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FACULTY OF CHEMICAL TECHNOLOGY AND BIOTECHNOLOGY
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**Synthesis of chiral crown ethers and their application in asymmetric
reactions**

PhD theses

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1. Introduction

The syntheses of enantiopure compounds is an important topic both in the pharmaceutical industry and in other areas of the chemical industry, therefore intensive research is focused on the syntheses of efficient enantioselective catalysts. Despite the numerous available chiral catalysts, it is still a real challenge to develop new chiral catalyst, especially from cheap, naturally occurring starting materials (*e.g.* from carbohydrates). Different type of efficient enantioselective catalysts have already been synthesized starting from monosaccharides. In asymmetric syntheses an attractive option is the phase transfer catalytic technique, which is generally considered a „green” method, because of the mild reaction conditions used.

The enantiomeric recognition ability of chiral crown compounds is well known since the 1970s. Usually the complexation ability of these chiral macrocycles has been investigated toward chiral amines or amino acids in optical sensors or in chromatographic separation. But chiral crown ethers also have the ability to induce enantioselectivity as phase transfer catalysts in certain reactions. However, only a few researchers have managed to perform asymmetric synthesis using chiral crown compounds with good enantioselectivity so far.

In the Department of Organic Chemistry and Technology, monoaza-15-crown-5-type lariat ethers have been synthesized starting from different monosaccharides, which macrocycles generated significant asymmetric induction in a few reactions. Despite all the good results in the research area of carbohydrate-based crown compounds, this method has the disadvantage that the catalysts cannot be recovered, which prevents the widespread application of this type of catalysts.

2. Objectives

The aim of this research was to synthesize new chiral crown ethers and to test these catalysts in asymmetric phase transfer reactions. Previously, it has already been revealed, that a small change in the structure of carbohydrate-based crown catalysts may cause significant increase or decrease in the observed enantioselectivity. Thus, my goal was the fine tuning of the structure of carbohydrate-based crown compounds by synthesizing numerous structurally similar catalysts and to obtain structure-activity relationships. Another objective was to develop a method for the recovery of the catalysts. The idea was to form salt from the monoaza crown ethers, which can be separated from the reaction mixture by a simple

aqueous extraction. However, efficient carbohydrate-based catalysts generally contain acid sensitive functional group, therefore the synthesis of hydrobenzoin-based macrocycles was planned for this purpose

3. Experimental methods

During the research, the instruments and methods of classical preparative chemistry was used (*e.g.* crystallization, distillation, column chromatography, preparative TLC). For the characterization of the compounds, ^1H and ^{13}C NMR and MS spectroscopy was used. For the known compounds the measurement of melting points and specific rotations was also performed. The determination of the enantiomeric excess was usually performed by chiral HPLC, but in some cases the measured specific rotation was compared to the literature value. In one case, the absolute configuration of a product was determined using CD spectroscopy and theoretical calculations.

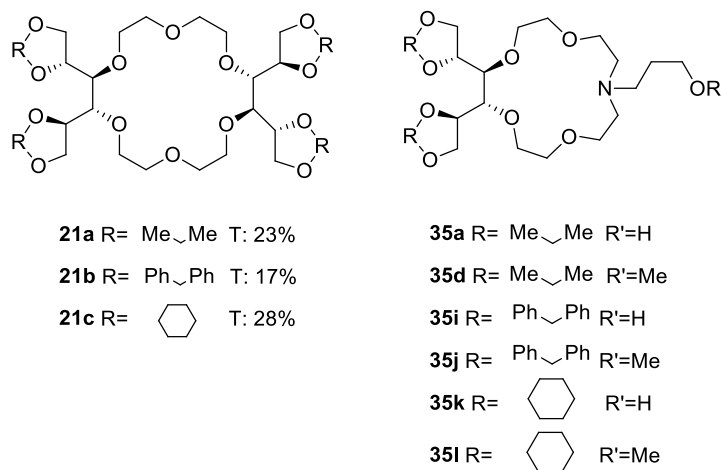
4. Summary

First, the synthesis of the new chiral crown ethers was accomplished from readily available and cheap enantiopure starting materials. Then the synthesized catalysts were tested in a few asymmetric reactions, in which carbohydrate-based crown compounds were effective in previous experiments. Finally, some new enantioselective syntheses were also performed partly with the new catalysts and partly with previously synthesized macrocycles.

4.1. The syntheses and application of the new crown ethers

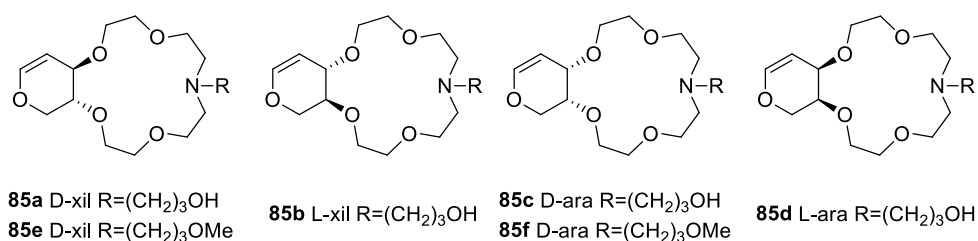
During the research, twenty-seven new crown ethers have been synthesized starting from different carbohydrates such as D-mannitol, L- and D-arabinose L- and D-xylose, D-galactose and from (*R,R*)- and (*S,S*)-hydrobenzoin.

Nine crown ethers have been synthesized starting from D-mannitol, six of which are new (Scheme 1). The syntheses of the monoaza-15-crown-5 type compounds were performed in four steps, while the 18-crown-6 type macrocycles were synthesized in two steps. The **21a-c** derivatives with eighteen-membered ring did not show significant enantioselectivity, but the monoaza type catalysts (**35a**, **35d**, **35i-l**) proved to be efficient in a few *Michael* additions, MIRC-type cyclopropanations and *Darzens* condensations (up to 85% ee). The acetal function and the side chain of the catalysts had a significant effect on the established asymmetric induction. The most effective catalyst was crown ether **35k**.



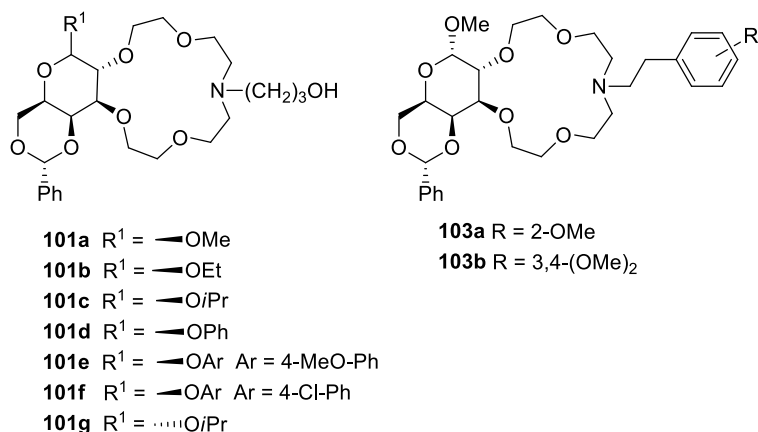
Scheme 1: the synthesized D-mannitol-based crown ethers

Six new arabinal- and xylal-based monoaza-15-crown-5 ethers have been synthesized in seven steps starting from L- and D-arabinose, or L- and D-xilose (Scheme 2). Only the **85a** and **85b** xylal-based macrocycles with hydroxypropyl side arm proved to be effective. These macrocycles generated high asymmetric induction in the epoxidation of *trans*-chalcone and its derivatives. Since **85a** and **85b** are pair of enantiomers, both enantiomers of the appropriate products could be synthesized with approximately the same enantiomeric excess.



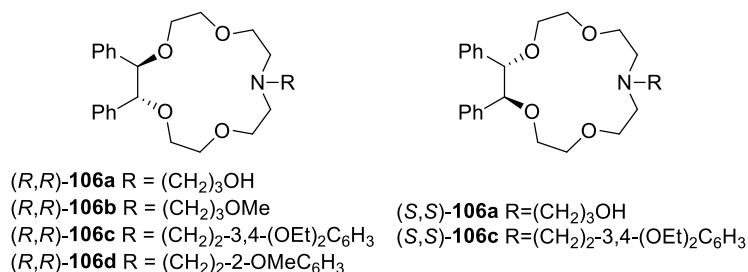
Scheme 2: the synthesized D- and L-xylal- and D- and L-arabinal-based crown ethers

Nine new D-galactose-based lariat ethers have been synthesized with different substituents in the C-1 position of the sugar unit, and with different side chain on the nitrogen of the crown ring (Scheme 3). The β -galactoside derivatives generated higher asymmetric induction in every reaction as compared to the appropriate α -analogues. The β -alkyl substituted macrocycles showed excellent enantioselectivity (91-96% ee) in the MIRC reaction of 2-benzylidene-1,3-indandione and diethyl bromomalonate.



Scheme 3: the synthesized D-galactose-based crown ethers

Finally, six new monoaza crown ether have been synthesized starting from (*R,R*)- and (*S,S*)-hydrobenzoin in three steps. Since both enantiomers of catalysts **106a** and **106c** have been synthesized, the desired enantiomer of the appropriate products in the asymmetric reactions could be prepared (Scheme 4). The hydrobenzoin-based macrocycles proved to be efficient in the epoxidation of a few chalcone derivatives (68-88% ee) and also in some MIRC reactions (51-75% ee). A new method for the recycling of these catalysts was also developed using salt formation and extraction. Crown ether **106a** was regenerated in good yields and was reused without the loss of activity and enantioselectivity.

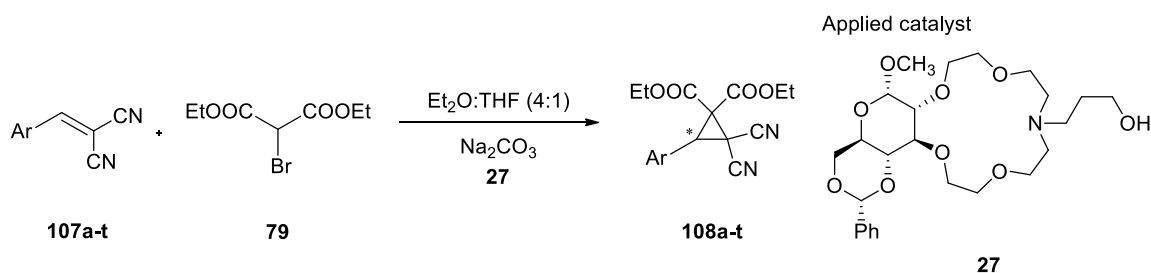


Scheme 4: the synthesized hydrobenzoin-based crown ethers

4.2. Enantioselective syntheses

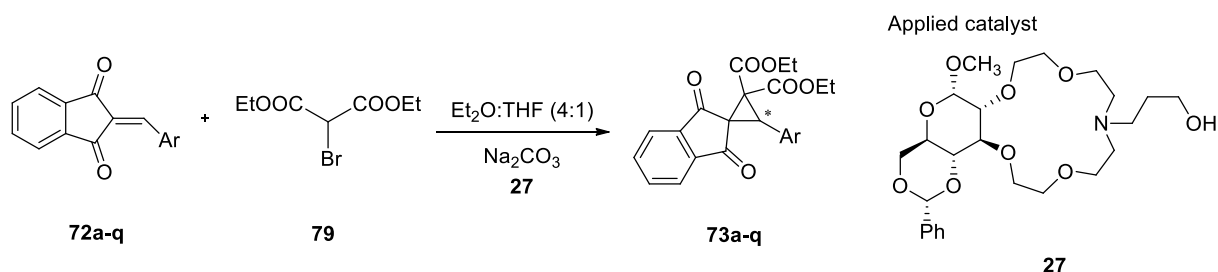
Besides testing the new lariat ethers in asymmetric reactions, a few new or less studied asymmetric syntheses were also performed using the new or previously synthesized macrocycles.

The asymmetric MIRC reaction of benzylidenemalononitrile derivatives (**107a-t**) with diethyl bromomalonate (**79**) was investigated using the D-glucose-based catalyst **27** (Scheme 5). The appropriate products (**108a-t**) were synthesized in various yields (41-86%) and enantioselectivity (0-99%).



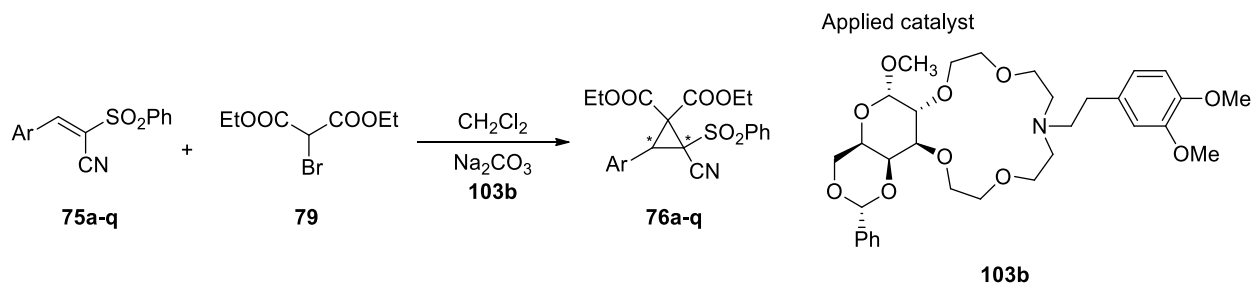
Scheme 5: the asymmetric MIRC reaction of benzilidenemalononitrile derivatives and diethyl bromomalonate catalyzed by **27**

The MIRC reaction of benzylideneindandion (**72a**) and its derivatives (**72b-q**) with diethyl bromomalonate (**79**) was also investigated by using catalyst **27** (Scheme 6). The corresponding cyclopropanes were obtained in 34-96% yield and 28-93% ee.



Scheme 6: the asymmetric MIRC reaction of benzylideneindandion derivatives and diethyl bromomalonate catalyzed by **27**

In the enantioselective cyclopropanation of α,β -unsaturated cyanosulfones (**75a-q**), the D-galactose-based crown ether **103b** proved to be the most efficient (Scheme 7). Among the substituted products, the *meta*- and *para*-derivatives were obtained in good enantioselectivity (75-84% ee), while the *ortho*-analogues were formed in almost racemic form (0-12% ee).



Scheme 7: the asymmetric MIRC reaction of α,β -unsaturated cyanosulfone derivatives and diethyl bromomalonate catalyzed by **103b**

5. Theses

1. New fifteen- and eighteen-membered crown ethers have been synthesized starting from D-mannitol and used in asymmetric syntheses. The monoaza-15-crown-5 ethers generated high asymmetric induction (up to 85% ee) in a few *Michael* additions, MIRC type cyclopropanations and *Darzens* condensations, while the derivatives with eighteen-membered ring proved to be inefficient in every reaction [B2].

2. Monoaza-15-crown-5-type lariat ethers have been synthesized starting from D- and L-xylose, as well as from D- and L-arabinose. Only the xylal-based catalysts with hydroxypropyl side chain proved to be efficient, which showed significant asymmetric induction (44-96% ee) in the epoxidation of a few chalcone derivatives. Since both enantiomers of the applied catalyst were available, the desired enantiomer of the corresponding products in the asymmetric reactions could be prepared with approximately the same enantiomeric excess [B5].

3. Monoaza crown ethers with different alkyl and aryl substituents and with different stereo structure (α or β) on the C-1 position of the sugar unit and with different side chains have been prepared starting from D-galactose. The β -galactoside derivatives were more efficient in every reaction as compared to the appropriate α -analogues. The asymmetric MIRC reaction of benzylidenemalononitrile and benzylideneindanedione with diethyl bromomalonate was performed with 86% and 96% ee using D-galactose-based crown ethers [B4].

4. Monoaza crown ethers with different side arms have been prepared starting from enantiopure (*R,R*)- and (*S,S*)-hydrobenzoin. The macrocycles with hydroxypropyl side arm showed significant enantioselectivity (68-88%) in the epoxidation of a few chalcone derivatives. A new method has been developed for the recycling of the hydrobenzoin-based crown ethers [B6].

5. Good enantioselectivities and yields have been achieved in the MIRC reaction of benzylidenemalononitrile, benzylideneindandione, *trans*-chalcone, and benzylidene-1,3-diphenyl-1,3-propandione with diethyl bromomalonate in the presence of a methyl- α -D-

glucose-based catalyst. The absolute configuration of benzylidenemalonitrile derivative was also determined using CD spectroscopy and theoretical calculations [B1, B3].

6. Significant asymmetric induction and good yields (83-95%) were achieved in the asymmetric MIRC reaction of α,β -unsaturated cyanosulfones and diethyl bromomalonate using a methyl- α -D-galactoside-based crown ether with 3,4-dimethoxyphenylethyl side arm. The *m*- and *p*-substituted products were formed in good yields (84-95%) and with high ee values (75-84%), while the *ortho*-substituted analogues were isolated in almost racemic form (0-12% ee) [B7].

6. Possible application

Asymmetric phase transfer catalysis is an important and „green” method for the syntheses of enantiopure compounds. This research helped to get a better understanding of the application of chiral crown ethers in asymmetric syntheses. By synthesizing and using numerous macrocycles having similar structure, important structure-activity relationships have been revealed, which can be useful in further catalyst development. Regarding the possible applications, the developed method for the recycling of hydrobenzoin-based crown ethers could be highlighted. One of these macrocycle could be regenerated with excellent yields and the recovered catalyst was reused without the loss of its activity and selectivity. We hope that this recovery technique can help to expand the sphere of application of chiral monoaza crown ethers in asymmetric catalysis by eliminating the drawback of their high price and poor recyclability.

Different valuable chiral products and intermediates were synthesized during the application of chiral monoaza crown ethers. One good example is the synthesis of enantioenriched epoxides, which can be converted into different biologically active products. The products of the asymmetric MIRC reactions of α,β -unsaturated cyanosulfones and diethyl bromomalonate are also important chiral intermediates, for example in the synthesis of δ -amino acids.

7. Publications and oral presentations

7.1. Publications in the subject of the dissertation

[B1] Bakó Péter, Rapi Zsolt, Grün Alajos, **Nemcsok Tamás**, Hegedűs László, Keglevich György: Asymmetric *Michael* Addition of Malonates to Enones Catalyzed by an α -D-Glucopyranoside-Based Crown Ether, *Synlett*, **2015**, 26, 1847-1851. [IF(2015): 2.323; Citations: 13]

[B2] **Nemcsok Tamás**, Rapi Zsolt, Keglevich György, Grün Alajos, Bakó Péter: Synthesis of D-mannitol-based crown ethers and their application as catalyst in asymmetric phase transfer reactions, *Chirality*, **2018**, 30, 407-419. [IF(2018/19): 1.927; Citations: 5]

[B3] Rapi Zsolt, **Nemcsok Tamás**, Grün Alajos, Pálvölgyi Ádám, Samu Gyula, Hessz Dóra, Kubinyi Miklós, Kállay Mihály, Keglevich György, Bakó Péter: Asymmetric cyclopropanation reactions catalyzed by carbohydrate-based crown ethers, *Tetrahedron*, **2018**, 74, 3512-3526. [IF(2018/19): 2.379; Citations: 3]

[B4] Rapi Zsolt, **Nemcsok Tamás**, Bagi Péter, Keglevich György, Bakó Péter: Synthesis of chiral crown ethers derived from D-galactose and their application in enantioselective reactions, *Tetrahedron*, **2019**, 75, 3993-4004. [IF(2018/19): 2.379; Citations: 1]

[B5] **Nemcsok Tamás**, Rapi Zsolt, Bagi Péter, Keglevich György, Bakó Péter: Synthesis of xylal- and arabinal-based crown ethers and their application as asymmetric phase transfer catalysts, *Chirality*, **2020**, 1, 107-119. [IF(2018/19): 1.927; Citations: -]

[B6] **Nemcsok Tamás**, Rapi Zsolt, Bagi Péter, Oláh Attila, Keglevich György, Bakó Péter: The synthesis of hydrobenzoin-based monaza crown ethers and their application as recyclable phase transfer catalysts, *Catalysis Letters*, **2019**, available online, <https://doi.org/10.1007/s10562-019-03013-0>. [IF(2018/19): 2.372; Citations: -]

[B7] **Nemcsok Tamás**, Rapi Zsolt, Bagi Péter, Hou Guan Ying, Keglevich György, Bakó Péter: Enantioselective cyclopropanation of conjugated cyanosulfones using carbohydrate-based crown ether catalysts, *Tetrahedron*, **2020**, available online, <https://doi.org/10.1016/j.tet.2020.130965>.

7.2. Other related publications

[B8] Rapi Zsolt, Ozohanics Olivér, Tóth Gábor, Bakó Péter, Höfler Lajos, **Nemcsok Tamás**, Kánya Nándor, Keglevich György: Syntheses and complexing ability of α -D-gluco- and α -D-

xylofuranoside-based lariat ethers, *Journal of Inclusion Phenomena*, **2016**, 85, 19-32. [IF(2016): 1,095; Citations: 2]

[B9] Rapi, Zsolt, Grün Alajos, **Nemcsok Tamás**, Hessz Dóra, Kállay Mihály, Kubinyi Miklós, Keglevich György, Bakó P.éter: Crown ether derived from D-glucose as an efficient phase-transfercatalyst for the enantioselective *Michael* addition of malonates to enones, *Tetrahedron: Asymmetry*, **2016**, 27, 960-972. [IF(2016): 2.126 Citations: 3]

[B10] Rapi Zsolt, **Nemcsok Tamás**, Pálvölgyi Ádám, Keglevich György, Grün Alajos, Bakó Péter: Synthesis of L-threitol-based crown ethers and their application as enantioselective phase transfer catalyst in *Michael* additions, *Chirality*, **2017**, 29, 257-272. [IF(2017): 1.833 Citations: 4]

[B11] **Nemcsok Tamás**, Rapi Zsolt, Bagi Péter, Bakó Péter: Synthesis and application of novel carbohydratebased ammonium and triazolium salts, *Synthetic Communications*, **2019**, 49. 2388-2400. [IF(2018/19): 1.439; Citations: -]

7.3. Oral presentations and posters

- 1, **Nemcsok Tamás**, Rapi Zsolt, Bakó Péter: Monoszacharid alapú királis koronaéterek szintézise és alkalmazása enantioszelektív katalizátorként 2014. november 3-5. XXXVII. Kémiai Előadói Napok, Szeged.
- 2, **Nemcsok Tamás**, Rapi Zsolt, Bakó Péter: Királis koronaéterek szintézise és alkalmazása enantioszelektív katalizátorként 2015. october 26-28. XXXVIII. Kémiai Előadói Napok, Szeged.
- 3, **Nemcsok Tamás**, Rapi Zsolt, Bakó Péter: D-Mannit alapú koronaéterek szintézise és alkalmazása. 2016. october 17-19. XXXIX. Kémiai Előadói Napok, Szeged.
- 4, **Nemcsok Tamás**: Szénhidrát alapú lariát koronaéterek szintézise és alkalmazása aszimmetrikus szintézisekben, Oláh György Doktori Iskola XV. Konferencia, 2018. februar 1. Budapest.
- 5, **Nemcsok Tamás**, Rapi Zsolt, Bakó Péter: Szénhidrát alapú kvaterner ammóniumsók szintézise és alkalmazása, 2018. october 15–17. XLI. Kémiai Előadói Napok, Szeged.
- 6, **Nemcsok Tamás**: Királis monoaza koronaéterek alkalmazása aszimmetrikus szintézisekben, Oláh György Doktori Iskola XVI. Konferenciája, Poster section, 2019. januar 31. Budapest.