FINAL REPORT ON THE PROJECT ENTITLED "SYNTHESIS, MOLECULAR RECOGNITION STUDIES AND APPLICATIONS OF CROWN ETHER DERIVATIVES" (GRANT NUMBER: K112289)

This final report consists of four parts: 1. INTRODUCTION, 2. PYRIDINO-CROWN ETHER DERIVATIVES, 3. ACRIDONO- AND ACRIDINO-CROWN ETHER DERIVATIVES, 4. CROWN ETHER DERIVATIVES CONTAINING PHOSPHORUS

1. INTRODUCTION

Molecular recognition is a vital and ubiquitous phenomenon in Nature. As examples for its action enzyme–substrate interactions, selective complexation and transport of ions by natural ionophores across cell membranes, storage and retrieval of genetic information by the DNA double helix, biochemical catalysis and antibody–antigen interaction can be mentioned. By the action of molecular recognition a molecule called the „host" is able to pull out another molecule called the „guest" from a mixture of molecules selectively forming an organized aggregation called a complex [1]. This complex is held together by intermolecular non-covalent or weak interactions such as hydrogen bonding, electrostatic forces, π–π stacking, ion–dipole, dipole–dipole and *van der Waals* forces. Enantiomeric recognition, as a special case of molecular recognition involves the discrimination between the enantiomers of a chiral guest by a chiral host [2]. A good example for its action can be the metabolism of single enantiomeric forms of amino acids and sugars in biochemical pathways. The studies on molecular recognition using relatively simple synthetic hosts such as crown ethers are not only important, because by these we can understand better this phenomenon working in Nature, but also, because these studies can lead to the development of selective sensor and selector molecules with wide applications [3].

2. PYRIDINO-CROWN ETHER DERIVATIVES

Starting from commercially available and relatively cheap materials we prepared several enantiopure pyridino-18-crown-6 ethers (*S*,*S*)-**1**–(*S*,*S*)-**13** (see Figure 1.) [4–7] and studied their enantiomeric discriminating ability toward the enantiomers of protonated primary amines and amino acid esters such as 1-(1-naphthyl)ethylamine hydrogen perchlorate (NEA), 1-phenylethylamine hydrogen perchlorate (PEA), phenylglycine methyl ester hydrogen perchlorate (PGME) and phenylalanine methyl ester hydrogen perchlorate (PAME) (see Figure 2.)

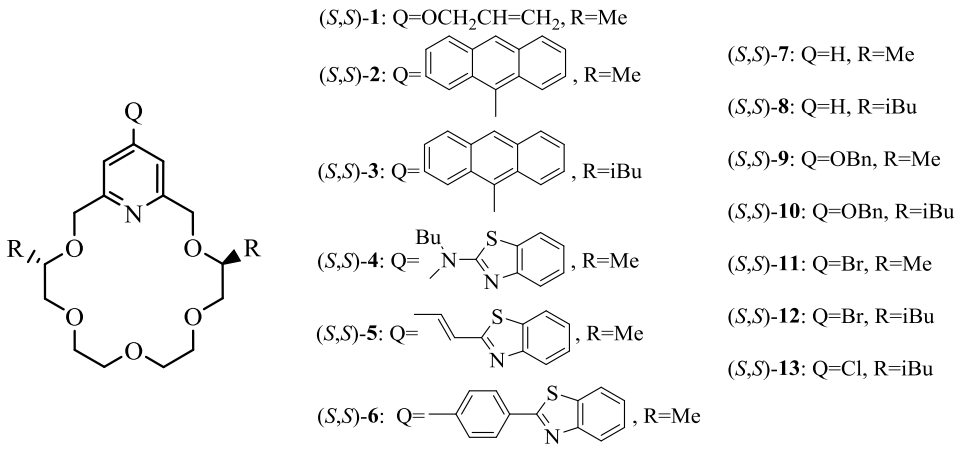


Figure 1.

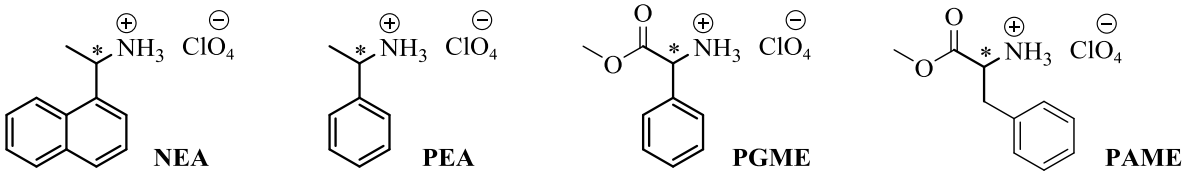


Figure 2.

Allyloxy-substituted pyridino-crown ether (*S*,*S*)-**1** was used as a functional monomer anchor of chiral imprinting polymer for NEA [4]. Pyridino-crown ether (*S*,*S*)-**2**–(*S*,*S*)-**6** showed appreciable or small degrees of enantiomeric recognition toward the enantiomers of NEA, PEA, PGME and PAME determined by fluorescence spectroscopy [5,6,8]. Pyridino-crown ethers (*S*,*S*)-**7**–(*S*,*S*)-**13** were prepared by applying a new continuous flow synthesis in a packed-bed reactor where the *Williamson*-type ether forming macrocyclization was carried out with potassium hydroxide as a heterogeneous base instead of the stronger and more dangerous one sodium hydride [9].

Pyridino-crown ethers (*S*,*S*)-**14**–(*S*,*S*)-**19** (see Figure 3.) containing two amide units were also prepared. Catalytic hydrogenation of crown ethers (*S*,*S*)-**14** and (*S*,*S*)-**17** rendered piperidino-crown ethers (*R*,*S*,*S*,*S*)-**20** and (*R*,*S*,*S*,*S*)-**21**. We determined the basicity and acidity of these crown ethers and found that they are suitable organocatalysts for *Michael* addition reactions [10,11].

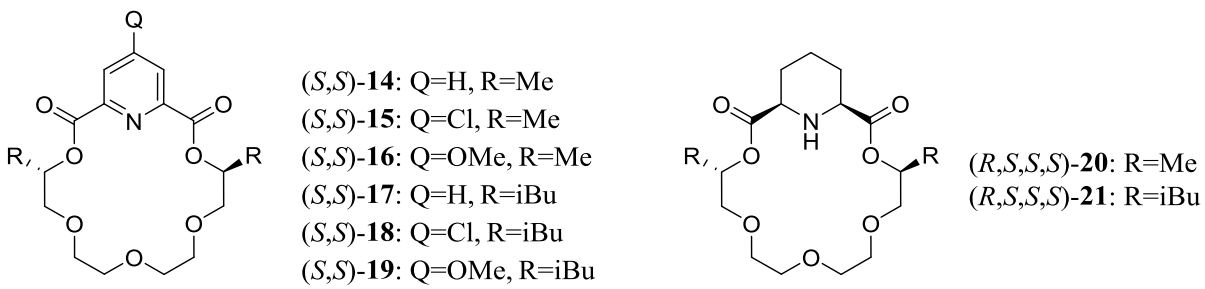
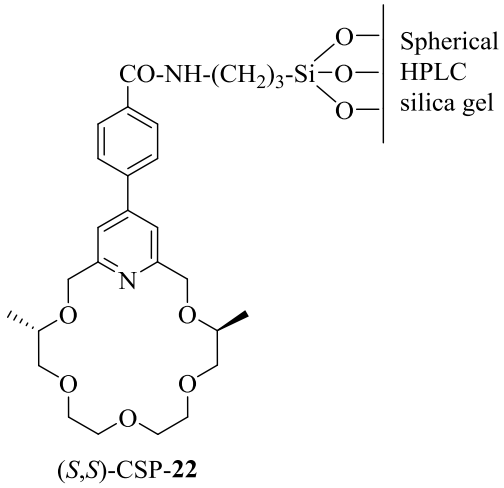


Figure 3.

Using the earlier prepared pyridino-18-crown-6 ether-based chiral stationary phase (*S*,*S*)-CSP-**22** (see Figure 4.) [12] we separated the enantiomers of several biogenic chiral protonated aralkylamines and amino acid derivatives containing an aromatic unit efficiantly by high-performance liquid chromatography (HPLC). The high enantioselectivity was rationalized by the strong intermolecular π–π interactions between the aromatic moieties of the host and the guests [11,13].

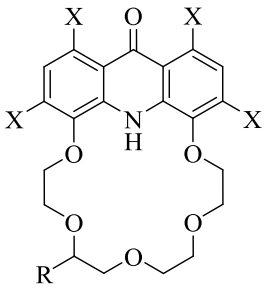


(*S*,*S*)-CSP-**22**

Figure 4.

3. ACRIDONO- AND ACRIDINO-CROWN ETHER DERIVATIVES

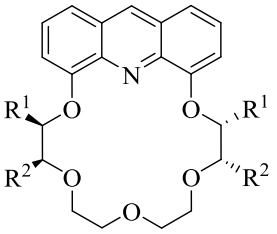
We extensively studied the metal ion recognition ability of earlier reported acridono-crown ether **23** (see Figure 5.) [14] and its new analogue **24** [15] toward Ag^{+}, Ca^{+}, Cd^{2+}, K^{+}, Mg^{2+}, Na^{+}, Pb^{2+}, Zn^{2+} by UV/Vis spectroscopy. Ligand **23** showed appreciable selectivity toward Pb^{2+} [15]. We prepared suitable single crystals of the complex of acridono-crown ether **23** and lead(II) perchlorate, and studied it by X-ray analysis. The studies revealed a strong cation–π interaction between Pb^{2+} and the electron-rich acridone unit [16]. Later we developed a quick detection method of Pb^{2+} using a polyvinyl chloride (PVC)-based ion selective membrane electrode containing lipophilic acridono-crown ether *rac*-**25** (see Figure 5.) The applicability of this sensor was verified by measuring a multicomponent aqueous sample. We demonstrated that this electrode is suitable for the selective quantitative analysis of Pb^{2+} in the presence of many additional metal ions [17].



23: R=X=H
24: R=H, X=Me
rac-**25**: R=$C_{10}H_{21}$, X=H

Figure 5.

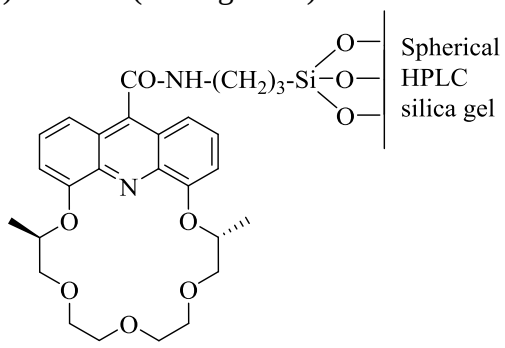
We also studied the enantioselective complexation ability of earlier reported [18] acridino-crown ethers (*R*,*R*)-**26** and (*S*,*S*)-**27** (see Figure 6.). Our earlier studies using fluorescence spectroscopy showed a high enantioselectivity of (*R*,*R*)-**26** toward the (*S*)-enantiomer of NEA, but there was no enantioselectivity observed in the case of (*S*,*S*)-**27** toward any enantiomer of NEA [18]. To get a deeper insight for this observation we prepared single crystals suitable for X-ray analysis from both diastereomeric complexes of the enantiomers of NEA and (*R*,*R*)-**26**. In the case of the heterochiral complex (*R*,*R*)-**26**–(*S*)-NEA, the X-ray analysis revealed a strong intermolecular π–π interaction between the naphthyl unit and the acridine moiety. However, in the case of the homochiral complex (*R*,*R*)-**26**–(*R*)-NEA, π–π interaction was not found. We suggested that the existence or absence of the π–π interaction and the difference in steric repulsions in the diastereomers are responsible for the enantiomeric discrimination [19].



(*R*,*R*)-**26**: R^1=Me, R^2=H
(*S*,*S*)-**27**: R^1=H, R^2=Me

Figure 6.

Later we also tried to prepare single crystals of the complexes of (*S*,*S*)-**27** with the enantiomers of chiral primary aralkylamine hydrogen perchlorates. To our surprise once the sodium perchlorate–acridino-crown ether (*S*,*S*)-**27** complex crystallized out from an alcoholic solution. We studied the crystal structure of this complex by X-ray analysis. Crystallography data suggested that Na^+–(*S*,*S*)-**27** monomers formed a dimer by strong π–π interaction in the crystal. Fluorescence titration was also performed in order to determine the stoichiometry and stability constant of the complex: global fitting of the fluorescence spectra and elemental analysis indicated 1:1 stoichiometry [20]. We developed a novel method for the preparation of chiral stationary phase (*R*,*R*)-CSP-**28** (see Figure 7.).

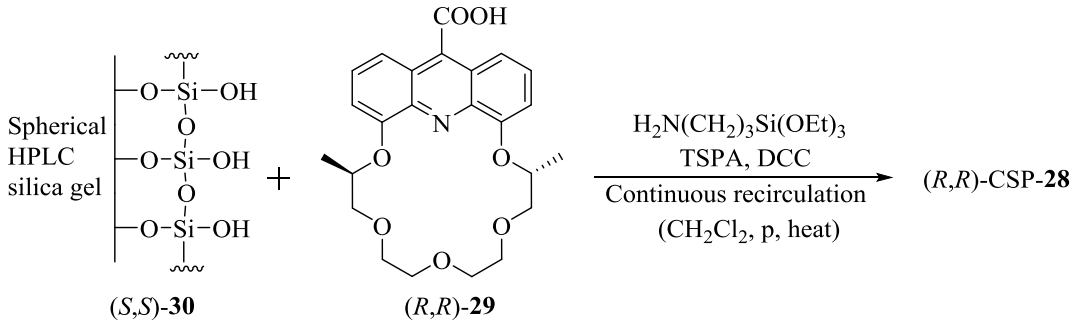


(*R*,*R*)-CSP-**28**

Figure 7.

(*R*,*R*)-CSP-**28** was obtained by *in situ* continuously recirculating the solution of carboxyl-subsituted acridino-18-crown-6 ether (*R*,*R*)-**29**, *N*,*N*'-dicyclohexylcarbodiimide (DCC) and 3-(triethoxysilyl)propylamine (TSPA) through a HPLC column containing blank silica gel SP-

30 under high pressure and at elevated temperature (see Scheme 1.). (*R*,*R*)-CSP-**28** separated the mixtures of enantiomers of selected protonated primary aralkylamines efficiently [21–23].



Scheme 1.

Starting from commercially avaible and relatively cheap materials we prepared by multistep synthesis new acridino-18-crown-6 [(*R*,*R*)-**31**–(*S*,*S*)-**33**] and acridino-21-crown-7 [(*R*,*R*)-**34** and (*S*,*S*)-**35**] ethers containing a carboxyl group at position 9 of the acridine ring (see Figure 8.). The pK_a values of these new crown ethers were determined by UV-pH titration. Crown ether (*S*,*S*)-**33** was attached to silica gel by covalent bonds (see Scheme 2.) and the enantiomeric separation ability of new chiral stationary phase (*S*,*S*)-CSP-**36** for the enantiomers of selected chiral protonated aralkylamines was studied by HPLC.

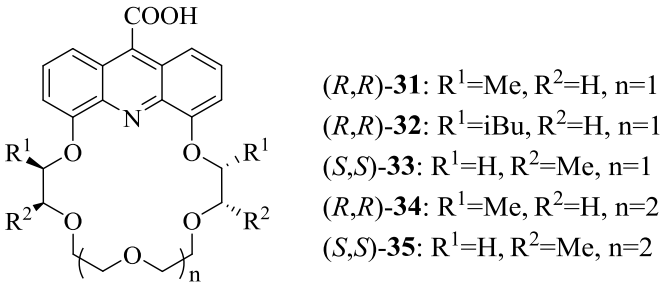
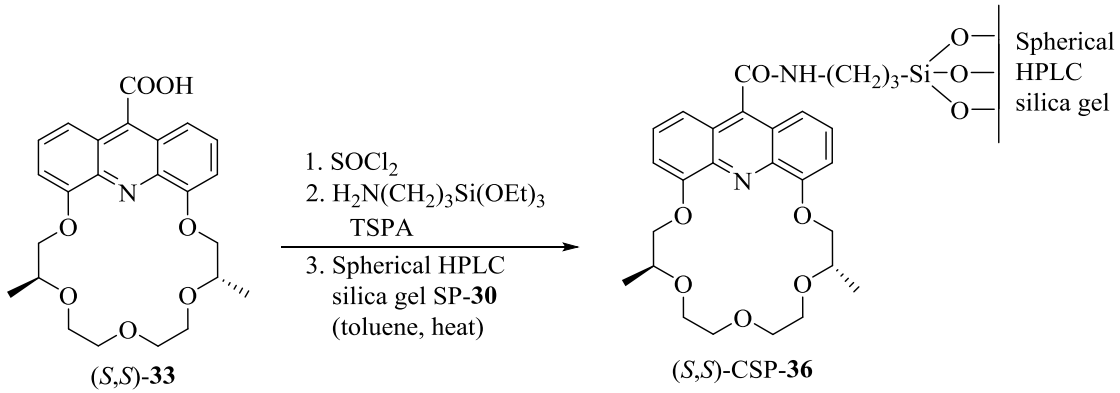


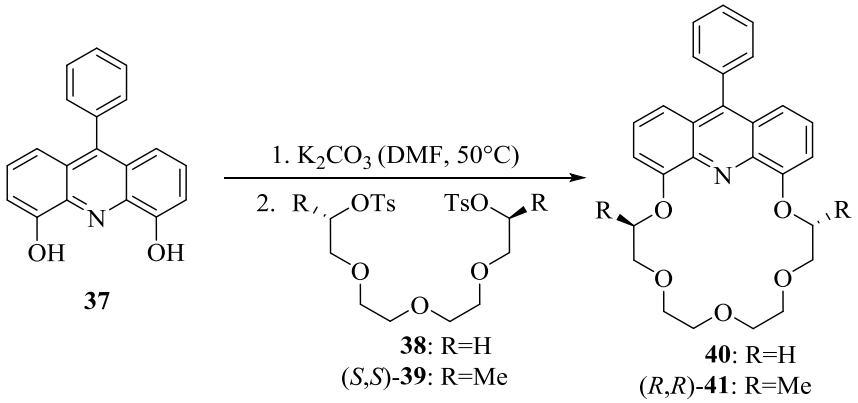
Figure 8.



Scheme 2.

Homochiral preference [(*S*,*S*)-CSP-**36**–(*S*)-protonated aralkylamine] was observed and the best separation was achieved for the enantiomers of NEA [24]. Starting from 9-phenylacridine-4,5-diol (**37**) and tetraethylene glycol ditosylates **38** and (*S*,*S*)-**39** two new 9-

phenylacridino-18-crown-6 ether-type sensor molecules **40** and (*R*,*R*)-**41** were prepared (see Scheme 3.)

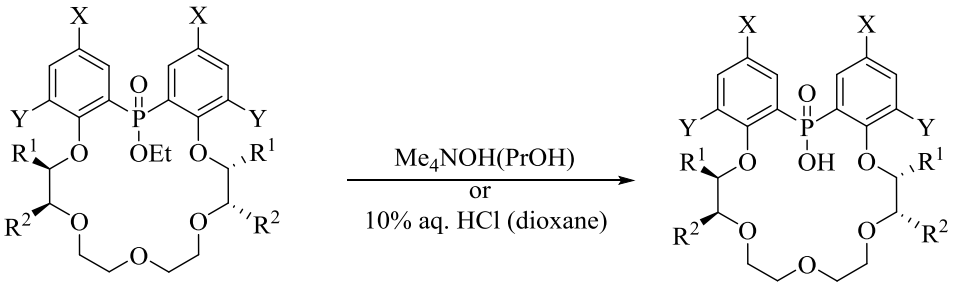


Scheme 3.

Scheme 3. shows only the last macrocyclization step, which in the case of the reaction of deprotonated **37** with (*S*,*S*)-**39** takes place by total inversion of configuration in the applied reaction conditions. The direct precursors **37**, **38** and (*S*,*S*)-**39** were prepared by multistep syntheses. The cation recognition ability of the achiral sensor molecule **40** toward Ag^{+}, Cd^{2+}, Ni^{2+}, Pb^{2+}, Zn^{2+} and NH_4^{+} was studied in acetonitrile by UV/Vis and fluorescence spectroscopies. Selectivity of the chiral dimethyl-substituted analogue (*R*,*R*)-**41** was studied toward the enantiomers of NEA, PEA, PGME and PAME (see Figure 2.) using fluorescence spectroscopy. Heterochiral [(*R*,*R*)-**41**–(*S*)-NEA] preference was found, and the highest degree of enantiomeric recognition was observed for NEA [8,25].

4. CROWN ETHER DERIVATIVES CONTAINING PHOSPHORUS

Starting from phenol or 4-*tert*-butylphenol and tetraethylene glycol we prepared several achiral pseudo-18-crown-6 ether-type macrocycles containing an ethyl diarylphosphinate unit **42**–**46** (see Scheme 4.) by multistep syntheses [26–29]. Starting also from phenol or 4-*tert*-butylphenol and racemic 1,2-epoxydodecane we prepared a great number of enantiopure pseudo-18-crown-6 ether-type macrocycles containing an ethyl diarylphosphinate unit [(*R*,*R*)-**47**–(*S*,*S*)-**53**] by multistep syntheses [26–32]. Hydrolysis of ethyl phosphinates **42**–(*S*,*S*)-**53** either in basic or acidic conditions rendered pseudo-18-crown-6 ether-type macrocycles **54**–(*S*,*S*)-**65** containing a proton-ionizable diaryl-phosphinic acid unit [26–32]. The acidity of achiral macrocycles **42**–**46** containing different substituents at the aromatic rings was studied extensively. An anomaly was discovered in the pK_a values and an explanation was given based on quantum mechanical calculations and dynamics simulations [26]. Enantiopure proton-ionizable macrocycles (*R*,*R*)-**60**–(*S*,*S*)-**65** containing decyl groups at their chiral centers and a diarylphosphinic acid unit were used as carrier molecules for a pH-controlled enantioselective active transport of chiral amines across an aqueous source phase/lipophilic organic memrane/aqueous receiving phase system [30–32].

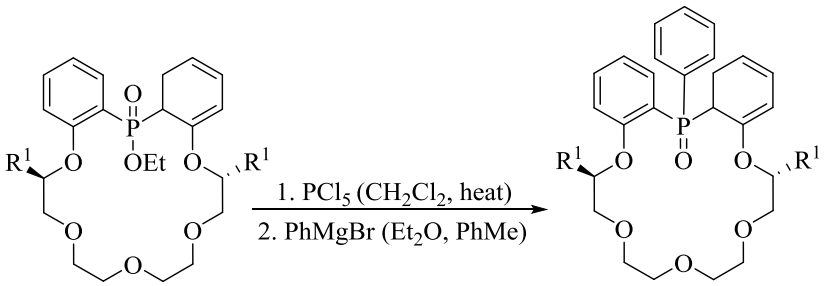


42: $R^1=R^2=X=Y=H$
43: $R^1=R^2=H$, X=*t*Bu, Y=H
44: $R^1=R^2=H$, $X=NO_2$, Y=H
45: $R^1=R^2=H$, X=*t*Bu, $Y=NO_2$
46: $R^1=R^2=H$, $X=Y=NO_2$
(*R*,*R*)-**47**: R^1=Me, R^2=H, X=Y=H
(*R*,*R*)-**48**: R^1=H, $R^2=C_{10}H_{21}$, X=Y=H
(*S*,*S*)-**48**: R^1=H, $R^2=C_{10}H_{21}$, X=Y=H
(*R*,*R*)-**49**: R^1=H, $R^2=C_{10}H_{21}$, X=*t*Bu, Y=H
(*S*,*S*)-**49**: R^1=H, $R^2=C_{10}H_{21}$, X=*t*Bu, Y=H
(*R*,*R*)-**50**: R^1=H, $R^2=C_{10}H_{21}$, $X=NO_2$, Y=H
(*S*,*S*)-**50**: R^1=H, $R^2=C_{10}H_{21}$, $X=NO_2$, Y=H
(*R*,*R*)-**51**: R^1=H, $R^2=C_{10}H_{21}$, X=*t*Bu, $Y=NO_2$
(*S*,*S*)-**51**: R^1=H, $R^2=C_{10}H_{21}$, X=*t*Bu, $Y=NO_2$
(*R*,*R*)-**52**: $R^1=C_{10}H_{21}$, R^2=X=Y=H
(*S*,*S*)-**52**: $R^1=C_{10}H_{21}$, R^2=X=Y=H
(*R*,*R*)-**53**: $R^1=C_{10}H_{21}$, R^2=H, X=*t*Bu, Y=H
(*S*,*S*)-**53**: $R^1=C_{10}H_{21}$, R^2=H, X=*t*Bu, Y=H

54: $R^1=R^2=X=Y=H$
55: $R^1=R^2=H$, X=*t*Bu, Y=H
56: $R^1=R^2=H$, $X=NO_2$, Y=H
57: $R^1=R^2=H$, X=*t*Bu, $Y=NO_2$
58: $R^1=R^2=H$, $X=Y=NO_2$
(*R*,*R*)-**59**: R^1=Me, R^2=H, X=Y=H
(*R*,*R*)-**60**: R^1=H, $R^2=C_{10}H_{21}$, X=Y=H
(*S*,*S*)-**60**: R^1=H, $R^2=C_{10}H_{21}$, X=Y=H
(*R*,*R*)-**61**: R^1=H, $R^2=C_{10}H_{21}$, X=*t*Bu, Y=H
(*S*,*S*)-**61**: R^1=H, $R^2=C_{10}H_{21}$, X=*t*Bu, Y=H
(*R*,*R*)-**62**: R^1=H, $R^2=C_{10}H_{21}$, $X=NO_2$, Y=H
(*S*,*S*)-**62**: R^1=H, $R^2=C_{10}H_{21}$, $X=NO_2$, Y=H
(*R*,*R*)-**63**: R^1=H, $R^2=C_{10}H_{21}$, X=*t*Bu, $Y=NO_2$
(*S*,*S*)-**63**: R^1=H, $R^2=C_{10}H_{21}$, X=*t*Bu, $Y=NO_2$
(*R*,*R*)-**64**: $R^1=C_{10}H_{21}$, R^2=X=Y=H
(*S*,*S*)-**64**: $R^1=C_{10}H_{21}$, R^2=X=Y=H
(*R*,*R*)-**65**: $R^1=C_{10}H_{21}$, R^2=H, X=*t*Bu, Y=H
(*S*,*S*)-**65**: $R^1=C_{10}H_{21}$, R^2=H, X=*t*Bu, Y=H

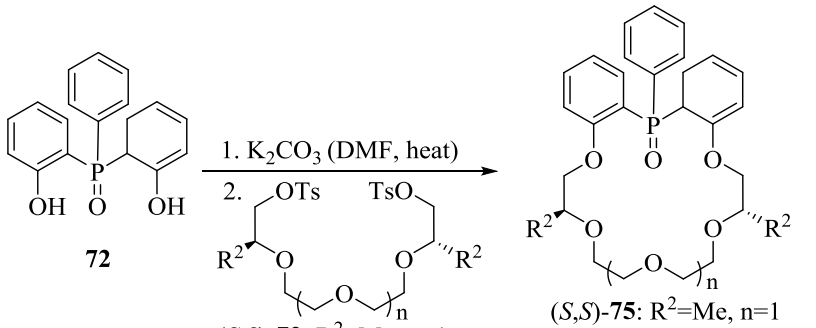
Scheme 4.

Reported achiral **66** [33], and three new enantiopure macrocycles (*R*,*R*)-**67**, (*S*,*S*)-**68** and (*S*,*S*)-**69** containing a triarylphosphane unit were prepared by new methods (see Scheme 5. and also Scheme 4.) [34]. Platinum complexes of monophospha-crown ethers **66**, (*R*,*R*)-**67** and (*S*,*S*)-**68** were synthesized and used as catalyst precursors in asymmetric hydroformylation of styrene. Chemoselectivities of up to 90% toward aldehydes were obtained The branched aldehyde (2-phenylpropanal) was slightly favoured for the reaction and enantiomeric excess up to 52% were achieved. Similar selectivities and higher activities were obtained in the presence of rhodium-monophospa-crown ether catalysts formed *in situ* [35].



42: R^1=H
(*R*,*R*)-**47**: R^1=Me

70: R^1=H
(*R*,*R*)-**71**: R^1=Me



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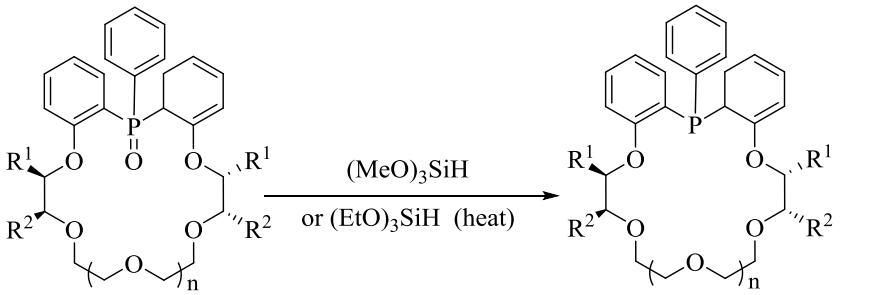
(*S*,*S*)-**73**: R^2=Me, n=1
(*S*,*S*)-**74**: R^2=C_8H_{17}, n=2

(*S*,*S*)-**75**: R^2=Me, n=1
(*S*,*S*)-**76**: R^2=C_8H_{17}, n=2



70: R^1=R^2=H, n=1
(*R*,*R*)-**71**: R^1=Me, R^2=H, n=1
(*S*,*S*)-**75**: R^1=H, R^2=Me, n=1
(*S*,*S*)-**76**: R^1=H, R^2=C_8H_{17}, n=2

66: R^1=R^2=H, n=1
(*R*,*R*)-**67**: R^1=Me, R^2=H, n=1
(*S*,*S*)-**68** R^1=H, R^2=Me, n=1
(*S*,*S*)-**69**: R^1=H, R^2=C_8H_{17}, n=2

Scheme 5.

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