationships, demonstrated practical catalyst and solvent recycling, and developed sustainable approaches for polymer depolymerization and renewable-molecule valorization. The combination of fundamental mechanistic studies with process-oriented investigations has created a strong basis for further development of sustainable asymmetric catalysis and circular chemical technologies.