

# Crown Ethers in Enantioselective Synthesis

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A number of new chiral crown compounds and lariat ethers have been synthesized starting from phenyl- $\beta$ -D-glucopyranoside, methyl- $\alpha$ -D-glucopyranoside and galactopyranoside, methyl- $\alpha$ -D-mannopyranoside and 1,2:5,6-di-O-isopropylidene-D-mannitol, but the main emphasis was laid on their application. Some of the sugar-based macrocycles showed significant asymmetric induction as phase transfer catalysts in liquid-liquid and solid-liquid phase reactions such as in two Michael addition reactions (84–95 % ee), in a Darzens condensation (74 % ee) and in the epoxidation of chalcones (92 % ee). The proposed mechanism of the selective reactions was supported by molecular mechanics calculations. The asymmetric self-condensation of phenacyl chloride took place in 64 % ee value. A novel deracemization of CH-acids has also been discovered and the reason of the enantioselective protonation is discussed.

Keywords: *Chiral crown ethers, chiral lariat ethers, asymmetric phase transfer catalysis, enantioselective induction*

A research group at the Technical University, Budapest, has long been dealing with the synthesis and utilization of crown ethers and related molecules.

A number of the sugar-based chiral crown ethers, as well as lariat ethers incorporating glucose, galactose, mannose and mannitol units in the hetero ring have been synthesized. The association constants of these compounds with  $\text{Li}^+$ ,  $\text{Na}^+$ ,  $\text{K}^+$  and  $\text{NH}_4^+$  cations were measured, but the main point was to explore the possibilities offered by the chirality of the macrocycles. We wished to examine if the sugar-based crown ethers are capable for the discrimination of enantiomers and if they can bring about asymmetric induction as catalysts.

## Syntheses of chiral crown ethers from monosaccharides

Several representatives of these molecules, as well as their synthetic pathways are shown in Fig. 1–4. Among others, the “head to leg” type bis-gluco-18-crown-6 (**1b**) and its derivatives obtained by functional group modifications,<sup>1,2</sup> are shown in Fig. 1. The stereo structure of the trans isomer **1b** was identified by single crystal X-ray crystallography. Crown ether **1b** has  $C_2$ -symmetry.<sup>3</sup> The solubility and complex-forming properties of the compounds were influenced by different substituents.<sup>4</sup>

Although, crowns shown in the next Figures do not have  $C_2$ -symmetry, due to their high complex stabilities towards the alkali ions and lipophilicities, they were assumed to be promising catalysts in solid-liquid, as well as in liquid-liquid phase transfer reactions.

The chiral cryptand **5** (Fig. 2) showed exceptionally high complex-forming properties, particularly with potassium and ammonium cations<sup>5</sup>.

Acylation of the diaza-crown ether (**3**) with the glucose-based diacid-dichloride (**2**) by using the high-dilution technique, gave bisamide **4**, from which chiral cryptand **5** was obtained by reduction.<sup>6</sup>

A typical synthetic route for the synthesis of 15-membered monoazacrown ethers (**6**) having different pendant arms (alkyl and aryl substituents)<sup>7</sup> or functionalised pendant arms (lariat ethers)<sup>7,8</sup> on the nitrogen atom is depicted in the Fig. 3. The latter compounds with *O* or *P* heteroatoms in the side arm, are named lariat ethers or armed crown ethers. The similar type compounds are known to display special complexation, high lipophilic character and unique guest specificity via the macroring-side arm cooperativity.<sup>9</sup>

Chiral macrocycles of similar type incorporating mannopyranoside- (**7**),  $\beta$ -phenyl-gluco-pyranoside- (**8**)<sup>10</sup> or mannitol units (**9**)<sup>11</sup> are shown in Fig. 4. They have been synthesized in a similar manner, as shown for compound **6**.

## Asymmetric Michael additions by chiral crown ethers

The present paper is dealing with the enantioface differentiating abilities of crowns synthesised by us in C–C, and C–H bond forming reactions, like additions of C–H acids to electrophilic double bonds in Michael reactions, in Darzens reaction, in epoxidations and in deracemizations. It is important to stress here that the chiral agents have been used not in equivalent, but only in about several mol per-

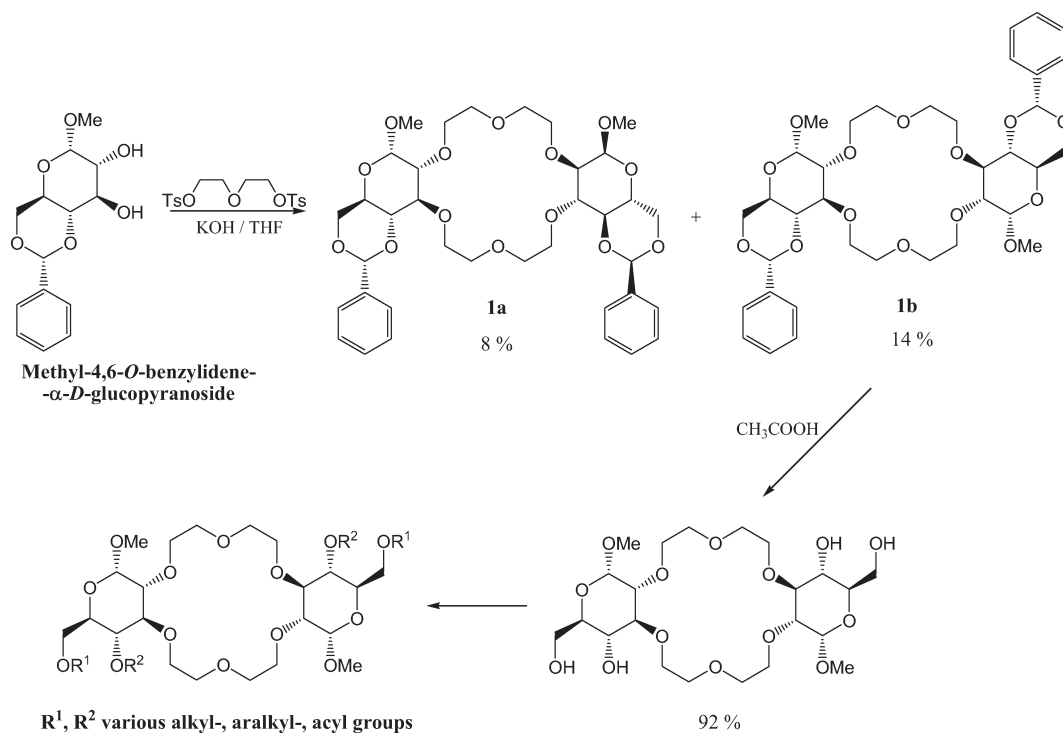


Fig. 1 – Synthesis of bis-glucopyranosido-18-crown-6 type macrocycles

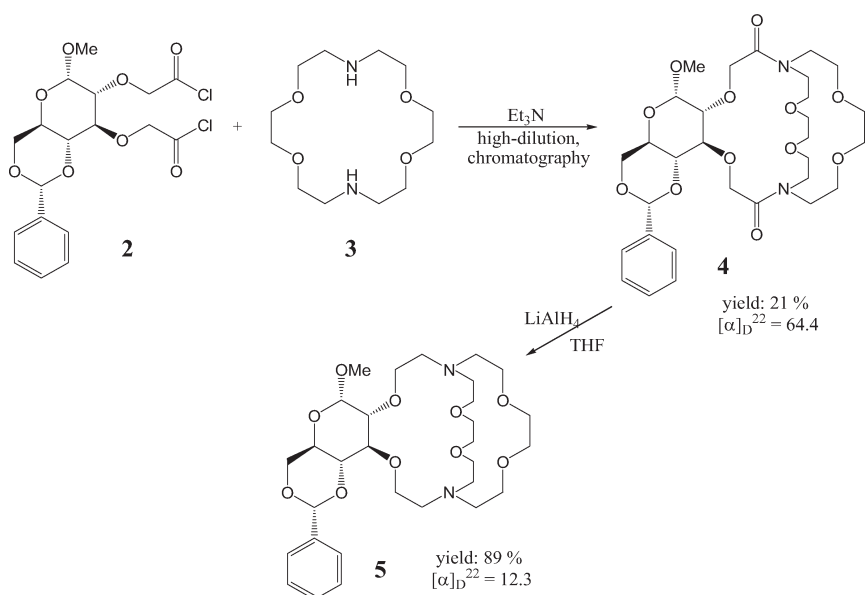


Fig. 2 – Synthesis of a chiral cryptand incorporating a glucopyranoside unit

cent quantity,  $x_{\text{col}}/\%$  (catalytic amount) that is the most attractive way of generating chirality.

They serve as phase transfer catalysts to solubilise and then to transfer the solid base, for instance potassium tertiary butoxide, into the toluene or hexane solution maximally to the extent of their molarity. We supposed that each molecule of the base or each molecule of the enolate ion formed by the effect of the base could exist in toluene or in hexane only in a chiral environment due to the presence of the crown meaning that the uncatalyzed reaction without chiral crown would be negligible.

First, we discuss a well-known C–C bond forming reaction via the example of the Michael reaction, involving the ad-

dition of C–H acids to electrophilic double bonds. In the paper on the catalytic enantioselective Michael reactions reviewed by Krause,<sup>12</sup> our method is called as an alkali-metal-catalyzed Michael addition.

Fig. 5 shows the conditions and the results of the reaction of methyl phenylacetate with methylacrylate using the “head to leg” type bis-glucocrown ethers (**10**) as the catalyst.<sup>13</sup> As can be seen, under certain conditions, the ee for the *S*-antipode reaches 85%. Explaining the stereochemical outcome of the reaction, we supposed that an equilibrium exists between the enolate – metal ion – crown ether ion-pair complexes (Fig. 6).

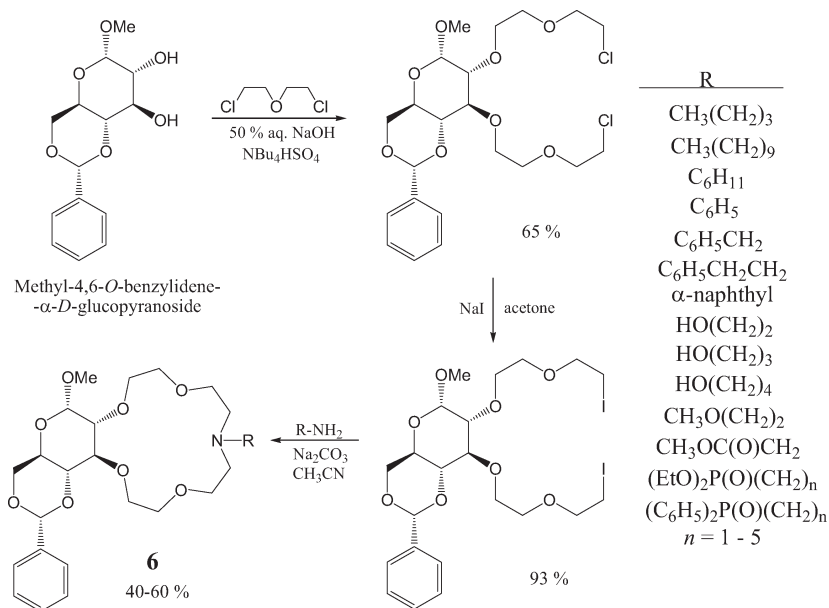


Fig. 3 – Synthesis of monoaza-15-crown-5 type crown- and lariat ethers incorporating a glucopyranoside unit

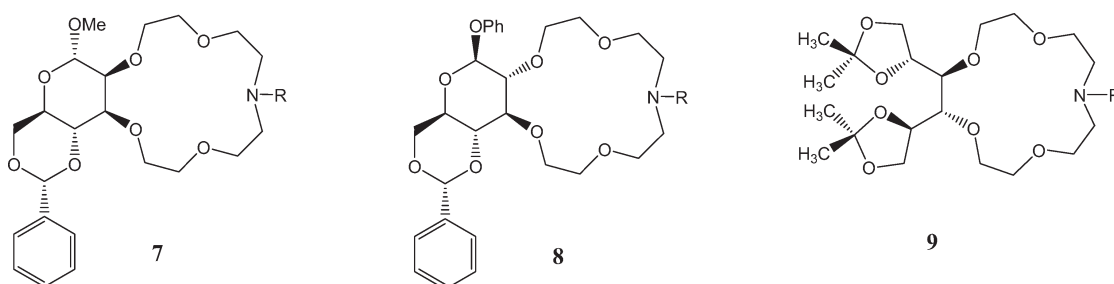


Fig. 4 – Monoaza-15-crown-5 type macrocycles incorporating different monosaccharides or mannitol units

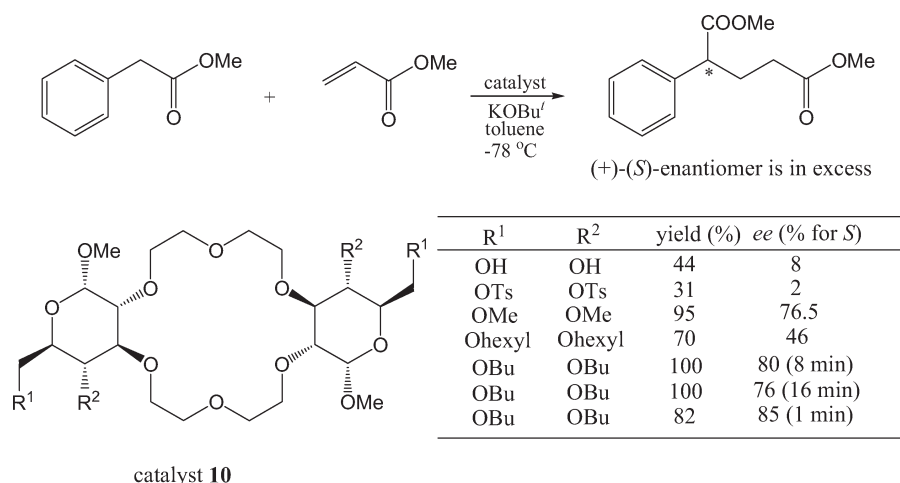


Fig. 5 – Effect of the substituents of the catalyst in the Michael addition of methyl phenylacetate to methyl acrylate in solid-liquid system (KOBu<sup>t</sup> – toluene, at -78 °C) in the presence of a chiral catalyst ( $\chi_{cat} = 6\%$ )

Only the presence of the more stable *Z*-enolate was supposed to exist in this equilibrium, hence four different ion-pair-complexes were taken into account in our considerations. Due to the better fit of the *Z*-enolate to the metal ion crown complexes, the first ion pair shown in the left part of Fig. 6 is the most stable among the four possibilities. Therefore, this complex dominates in the equilibrium, and

by the attack of the acrylate, it is this situation which gets frozen to give *S*-enantiomer excess. In this explanation we assumed that the antipode ratio is not modified heavily by the reaction rate differences of the acrylate with the different enolate-ionpair complexes in the equilibrium, that is the rate of all these elemental steps (steps 1.) were taken arbitrarily equal.<sup>13</sup>

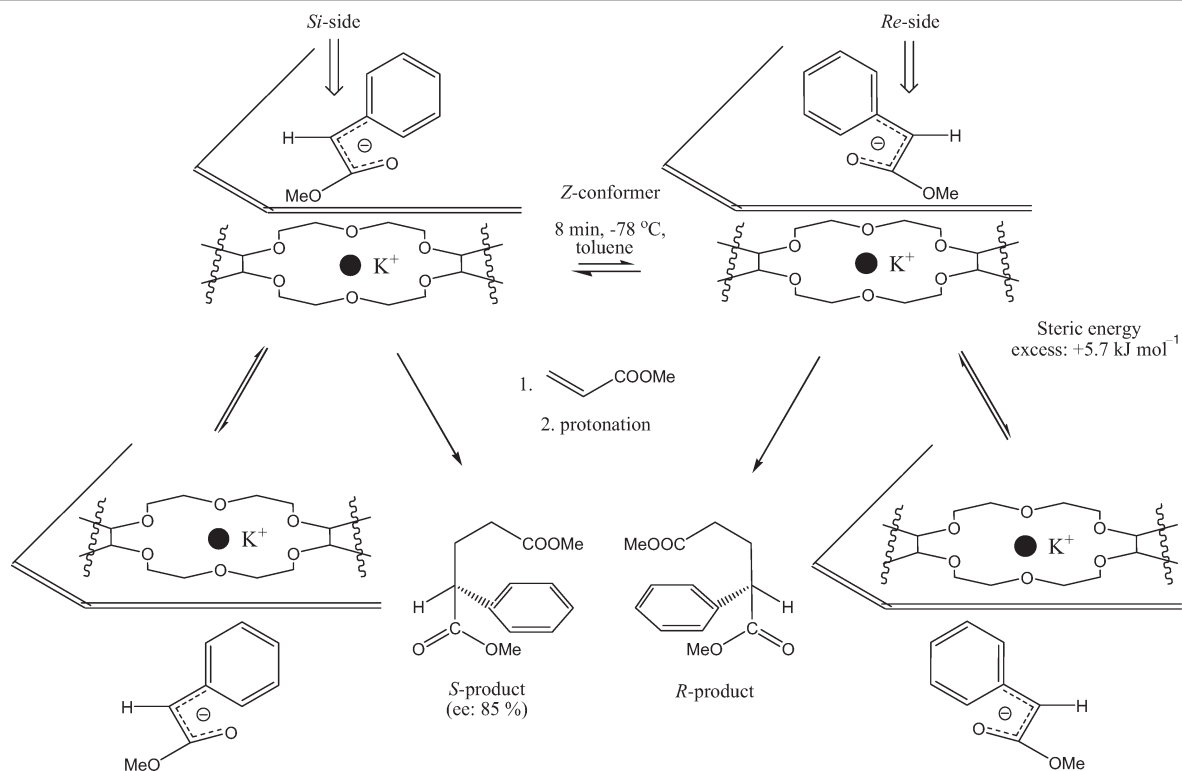


Fig. 6 – A possible mechanism for the asymmetric reaction of methyl phenylacetate with methyl acrylate in solid-liquid system

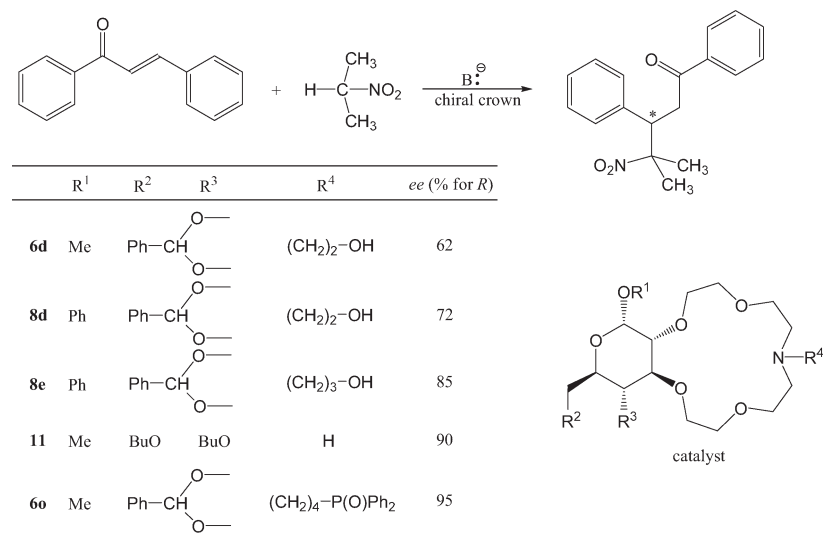
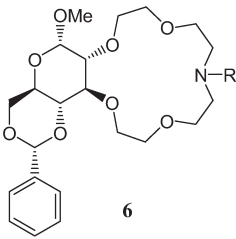


Fig. 7 – Effect of the substituents of the chiral catalyst on the addition of 2-nitropropane to chalcone in solid-liquid system, in the presence of NaOBu<sup>t</sup> ( $\chi_{\text{NaOBu}^t} = 30\%$ ) and glucose-based chiral catalyst ( $\chi_{\text{cat}} = 6\%$ )

This consideration was justified by molecular mechanics calculations, (SUMM-conformational search, MCOMM/MOLS). This calculation for the “tetramethyl-analogue” showed that the potassium or the sodium ion is not situated in the “plane” of the crown, but above it, as shown. As a consequence of this, not the four, but only the two ion pair energies had to be taken into account in the calculations. The two other possible structures are much richer in energy due to the bigger distance of the anion from the cation. The calculations suggested, that the steric energy content of the complex formed by the fit from the *Re*-side of the enolate is by 5.2 kJ mol<sup>-1</sup> higher, than the one leading to

the *S*-antipode. This means a 78 % excess of the *S*-antipode that is in good agreement with the experimentally found value (76.5 % ee for the *S*-antipode).<sup>13</sup>

As the ee value in this reaction could not be improved either by using other catalysts obtained from the bis-glucose crown by functional group modifications nor by the cryptand shown above, we began testing them in another Michael reaction, in the addition of 2-nitropropane to chalcone (Fig. 7). The results were, however disappointing; using the bis-glucose-crown (**10**, R<sup>1</sup> = R<sup>2</sup> = OBu) the best result was an ee of 28 % for the *R*-product. For this we



	R	ee (% for <i>R</i> )
<b>6a</b>	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub>	46
<b>6b</b>	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> CH <sub>2</sub>	61
<b>6c</b>	n-Bu	58
<b>6d</b>	HO(CH <sub>2</sub> ) <sub>2</sub>	62
<b>6e</b>	HO(CH <sub>2</sub> ) <sub>3</sub>	85
<b>6f</b>	HO(CH <sub>2</sub> ) <sub>4</sub>	85
<b>6g</b>	(EtO) <sub>2</sub> P(O)CH <sub>2</sub>	63
<b>6h</b>	(EtO) <sub>2</sub> P(O)(CH <sub>2</sub> ) <sub>2</sub>	61
<b>6i</b>	(EtO) <sub>2</sub> P(O)(CH <sub>2</sub> ) <sub>3</sub>	60
<b>6j</b>	(EtO) <sub>2</sub> P(O)(CH <sub>2</sub> ) <sub>4</sub>	83
<b>6k</b>	(EtO) <sub>2</sub> P(O)(CH <sub>2</sub> ) <sub>5</sub>	79
<b>6l</b>	(C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub> P(O)CH <sub>2</sub>	63
<b>6m</b>	(C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub> P(O)(CH <sub>2</sub> ) <sub>2</sub>	74
<b>6n</b>	(C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub> P(O)(CH <sub>2</sub> ) <sub>3</sub>	77
<b>6o</b>	(C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub> P(O)(CH <sub>2</sub> ) <sub>4</sub>	95
<b>6p</b>	(C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub> P(O)(CH <sub>2</sub> ) <sub>5</sub>	79

*α*-D-glucose-based catalyst

Fig. 8 – The effect of the side arms of the catalyst on the asymmetric induction in the addition of 2-nitropropane to chalcone

synthesized a number of new model compounds, the aza-15-crown-5 annelated to glucose and galactose and studied the chiral induction in the above reaction under solid-liquid phase transfer conditions using solid sodium tertiary butoxide as the base.<sup>14</sup>

It was found that the flexibility of the chiral macrocycle, the type of the annelating carbohydrate building blocks, the substituents in the carbohydrate unit and on the nitrogen atom of the macrocycle play the most important role in the generation of asymmetric induction.<sup>15</sup>

As can be seen from Fig. 7., the new catalyst proved to be more than promising, as depending on the *N*-substituent, the ee value for the product increased and, for instance in the case of the R = CH<sub>2</sub>–CH<sub>2</sub>–OH substituent (**6d**) the ee value reached 62 % for *R*-antipode. The absolute configuration of the Michael adduct was established by X-ray analysis.<sup>14</sup> A slight modification of that catalyst by exchanging the 4,6-benzylidene-protective group by di-butyls and simultaneously the *N*-substituent to hydrogen (**11**), the outcome of the reaction improved further to give an ee of 90 % for *R*-antipode.<sup>16</sup>

From these data it was imperative for us to evaluate the role of the *N*-substituents in the crown ring, as well as the effect of the substituents attached to the sugar unit (Fig. 8).<sup>17–22</sup>

As regards the role of the *N*-substituent, the effect of the alkyl group on the enantioselectivity is poor, but the ee value increases with its bulkiness, e.g. an *N*-phenylethyl group (**6b**) results in a 61 % excess of the *R* form. It is a much more important observation that in the cases, where the side arm cooperation in the complexation emerges (lariat ethers), again a significant increase in the ee could be detected; in the case of *N*-hydroxyethyl (**6d**) it was 62 %, while with at *N*-hydroxypropyl (**6e**) it was 85 %. A further increase in the chain length did not, however, increase the ee value: with hydroxy-butyl (**6f**) it remained 85 % (Fig. 8).

Fig. 8 also shows the effect of the diethyl phosphonoalkyl chain on the same addition. Again the importance of the

chain length and the role of the side chain cooperativity should be seen: the highest value (83 %) was observed for the phosphonobutyl group (**6j**, *n* = 4), there was no improvement with the phosphonopentyl moiety (**6k**, *n* = 5, 79 % ee)<sup>19</sup> Fig. 8 also shows the effect of diphenylphosphinoxido groups in the side chain: the maximum ee value of 95 % was again observed with (CH<sub>2</sub>)<sub>4</sub>P(O)Ph<sub>2</sub>, having four carbon atoms (**6o**).<sup>20</sup>

From all these facts we can conclude that the side arm – macrocoring cooperativity in the complexation of the sodium ion plays an important role in the differentiation of enantiomers and favors in the same direction as the chiral sugar unit substituents do (see Fig. 7), probably by increasing the energy differences of steric origin between the ionpair complexes formed at the two sides of the macrocoring (Fig. 9).

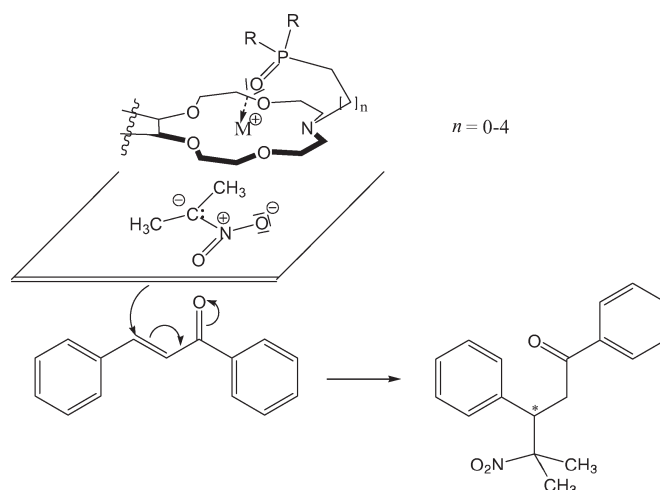


Fig. 9 – A possible mechanism for the asymmetric Michael addition of 2-nitropropane to chalcone in the presence of chiral lariat ether having a phosphorus atom in the side arm

In the light of this explanation, the bulkiness of the heteroatomic function in the *N*-substituent can also be an important factor and the higher enantioselectivity obtained with the diphenylphosphinoxido-group containing catalyst, as compared with the case of the diethyl-phosphono counterpart, can nicely be interpreted.

It was observed that the  $\delta$  in the <sup>31</sup>P-NMR spectra of the phosphinoxides (**6l–6p**) did not depend on the chain length, but remained almost constant going from *n* = 1 to *n* = 4, whereas the ee value increased from 60 % to 95 % for the *R*-antipode. (The change in the <sup>31</sup>P chemical shifts may fall in the range of NMR-experimental error).

The work is being continued to improve the efficiency of these type of catalyst by modifying the protective groups on the sugar units; for instance by exchanging the benzal to di-*O*-butyl groups<sup>19</sup> or exchange the glucosydic methyl to phenyl,<sup>17</sup> and to make azacrowns in which the sugar (glucose) is annelated not at positions 2 and 3 of the glucose, but at other two positions, e. g. at the 3,4- or the 4,6-atoms of the glucose. With the 3,4-annelated isomers, the enantio-preference may change from *R*- to *S*- as was suggested by molecular model examinations. As a part of



this type of calculations, we carried out the addition in the presence of galactose and mannitol anellated crown analogues and found that the best results could be obtained with the glucose-anellated derivatives.

## Asymmetric Darzens condensation

The versatility of our glucose-anellated azacrowns as effective catalyst in enantioselective reactions has also been shown in the Darzens reaction. This reaction, giving a keto-epoxyde in the reaction of a halogeno-ketone with an oxo-compound, is widely used in the syntheses of medicinal products like the well-known Ca-channel blocker, diltiazem, so the realisation of this reaction with good diastereoselectivity and high enantioselectivity is very important, both, from economical and from environmental point of view.

We studied the reaction of phenacylchloride with benzaldehyde (Fig. 10) applying the conditions and catalysts used in Michael reaction (in solid-liquid phase transfer conditions, solid sodium- or potassium *tert*-butoxyde as the base, toluene as the solvent and the bis-glucocrowns of  $C_2$ -symmetry, as well as glucose- or galactose anellated azacrowns), but these conditions did not bring about improvements in the enantioselectivity; the ee for the products were not higher than 5 % for the *2R,3S*-antipode.

The breakthrough for the problems has been brought by changing the PT (phase-transfer) conditions; applying liquid-liquid PT-conditions using 30 % aqueous sodium-hydroxide (as base), toluene, at  $-20\text{ }^\circ\text{C}$ , and the  $N$ -( $\text{CH}_2$ )<sub>2</sub>-OH or  $N$ -( $\text{CH}_2$ )<sub>3</sub>-OH substituted catalysts, we got the *trans*-epoxyde, as the only product with 62 % and 72 % ee, respectively, for the *2R,3S* antipode, showing again the importance of the chain length of the  $N$ -substituent and that of the space requirement of the sugar protecting groups, as the phenyl-glucoside analogue **8** gave an ee of 75 % for the *2R,3S* antipode.<sup>14,18</sup>

The brave and unusual change of the PT conditions go, from the solid-liquid to the liquid-liquid system proved to be decisive from the point of view enantioselectivity (from 5 % to 75 %!), and it may be even suitable also for other types of reaction, where under the solid-liquid PT-conditions could not be achieved a significant asymmetric induction.

Fig. 11 shows a possible arrangement of the anion formed from chloroacetophenone and its subsequent reaction with benzaldehyde to give the product. In the first step, the crown – sodium hydroxide complex deprotonates the chloroacetophenone at the phase boundary to give the enolate-sodium-crown-complex. In this complex, the *Si*-side of the enolate is free and is attacked by the aldehyde carbonyl carbon from its *Re*-side to give the adduct with *2S,3S*-configuration and finally the endproduct with *2R,3S*-configuration by an  $S_N^i$  process. The preference for this direction of the enantioselectivity may highly be influenced by the solvation of the ion pair complexes by water.

Similar experiments were carried out using *ortho*-, and *para*-substituted benzaldehyde and phenacylchloride. In these cases, the *trans* diastereomers were formed as the only products in the *2R,3S*-enantiomer form with an ee of 55–64 %. The *2R,3S* absolute configuration of the product obtained with the *p*-chloro-benzaldehyde was determined by X-ray crystallography.<sup>18</sup>

During the work-up of the Darzens reactions, an optically active by-product has been separated which proved to be the base-initiated self-condensation product of phenacyl-chloride (Fig. 12).

The product was known from the literature as a mixture of two racemic diastereomers. We prepared the compound in a separate experiment from phenacylchloride in the presence of the *N*-hydroxypropyl lariat ether and succeeded in separating, both, the *cis* and the *trans*-diastereomers in a ratio of 1 : 3, both in optically active form. Absolute configuration for the major component was found to be *2R,3S*, as suggested by X-ray analysis.<sup>18</sup>

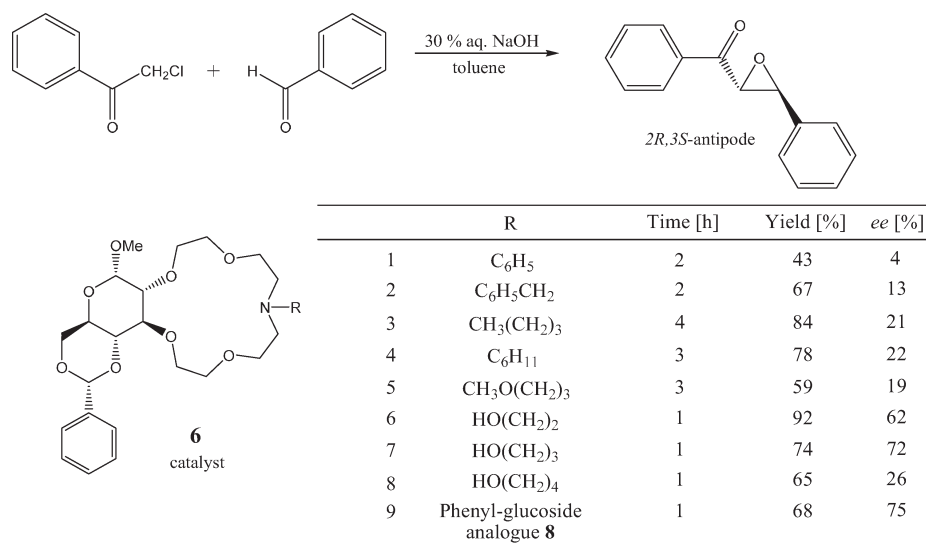


Fig. 10 – Asymmetric Darzens condensation of phenacylchloride with benzaldehyde in the presence of chiral crown ethers or lariat ethers

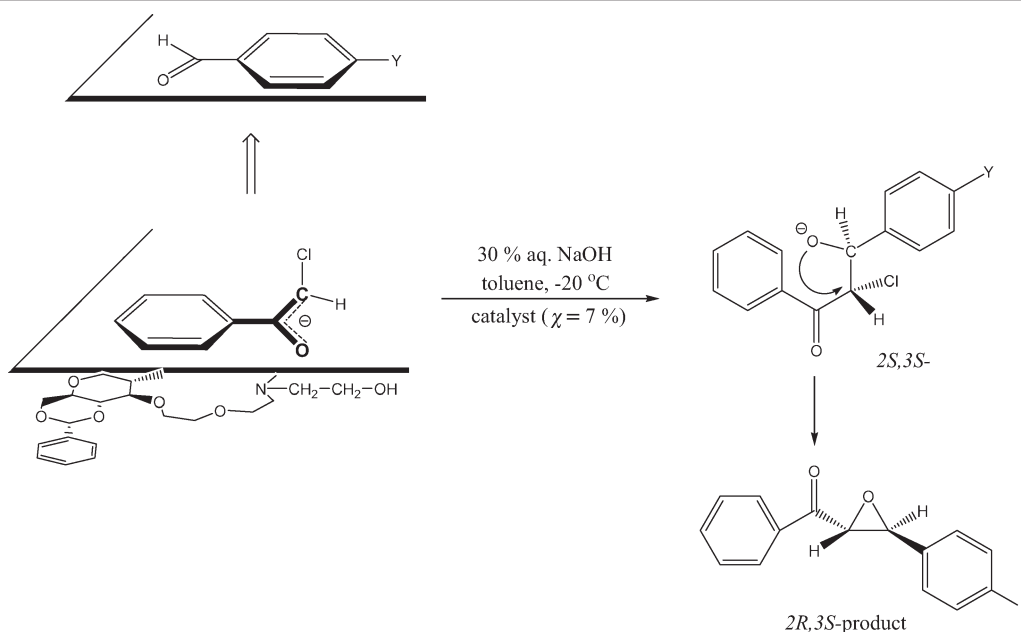
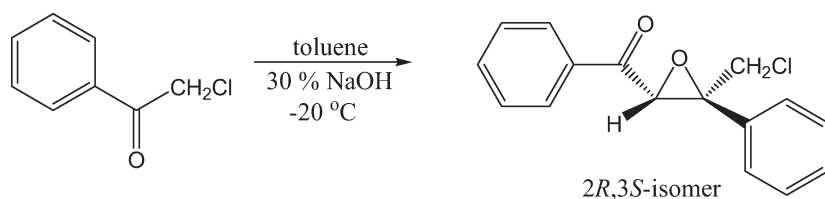


Fig. 11 – The mechanism proposed for the asymmetric Darzens condensation in liquid-liquid two-phase reaction in the presence of a sugar-based lariat ether



ratio of *cis:trans* isomers 23:77  
64 % *ee* (in the *trans* isomer) for 2*R*,3*S*

Fig. 12 – The asymmetric self-condensation of phenacyl chloride in the presence of sugar-based crown ethers

## Deracemization

In this section the enantioselective formation of the C–H bond, in the so called deracemization process, is discussed. We came across this problem during the study of the Michael addition of methylphenylacetate to methyl acrylate where we observed that the *ee* values for the adduct were dependent on the time.

As can be seen from Fig. 13, the reaction is very fast even at  $-78\text{ }^{\circ}\text{C}$ ; after a one minute's reaction time 82 % of the starting material has been converted into product with enantioselectivity of as high, as 85 % for the *S*-antipode. After 8 min, the reaction was complete, but the *ee* slightly decreased to 79 %. After additional 8 min, the *ee* value was 76 %. We also observed that the rate of the decrease of the *ee* value could somewhat be retarded by the excess of methyl phenylacetate, as in its absence the *ee* decreased faster reaching an *ee* of 40 % (after 8 min reaction time) and, which is worth mentioning, the *ee* value remained almost stable further on with time.

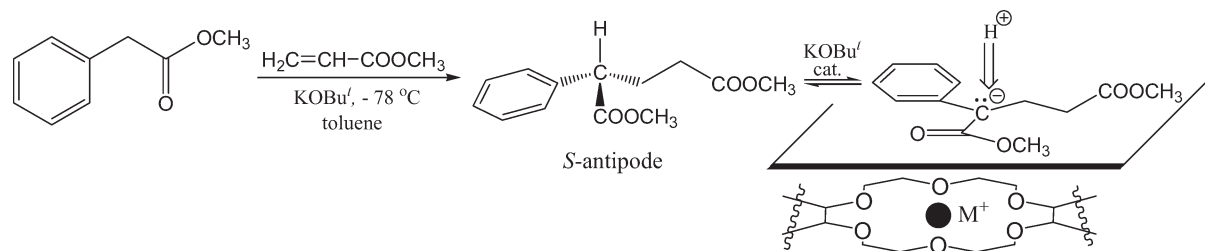
From these facts one can deduce that the *ee* values in this type of reaction are determined by two factors; the kinetically controlled result of the asymmetric C–C bond formation is continuously modified by a thermodynamically con-

trolled process; that is a deprotonation of the end-product by the crown-potassium *t*-butoxide base complex and protonation of the enolate so formed, that is still in chiral environment, by *t*-BuOH.

From these facts one can conclude – as a first consequence – that the highest *ee* values are obtained at the very beginning of the reaction, which worsens with time, so taking into account also the conversion there should be a time optimum for these type of reactions to get good yield with still highest possible *ee*.

On the other hand, it is also evident from the data of Fig. 13 that the position of the deprotonation – protonation equilibria in the presence of our chiral catalyst is around 40 % for *S*, so it can be expected that placing the product racemate into a condition imitating the conditions of the asymmetric Michael reaction (of course without adding the two reagents), a so called deracemization will occur till reaching the 40 % *S* value. Indeed we found that the product-racemate treated in this way showed optical activity, the size of which was increasing with the time and after 8 min stirring at  $-78\text{ }^{\circ}\text{C}$ , the *ee* value for the *S*-antipode approached 40 % *ee* for the *S* form.<sup>13</sup>

The preparation of the desired antipode from the racemate by deracemization is an attractive route, as one can get



Time (min)	Presence of the starting materials in the mixture	Conversion $\chi$ /%	S-antipode excess, ee/%
1	+	82	85
8	+	100	79
16	+	100	76
8	-	100	41
8	Deracemization starting from the product racemate		40

Fig. 13 – Time-dependence of the reaction of methyl phenylacetate with methyl acrylate and deracemization of the racemic Michael adduct

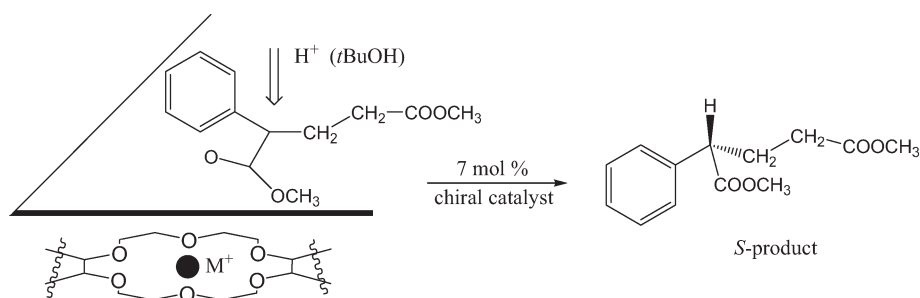


Fig. 14 – Enantioselective protonation of the enolate in the presence of a chiral crown ether catalyst

the racemate in a separate reaction using the best and cheapest synthetic method and subsequently in a process, called deracemization, both antipodes of the racemate can be converted into one, theoretically in 100 % yield.

A few good methods have been published recently for the deracemization of C–H acids by Vedejs,<sup>23</sup> Hünig,<sup>24</sup> Fehr,<sup>25</sup> Krause,<sup>26</sup> and Trost.<sup>27</sup> The acidic proton was removed by e.g. an organometallic reagent quantitatively and in an irreversible way, and the anion so formed was protonated by a chiral amine, or chiral alcohol or phenol.

Catalytic variants for the deracemization process are also known; in these cases less than one equivalent of the chiral proton source is used to protonate the anion at the suitable carbon and the missing proton equivalent is added or developed continuously from an achiral proton source.

In our case, the situation is a somewhat different as not the proton source, but the enolate, developed by the chiral crown potassium *t*-butoxide, is in a chiral neighbourhood and is protonated by an achiral proton source, by *t*-BuOH, or partly by the acidic proton from one of the antipodes of the starting racemate (Fig. 14).

Our deracemization method is of novelty and deserves more attention due to its efficiency.

Our method is analogous with the diastereoselective protonation of the enolate studied by Krause and his coworkers.<sup>26</sup> There is, however one difference: in our method the chiral entity is not covalently bound to the enolate to be protonated. Moreover, they used a chelating chiral proton source, such as salicylic acid ester and its substituted derivatives and pointed out that proton donors capable of forming six-membered chelate should be used to achieve high diastereoselectivities, while we used only *t*-BuOH for this purposes. The work is now being continued to evaluate the scope and limitations of the method.

Last but not the least, let us regard the enantioselective formation of the C–O bond, on the example of the epoxydation of the C–C-double bond in chalcone (Fig. 15).

*tert*-Butylhydroperoxide was applied first and, to our surprise, selectivity could be observed only under very strict experimental condition; the reaction should be run in an aqueous sodium hydroxide – toluene two-phase mixture containing the hydroperoxide and the phase transfer catalyst, which proved to be effective only if it was a laria-



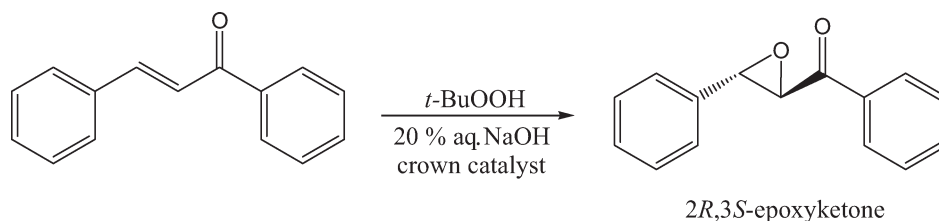
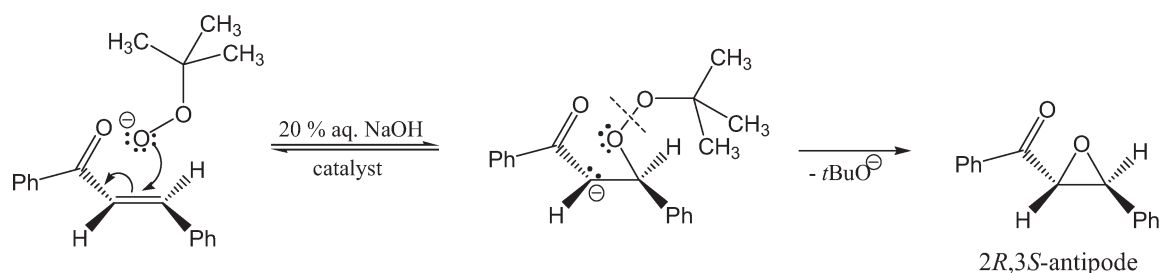


Fig. 15 – Asymmetric epoxidation of chalcone with *tert*-BuOOH in the presence of a chiral crown ether catalyst



**Catalyst: - glucose-based lariat ether:**  
92 % *ee* for (*2R,3S*)-antipode

- mannose-based lariat ether:  
80 % *ee* for (*2S,3R*)-antipode

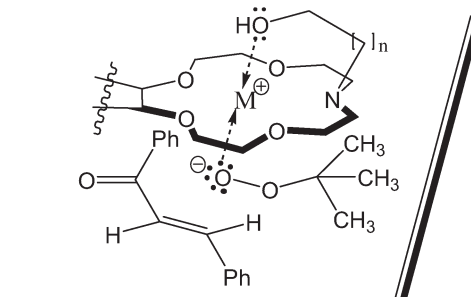


Fig. 16 – A possible mechanism for the asymmetric epoxidation of the chalcone in the presence of sugar-based lariat ethers

te ether **6–9**, shown in Fig. 3. Another requirement is that the double-bond to be oxidized should have a strong electron attracting group, such as a keto group in the vicinity.

Under the above conditions the reaction led to excellent enantioselectivity, for instance the *ee* was 92 % for the *2R,3S* epoxyketone (shown in Fig. 15) using the glucose based lariat ether having a hydroxypropyl substituent on the *N*-atom (**6e**, R = (CH<sub>2</sub>)<sub>3</sub>-OH). Moreover, an *ee* of 80 % was obtained with the mannose based lariat ether (**7**) having the same kind of side arm, to give the *2S,3R* antipode of the trans epoxide. Fig. 16 shows a possible mechanistic picture for the oxidation.

From the experimental conditions of the successful reaction one can assume that a hydroperoxide anion is formed at the phase boundary in an equilibrium which is then transferred into the organic phase by the catalyst, where the sodium ion – catalyst – peroxide anion complex meet the substrate to give an adduct that is transformed to the trans epoxide with *2R,3S* absolute configuration.

As regards the efficiency of the crown ethers in asymmetric induction, it is assumed that the substituent on the nitrogen atom assists the complexation of the cation of the salt in the third dimension. The complexing interaction was optimal with the hydroxypropyl substituent. Hence,

we could achieved a fine tuning between the structure of the catalyst and the measure of the enantioselectivity.

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#### SAŽETAK

##### Krunasti eteri u enantioselektivnoj sintezi

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Sintetiziran je niz novih krunastih spojeva polazeći od fenil- $\beta$ -D-glukopiranozida, metil- $\alpha$ -D-glukopi-ranozida i galaktopiranozida te metil- $\alpha$ -D-manopiranozida i 1,2,5,6-di-O-izopropiliden-D-manitola i opisana je njihova glavna primjena. Neki su od šećernih makrocikla pokazali značajnu kiralnu indukciju prilikom katalize prijenosom faza tekuće-tekuće i čvrsto-tekuće kod reakcija među kojima su Michaelova adicija, Darzensova kondenzacija i epoksidacija halkona. Predloženi mehanistički model selektivnih reakcija potvrđen je molekulsko mehaničkim računima. Asimetrična samokondenzacija fenacilklorida protekla je uz 64 % ee. Otkrivena je i nova deracemizacija CH-kiselina, a raspravljen je i mehanizam enantioselektivnog protoniranja.

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