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The Structure-Activity Relationship and Reusability of Chiral Azacrown Ethers Derived from L-Threitol

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In enantioselective reactions, several catalysts can be used, such as chiral crown ethers, which form a special group of them. In addition to the reaction conditions, the structure of the catalyst used also affects the outcome of the reaction. In the case of carbohydrate-based crown ethers, we previously found that the monoaza-15-crown-5 structure is the most effective, and the generated enantiomeric excess is influenced by the substituent of the nitrogen, the protecting groups of the carbohydrate, and the source of chirality. In this study, macrocycles derived from L-threitol were synthesized with a similar structure, and their catalytic activity and reusability were tested and compared in different model reactions along with some previously prepared compounds. Several types of effect-structure relationships were pointed out, while the enantiomeric excess varied widely. We demonstrated the recoverability of the crown ethers by acidic extraction and subsequent liberation of the azacrown moiety. The regeneration process was investigated more thoroughly in scaled-up reactions, where the selectivity of the catalysts preserved for three examined cycles.

1. Introduction

Since 1967, crown ethers have been expanding the toolbox of chemistry. In the beginning, their complex formation properties were more investigated, and then they were also applied as phase transfer catalysts.[1] By using chiral building blocks, chiral–chiral recognition and the utilization of asymmetric induction with crown ethers became possible. Several enantioselective syntheses were realized using various chiral crown ethers, in some cases the expected product was formed with an excellent enantiomeric excess.[2] The macrocycles that trigger asymmetric induction and are dissolved in the reaction mixture can be considered as homogeneous catalysts; therefore, their separation and reuse after the reaction have taken place is a challenge for researchers.

The relevance of catalyst recycling is shown by the growing number of publications in this field. Several techniques have been elaborated to recover these valuable compounds, among which both heterogeneous and homogeneous methods can be found.[3] The simplest and most obvious way to prepare reusable catalysts is by immobilization to solid support. Anchoring catalysts to silica gel, polystyrene resins, and magnetic nanoparticles is frequently used, and even self-supported catalysts have already been synthesized.[4,5] Although the removal of a heterogeneous catalyst is efficient, problems arise as the yield and enantiomeric excess are generally lower than in homogeneous systems. Therefore, especially in the field of organocatalysis, homogeneous chiral catalysts were developed, which can be selectively separated from other components of the reaction mixture. Recovery processes can be grouped according to the mode of separation, e.g., extraction, membrane filtration, or precipitation.[6–9] Selective extraction has already been implemented through acid/base properties, using perfluorinated side chains or ionic tags.[6,7,9] In some cases, ionic liquids (ILs) were used as an alternative reaction medium, from which the product and excess reagent could be extracted, and the catalyst remained in the IL solvent.[10]

Crown ethers are not really considered as organocatalysts because of the alkali ion content (although they are organic molecules that are sharply different from transition metal complexes or enzymes). Nevertheless, catalyst recovery strategies are very similar in the case of macrocycles. However, there are only a few examples of crown ethers utilized as reusable asymmetric phase-transfer catalysts.[11]

A simple recovery method was reported, in which a crown compound having an imidazolium unit was synthesized.[11a] During the work-up procedure, the organic products were selectively removed from the mixture by washing with ether. The remaining catalyst, which is an ionic liquid, was reused after drying without a decrease in activity. Maruoka and his research group synthesized a binaphthyl-derived quaternary ammonium salt bearing perfluorinated side chains.[11b] After the

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reactions, a perfluorinated solvent was applied to recover the catalyst. The main disadvantage of this method is the high price of the perfluorinated solvent and the fluorine-containing catalyst. However, the same solution was applied by other researchers. Pozzi and his group investigated the properties of a dibenzo-18-crown-6 macrocycle with perfluorinated groups.[11c] A perfluorinated solvent was used as the reaction medium, and after completion of the reaction, the product was extracted with an organic solvent, then the fluorinated phase was reused.

Asymmetric synthesis has become one of the most important topics in organic chemistry in the last decades: obtaining chiral products with high optical purity is crucial among active pharmaceutical ingredients (APIs) and agrochemicals.[12] Enantioselective reactions are usually carried out by applying transition metal complexes, enzymes, or organocatalysts. Asymmetric induction can be achieved by phase-transfer catalytic systems as well, e.g., using cinchona-derived ammonium salts or chiral crown ethers. A lot of examples can be found in the literature, where application of these chiral catalysts resulted in highly enantioenriched products in different asymmetric reactions.[13] Performing asymmetric synthesis usually requires careful optimization of the catalyst structure and the reaction conditions. In contrast, the expensive chiral catalysts cannot be recovered in most of the cases, which is the key problem of their application. Development of the recovery of these compounds is advantageous from both an economic and ecological perspective.

Recently, our research group developed a few hydrobenzoin-based chiral crown ethers, which were efficient and reusable enantioselective catalysts (up to 88% ee). These macrocycles were recovered with simple salt formation and extraction[11d] A different approach was applied to reuse glucose-based crown ethers in our latest work. Modified PVC was used as a solid carrier, to which lariat crown ethers were anchored via azid-alkyne reaction[11e] It was found that a glucose-based crown derivative bound to PVC in 4% has remarkable enantioselectivity (77% ee) in the Michael addition of diethyl acetamidomalonate to nitrostyrene, and it could be reused five times without significant loss of enantioselectivity.

This study continues the exploration of recoverable chiral crown ethers, with the objective of developing more efficient and recyclable catalysts based on the insights gained. Regeneration via salt formation is simpler than immobilizing the catalyst on a support. However, the chiral macrocycle should not contain an acid-labile group, as its structure would change during salt formation. Threitol-based monoaza crown ethers were chosen not only because they meet the above criteria, but also because they are easy to prepare and modify. Macrocycles derived from threitol (**1a–d**; **2a**,**b**; **3a**,**b**; and **4a–c**) and tartaric acid (**5a–d** and **6a–c**) were synthesized with similar structures (Figure 1) and were investigated in different model reactions. The effect of the source of chirality and the structural changes was compared and analyzed regarding the catalytic activity and the reusability.

2. Results and Discussion

2.1. Synthesis of L-Threitol-Based Crown Ethers

The synthesis of threitol-based lariat crown ethers has already been published by our group.[14] Isopropylidene-L-threitol (**7**) is the common intermediate derived from tartaric acid, from which crown ethers bearing methyl, butyl, and benzyl groups (**1a–d**, **2a**,**b**, and **3a**,**b**, respectively) were synthesized previously in five steps: introduction of the appropriate alkyl group was followed by the hydrolysis of the isopropylidene group to get the vicinal diol intermediates (**9a–c**). After that, formation of the podand structure on compounds **9a–c** was carried out by the di-*O*-alkylation with bis(2-chloroethyl)ether, then the more reactive diiodo derivatives (**11a–c**) were prepared via halogen exchange (Scheme 1). In the last step of the syntheses, macrocyclization was performed by the reaction of diiodo podands **11a–c** and primary amines.

The number of threitol-based lariat ethers was increased with macrocycles **1c** and **1d** bearing side chains, which affected positively the enantioselectivity of other carbohydrate-based crown ethers; and with catalysts **4a–c** bearing methoxyethyl substituents (Scheme 2). It was expected that the solubility of the protonated form of the macrocycles **4a–c** will be higher in water, which may improve recoverability.

As was mentioned, hydrobenzoin-based crown ethers have already been prepared and used as recyclable phase-transfer catalysts.[11d] Hydrobenzoin and threitol units are quite similar. While in the former the aromatic rings are directly connected to the chiral carbon atoms and the structure is more rigid, in the latter the hydroxymethyl groups and the units introduced to them by *O*-alkylation have greater conformational freedom. Despite the differences, crown ethers synthesized from both chiral building blocks were able to generate higher enantiomeric excess. Based on this, it was assumed that if the distance between the stereogenic center and the phenyl group was increased by one methylene unit, we would also get effective catalysts. As analogues of catalysts **3a** and **3b**, more flexible crown compounds **5a–d** and **6a–c** were synthesized from intermediate **7**.

The vicinal diols **15a** and **15b** were synthesized by the method of Robbins.[15] In the first step, isopropylidene-L-threitol (**7**) was mesylated to obtain dimethanesulfonate **12** (Scheme 3). The isopropylidene protecting group of **12** was hydrolyzed by *para*-toluenesulfonic acid in a water-ethanol mixture, and chiral bioxirane **14** was subsequently formed from diol **13** by γ-elimination. Thereafter, chiral diepoxide **14** was reacted with phenylmagnesium bromide and 1-naphthylmagnesium bromide to obtain the (2*S*,3*S*)-diols **15a** and **15b**, respectively. The ring-opening reactions were regioselective due to the copper(I) iodide catalyst.

Again, the macrocycles were formed in three steps (Scheme 4). The free hydroxy groups of **15a** and **15b** were double *O*-alkylated, and after the halogen exchange of dichloro podands **16a** and **16b**, the diiodo derivatives (**17a** and **17b**) were

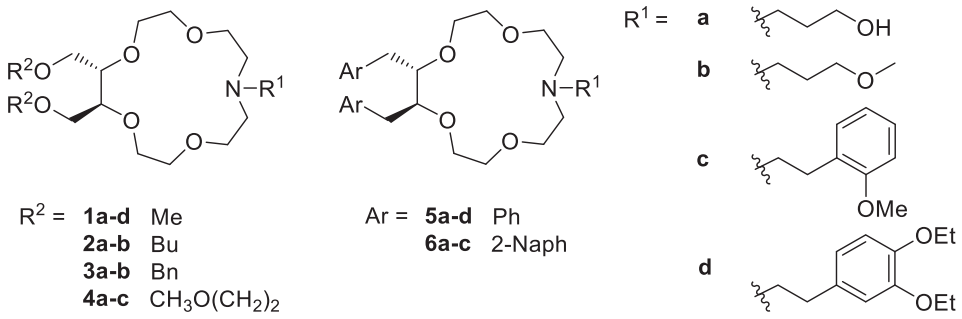
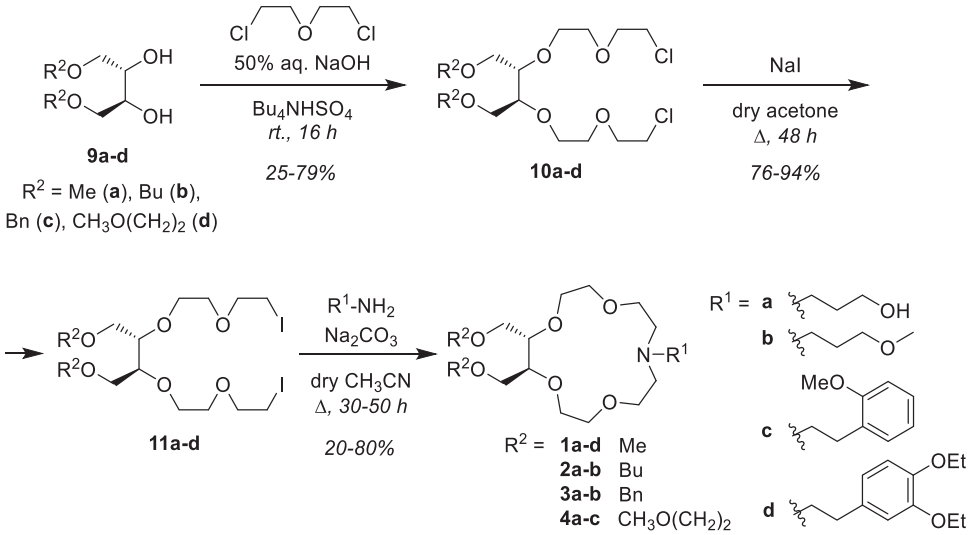
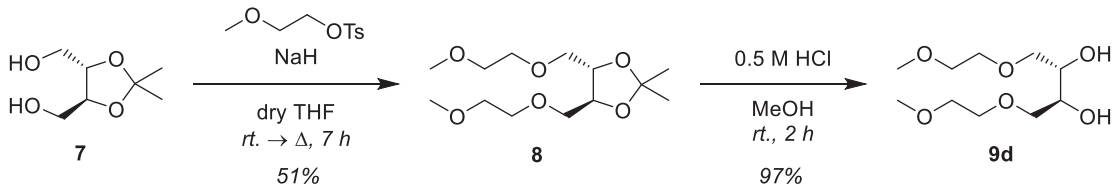


Figure 1. Chiral azacrown ethers used in the recovery experiments.



Scheme 1. Di-*O*-alkylation, halogen exchange, and macrocyclization of vicinal diols **9a–d**.



Scheme 2. Synthesis of key intermediate **9d**.

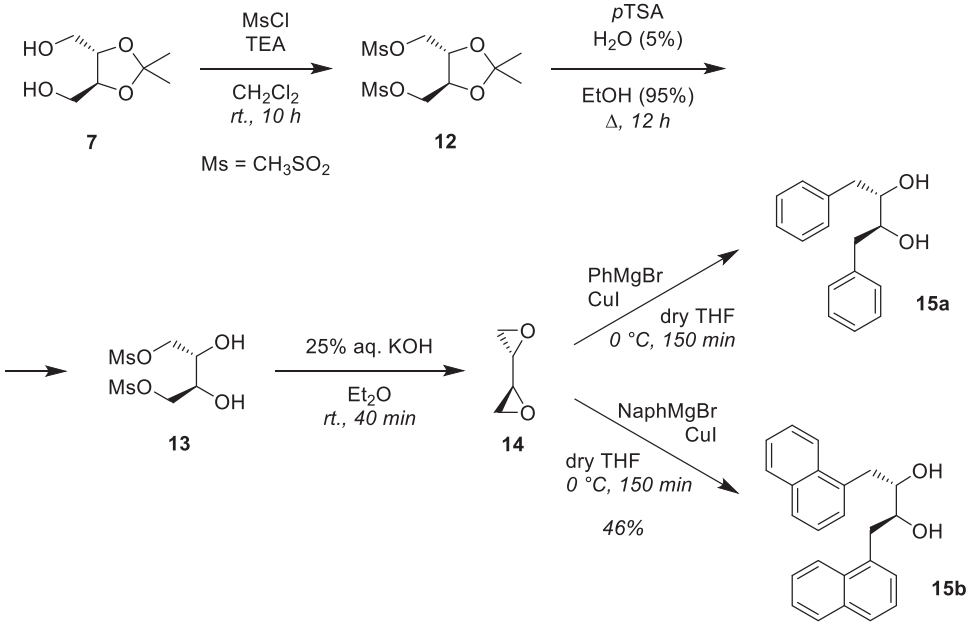
reacted with primary amines to prepare the desired crown ethers **5a–d** and **6a–c**.

2.2. Screening of the Crown Ethers in Asymmetric Reactions

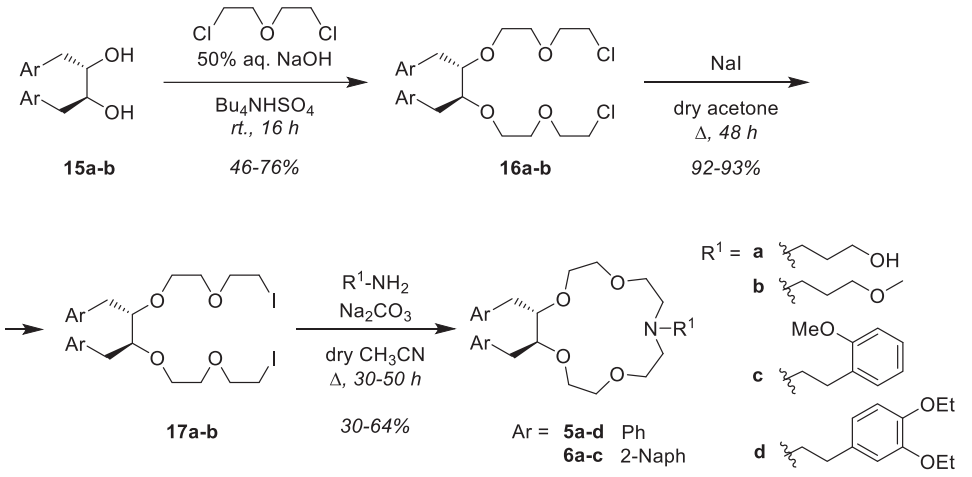
The novel crown ethers (**1c–d**, **4a–c**, **5a–d**, and **6a–c**) and the previously described macrocycles (**1a,b**; **2a,b**; and **3a,b**) were investigated in five base-initiated phase-transfer catalytic reactions. Two of them were liquid–liquid, and three of them were solid–liquid systems, in which some of the monosaccharide-based lariat ethers proved to be effective in earlier studies (up to 99% ee).[16,17] After the reaction reached full conversion, the crude product was purified by preparative TLC, and the enantiomeric excess was determined by chiral HPLC.

Crown compounds were tested first in the Darzens condensation of benzaldehyde (**18**) and 2-chloroacetophenone (**19**), where 30% aqueous NaOH solution was applied as the base (Scheme 5). All the reactions were carried out in toluene at room temperature and were worked up after 1 h – except in the case of catalyst **4a**, when 3 h was necessary to reach full conversion (see Supporting Information Table S1).

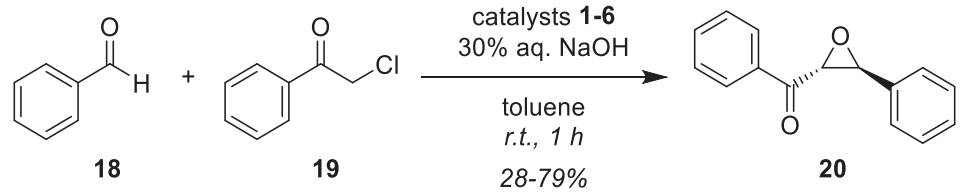
It can be seen from the results (Table 1) that catalysts with a hydroxypropyl side chain (**1a–6a**) produced the highest enantioselectivity among the macrocycles having the same source of chirality. When the substituent on the nitrogen was different, efficiency decreased significantly, both the presence of the



Scheme 3. Preparation of chiral diols **15a** and **15b**.



Scheme 4. Synthesis of crown ethers **5** and **6**.



Scheme 5. Asymmetric Darzens condensation of benzaldehyde (**18**) and 2-chloroacetophenone (**19**).

methoxypropyl group (**1b**–**6b**) and the 3,4-diethoxyphenethyl group provided (**1d** and **5d**) lower ee values in general. However, despite the similarity between the two aromatic side arms, catalysts containing the 2-methoxyphenethyl side arm (**1c** and **4c**–**6c**) even underperformed their analogues; practically, they were ineffective.

Threitol-based crown compounds **1a** and **2a** bearing simple alkyl chains (Table 1, entries 1 and 2) overperformed **3a** and **4a** (Table 1, entries 3 and 4), in which additional ether groups or aromatic rings are present. In the absence of the H-donor OH-group, these factors became negligible: **1b**, **3b**, and **4b** with the methoxypropyl side arm generated lower but similar enan-

Table 1. Enantiomeric excess (ee, %)[a] obtained in the Darzens reaction of benzaldehyde (**18**) and 2-chloroacetophenone (**19**).

Entry	Core Structure	Side Chain of the Nitrogen			
		—$(CH_2)_3OH$ (a)	—$(CH_2)_3OCH_3$ (b)	—$(CH_2)_2$(2-MeOPh) (c)	—$(CH_2)_2$(3,4-$(EtO)_2$Ph) (d)
1	1,4-di-*O*-Me-threitol (**1**)	45	26	12[b]	16
2	1,4-di-*O*-Bu-threitol (**2**)	49	7	–	–
3	1,4-di-*O*-Bn-threitol (**3**)	33[b]	29	–	–
4	1,4-di-*O*-(Methoxyethyl)-threitol (**4**)	37	25	4	–
5	1,4-di-*O*-Ph-butanediol (**5**)	35	19	8	33
6	1,4-di-*O*-Naph-butanediol (**6**)	52	4	4	–

[a] Determined by chiral RP-HPLC. [b] Determined by chiral NP-HPLC.

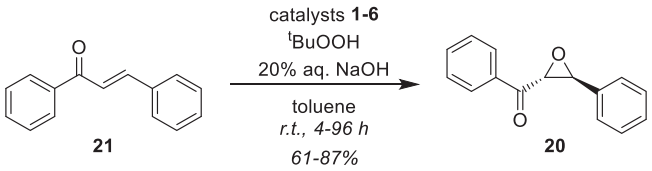
tiomeric excess (26%, 29%, and 25% ee, respectively) (Table 1, entries 1, 3, and 4). These data suggest that the conformation of the diastereomeric complexes in the transition state differs in the presence of an OH group and their energy level is different, as if only non-bonding and π-electrons are involved in their formation. Interestingly, catalyst **2b** is out of line, presumably due to the increased lipophilicity caused by the butyl groups (7% ee, Table 1, entry 2).

Crown compounds **5** and **6** show structural and effectual similarities to catalyst **3**—almost the same enantiomeric excess was measured using **3a** and **5a** (33% and 35%, Table 1, entries 3 and 5). The distance of the aromatic rings from the crown ring and the absence of external oxygen atoms did not significantly affect the catalytic activity. Crown ether **6a** containing naphthyl units was able to induce even better enantioselectivity (52% ee, Table 1, entry 6), which may be due to the formation of a more favorable π–π interaction. However, in the absence of the OH group, despite the more extensive aromatic system, macrocycle **6b** was ineffective (4% ee, Table 1, entry 6). As in the case of the butyl derivative **2b**, lipophilicity may be the main cause of their ineffectiveness.

Crown ethers of series **c** (**1c** and **4c–6c**) generated only low enantiomeric excess (4%–12% ee, Table 1). Comparing the results obtained with catalysts **1d** and **5d**, the presence of an *ortho* substituent on the aromatic ring appears to be unfavorable. The steric hindrance of the methoxy group can prevent the aromatic ring from taking the most favorable position in the complex; thus, the energy difference between the transition states leading to the individual enantiomers can be smaller. This is supported by the fact that the macrocycles of series **d** (**1d** and **5d**), which have a 3,4-diethoxyphenylethyl side chain, generated a higher enantiomeric excess (16% and 33% ee, Table 1, entries 1 and 5).

The catalysts prepared were tested in a similar liquid–liquid PTC reaction, where epoxide **20** was obtained via epoxidation. *trans*-Chalcone (**21**) was reacted with *tert*-butyl hydroperoxide and 20% aqueous NaOH solution at room temperature (Scheme 6). The time needed to achieve full conversion varied between 4 and 96 h, but typical reaction times were 1–3 days (see Table S2).

During the epoxidation, crown ethers containing a hydroxypropyl side chain (**1a–6a**) were the most effective, again (see Table 2). This is consistent with our previous experience that



Scheme 6. Asymmetric epoxidation of *trans*-chalcone (**21**).

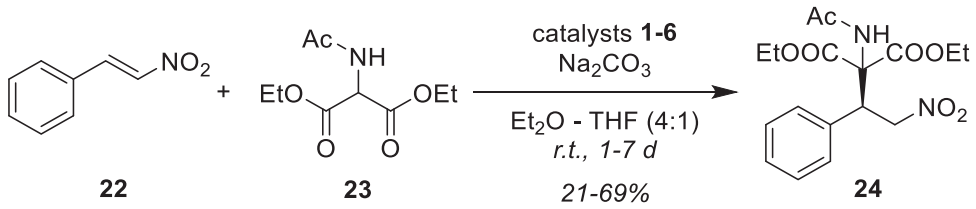
in liquid–liquid two-phase systems, macrocycles with this substituent generate the highest asymmetric induction. Regarding the 1,4-dialkylthreitol-based catalysts **1a–3a**, the lipophilicity of the protecting group influenced the selectivity: it decreased in the methyl > butyl > benzyl order (56%, 49%, and 37% ee) (Table 2, entries 1 and 3). However, with the appearance of newer external oxygens (**4a**), the asymmetric induction was somewhat higher (53% ee, Table 2, entry 4). These results are in correlation with the clogP values of the crown ethers, which are: −0.774, 1.874, 2.675, and −0.868 for **1a**, **2a**, **3a**, and **4a**, respectively.[18] These data suggest that as lipophilicity (or clogP) increases, enantioselectivity decreases. Furthermore, crown ethers based on threitol (**1b–c**, **2b**, **3b**, and **4b–c**) and butanediol (**5b–c**, **6b**,**c**) were ineffective (0%–3% ee) in the absence of an OH group on the side arm. This indicates that a hydrogen bridge is formed in the complex, which has a decisive role in the formation of enantioselectivity. Neither the presence of an aromatic unit nor the etheric oxygen could compensate for the lack of the hydrogen donor moiety. The 1,4-diphenylbutane-based **5a** macrocycle—compared to **3a**—generated lower enantiomeric excess (26% ee, Table 2, entry 6). Regarding the selectivity, the benzene ring located closer to the cavity seems to be unfavorable in the transition state of this reaction. Interestingly, the larger aromatic unit again favored the asymmetric induction, in the presence of analogue **6a**, product **20** was formed with a higher enantiomeric excess (65%, Table 2, entry 6). This suggests that the quality and extension of the π–π interaction are important for enantioselectivity. The verification of this hypothesis would need further studies; however, in these liquid–liquid phase reactions, **6a** overperformed all the other 17 catalysts.

As a solid–liquid PTC reaction, the Michael addition of *trans*-β-nitrostyrene (**22**) and diethyl acetamidomalonate (**23**) was investigated, in which solid sodium carbonate was the base (Scheme 7). The experiments were carried out in a 4:1 mixture

Table 2. Enantiomeric excess (ee, %)[a] measured in the epoxidation of *trans*-chalcone (**21**).

Entry	Core Structure	Side Chain of the Nitrogen			
		—$(CH_2)_3OH$ (a)	—$(CH_2)_3OCH_3$ (b)	—$(CH_2)_2$(2-MeOPh) (c)	—$(CH_2)_2$(3,4-$(EtO)_2$Ph) (d)
1	1,4-di-*O*-Me-threitol (**1**)	56	1	0	3
2	1,4-di-*O*-Bu-threitol (**2**)	49	3	–	–
3	1,4-di-*O*-Bn-threitol (**3**)	37	2	–	–
4	1,4-di-*O*-(Methoxyethyl)-threitol (**4**)	53	0	0	–
5	1,4-di-*O*-Ph-butanediol (**5**)	26	3	3	3
6	1,4-di-*O*-Naph-butanediol (**6**)	65	0	0	–

[a] Determined by chiral RP-HPLC.



Scheme 7. Asymmetric Michael addition of diethyl acetamidomalonate (**23**) to β-nitrostyrene (**22**).

Table 3. Enantiomeric excess (ee, %)[a] observed in the Michael addition of diethyl-acetamidomalonate (**23**) to *trans*-β-nitrostyrene (**22**).

Entry	Core Structure	Side Chain of the Nitrogen			
		—$(CH_2)_3OH$ (a)	—$(CH_2)_3OCH_3$ (b)	—$(CH_2)_2$(2-MeOPh) (c)	—$(CH_2)_2$(3,4-$(EtO)_2$Ph) (d)
1	1,4-di-*O*-Me-threitol (**1**)	58[b]	38[b]	35[c]	44[c]
2	1,4-di-*O*-Bu-threitol (**2**)	64	55	–	–
3	1,4-di-*O*-Bn-threitol (**3**)	95[b]	51[b]	–	–
4	1,4-di-*O*-(Methoxyethyl)-threitol (**4**)	61	52	35	–
5	1,4-di-*O*-Ph-butanediol (**5**)	46	29	10	27
6	1,4-di-*O*-Naph-butanediol (**6**)	59	27	35	–

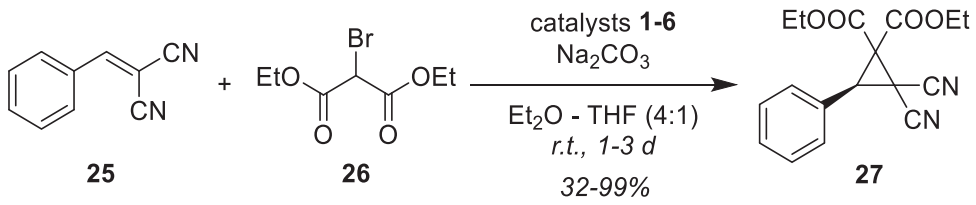
[a] Determined by chiral RP-HPLC. [b] Published before.[14] [c] Determined by chiral NP-HPLC.

of diethyl ether and THF (previously optimized solvent).[16] Comparing the two classes of the examined catalysts, in the Michael addition of nitrostyrene (**22**) and diethyl acetamidomalonate (**23**), applying compounds containing a threitol unit (**1–4**) resulted in higher enantiomeric excess in general (Table 3).

Although the absence of the hydroxy group did not have as drastic effect as in the case of liquid–liquid two-phase reactions, catalysts of series **a** (**1a–6a**) had the best selectivity (46%–95% ee) among macrocycles with the same core structure. The result achieved with compound **3a** stands out (95% ee, Table 3, entry 3), in this structure the hydrogen-donating OH group and the electron-rich benzene ring are probably located in the appropriate position to maximize the enantioselectivity.

Crown compounds **5** and **6** showed comparable activity with catalysts **1–4**, which is not so surprising due to the structural similarity. If we observe the enantiomeric excess measured with compounds **3a**,**b**; **5a**,**b**; and **6a**,**b**, the distance of the aromatic unit from the macroring is an important factor in terms of enantioselectivity. This is indicated by the fact that the 95% ee measured with catalyst **3a** (Table 3, entry 3) dropped to 46% in the case of macrocycle **5a** (Table 3, entry 5), while the measured value was 59% in the presence of the larger naphthyl ring (**6a**) (Table 3, entry 6), and similar decreases can be observed comparing **3b** with **5b** and **6b**.

When solid–liquid phase MIRC reaction of benzylidene malononitrile (**25**) and diethyl bromomalonate (**26**) was examined (Scheme 8), threitol-based crown compounds **1** and **4**, and catalysts **5** and **6** containing butanediol units, the side chain did not play an important role in the asymmetric induction (Table 4, entries 1 and 4–6). The results obtained with macrocycles **2a** and **2b** followed the pattern experienced so far, while the enantiomeric excess with the hydroxypropyl side chain was 85% (Table 4, entry 1), with the appearance of the methoxypropyl group, the ee value dropped to 38% (Table 4, entry 2). The

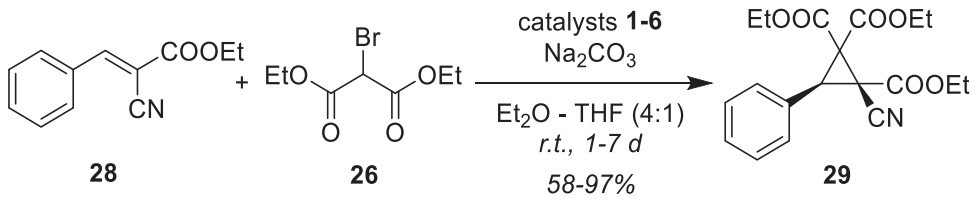


Scheme 8. Asymmetric cyclopropanation of benzylidene malononitrile (**25**) with diethyl bromomalonate (**26**).

Table 4. Enantiomeric excess (ee, %)[a] measured in the MIRC reaction of diethyl bromomalonate (**26**) and benzylidene malononitrile (**25**).

Entry	Core Structure	Side Chain of the Nitrogen			
		—$(CH_2)_3OH$ (a)	—$(CH_2)_3OCH_3$ (b)	—$(CH_2)_2$(2-MeOPh) (c)	—$(CH_2)_2$(3,4-$(EtO)_2$Ph) (d)
1	1,4-di-*O*-Me-threitol (**1**)	51[b]	45[b]	59	58
2	1,4-di-*O*-Bu-threitol (**2**)	85[b]	38[b]	–	–
3	1,4-di-*O*-Bn-threitol (**3**)	42[b]	69	–	–
4	1,4-di-*O*-(Methoxyethyl)-threitol (**4**)	50	62	62	–
5	1,4-di-*O*-Ph-butanediol (**5**)	42	46	37	49
6	1,4-di-*O*-Naph-butanediol (**6**)	24	28	24	–

[a] Determined by chiral RP-HPLC. [b] Published before.[14]



Scheme 9. Asymmetric cyclopropanation of ethyl 2-cyano-3-phenylacrylate (**28**) with diethyl bromomalonate (**26**).

outstanding enantioselectivity of **2a** (85% ee, Table 4, entry 2) is interesting because the only difference between catalysts **1a** and **2a** is the length of the alkyl chain (lipophilicity), although it is possible that the presence or absence of a weak van der Waals interaction can cause such a difference.

It is interesting that the exact opposite phenomenon was observed with crown ethers **3a** and **3b**, the presence of the methoxy group was more beneficial in terms of enantiomeric excess than that of the OH group (42% and 69% ee, Table 4, entry 3). The effect induced by lariat ethers **5a** and **6a** is also opposite to what was described above (42% and 24% ee, Table 4, entries 5 and 6). In the Darzens condensation, epoxidation, and Michael addition, the presence of the larger naphthyl unit had a more favorable effect on the catalytic activity than that of the benzene ring.

In this MIRC reaction, this effect was reversed, and the appearance of the naphthyl unit led to a decrease in the enantiomeric excess. This may be due to steric effects. The distance of the benzene ring from the crown ring was rather indifferent, as can be seen from the ee values obtained with compounds **3a** and **5a** (both 42% ee, Table 4, entries 3 and 5).

Compounds **28** and **25** only differ in one substituent; however, their application in a MIRC reaction (under the same conditions) (Scheme 9) with diethyl bromomalonate (**26**) gave different results, as can be seen from the ee values of Table 5; although, some trends did not change. In the case of threitol-containing macrocycles **1** and **4**, changing the side arm did not have a powerful impact, the enantiomeric excess varied within a narrow range (Table 5, entries 1 and 4). Nevertheless, catalysts containing aromatic side arms (**1c**, **1d**, and **4c**) performed slightly better, which effect was smaller in the previous MIRC reaction (Table 4, entries 1 and 4). In the case of macrocycles **2a** and **2b**, the same phenomenon occurred as in the MIRC reaction of benzylidene malononitrile, i.e., the replacement of the hydroxypropyl side chain with a methoxypropyl unit caused a large drop in the measured enantiomeric excess (57% and 16% ee, Table 5, entry 2). The enantioselectivity induced by crown ethers **3a** and **3b** also showed the same pattern as it was described in the previous MIRC reaction, that compound **3b** performed better (64% ee, Table 5, entry 3). This may indicate that the hydrogen bond is a dominant interaction in the complex, but its formation does not involve a large energy difference between the complexes, leading to the individual enantiomers. If there is no H-bridge, the secondary interactions of the benzyl group and the methoxy group may prevail, leading to a higher enantiomeric excess. In contrast, when (*S*,*S*)-butanediol was the

Table 5. Enantiomeric excess (ee, %)[a] obtained in the MIRC reaction of diethyl bromomalonate (**26**) and benzylidene cyanoacetate (**28**).

Entry	Core Structure	Side Chain of the Nitrogen			
		—$(CH_2)_3OH$ (a)	—$(CH_2)_3OCH_3$ (b)	—$(CH_2)_2$(2-MeOPh) (c)	—$(CH_2)_2$(3,4-$(EtO)_2$Ph) (d)
1	1,4-di-*O*-Me-threitol (**1**)	55	57	67[b]	66[b]
2	1,4-di-*O*-Bu-threitol (**2**)	57	16	–	–
3	1,4-di-*O*-Bn-threitol (**3**)	23[b]	64	–	–
4	1,4-di-*O*-(Methoxyethyl)-threitol (**4**)	46	50	59	–
5	1,4-di-*O*-Ph-butanediol (**5**)	63	44	34	44
6	1,4-di-*O*-Naph-butanediol (**6**)	55	33	27	–

[a] Determined by chiral RP-HPLC. [b] Determined by chiral NP-HPLC.

Table 6. Mass of the recovery of the catalysts after one reaction.

Catalyst	1a	1c	2a	3a	4a	4b	4c	5a	5b	6a	6b	6c
Recovered yield [%]	61 and 62	52–73	48	40–116[a]	114[a]	31	32	39	30	30	17	15

[a] The mass of the recovered material increased due to the presence of impurities.

source of chirality (**5** and **6**), the presence of the hydroxypropyl group (**5a–6a**) resulted in a higher ee value by 19–29 percentage points than in the other cases (Table 5, entries 5 and 6). The distance of the benzene ring from the crown ring was not indifferent, as it was in the previous MIRC reaction. The ee value obtained with compound **5a** was higher (63%, Table 5, entry 5) than it was measured in the presence of catalyst **3a** (23%, Table 5, entry 3). In this case, the appearance of the larger naphthyl ring was also associated with a slight decrease in selectivity, i.e., size plays an important role here as well.

2.3. Recycling of the Crown Ethers

The recoverability of some of the chiral catalysts was investigated in different reactions (Table 6 or see Table S6 for more details) throughout the catalyst screening to acquire some initial information. After completion of the reactions, crown ethers were extracted to the aqueous phase with 10% aq. HCl as hydrochloride salts. Then the pH of the solution was set to 9 and 10 using 10% sodium hydroxide solution, and the neutral lariat ethers were extracted with dichloromethane. After the organic layer was concentrated, the catalysts were dried in a desiccator. The masses of the recovered catalysts show that, on one hand, the deviation of the recovery yield is large—probably because of the small quantity of the crown ethers in a large solvent volume; hence, preparative errors had a bigger effect. On the other hand, these imperfect results were able to give an illustration of the general tendencies. The threitol-based crown ethers **1–4** were recovered with a better yield in average than butanediol derivatives **5** and **6**, and the OH-propyl substituted catalysts (series **a**) seemed to be more recoverable. Difficulties have already arisen earlier in our group with the reusability of threitol-based crown ethers. Additional TLC analysis showed that either the hydrochloric acid salts were less soluble in the acid solution (e.g., catalysts **6a–c**), or the neutral crown ethers were very soluble in aqueous medium (in the case of **1a**). In any case, more solvents and more repetitions were required for the extraction.

After the abovementioned experiences, repeated experiments were performed on a larger 2 mmol scale— instead of the 0.5 mmol scale used previously, to avoid possible preparative errors— aiming directly the investigation of recycling. The recovered catalyst was then reused in the next experiment. Four asymmetric reactions, which possess advantageous properties, were chosen: two with the highest selectivity (the Michael addition with **3a** and the MIRC reaction of benzylidene malononitrile (**25**) with **2a**), and two with surprisingly short reaction time (**6a** and **6b** in the same MIRC reaction). In the latter two cases, full conversion was reached after 2–6 h, in contrast to the 1–3 days reaction times when other catalysts were used.

Since in the Michael addition of β-nitrostyrene (**22**) and diethyl acetamidomalonate (**23**) (Scheme 7), lariat ether **3a** generated 95% ee previously (Table 3, entry 3), this model reaction was investigated for recoverability. We observed a rather interesting phenomenon. After the first cycle, there was no selectivity at all, which was confirmed in three independent HPLC measurements. However, 64% and 67% enantiomeric excess were obtained in the second and third cycles (Figure 2). The recovered catalyst **3a** proved to be barely contaminated according to TLC and ^{1}H NMR. Meanwhile, the recoverability of crown **3a** was only below 60% (49%–60%, Figure 2). The experimental results left us puzzled; we have not been able to discover why a racemic mixture was obtained after the first use (in a four-fold larger reaction than before). In the MIRC reaction of benzylidene malononitrile (**25**) and diethyl bromomalonate (**26**) (Scheme 8), the best

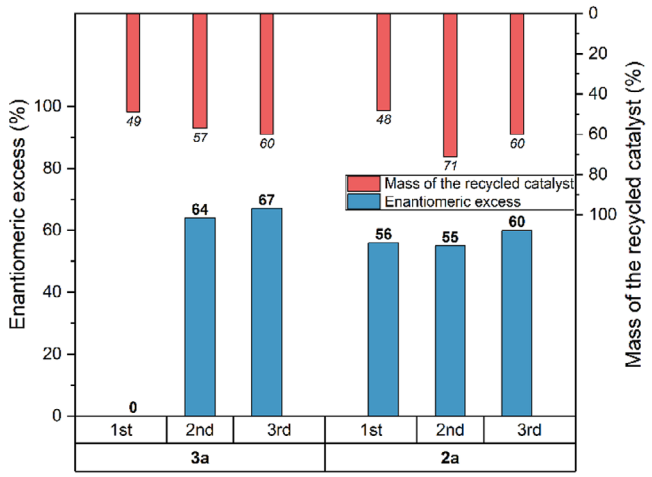


Figure 2. Recycling of crown ether **2a** in the Michael addition of **22** and the catalyst **3a** in the cyclopropanation of **25**.

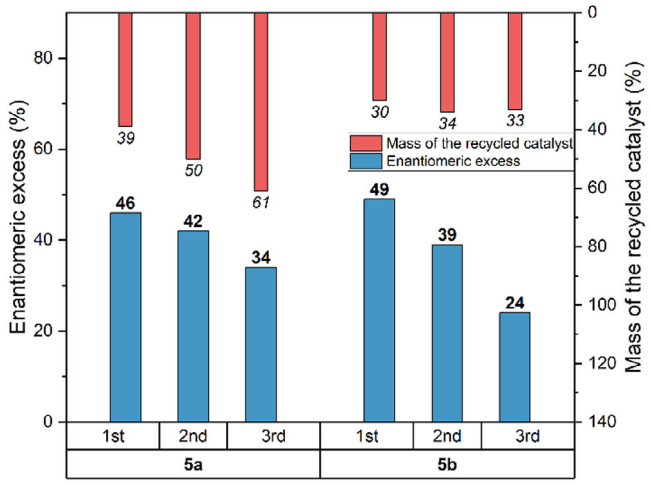


Figure 3. Recycling of catalysts **5a** and **5b** in the MIRC reaction of **25**.

performance of the screening was provided by the macrocycle **2a**, when 85% ee was achieved (Table 4, entry 2). Despite the high selectivity measured before, the enantiomeric excess decreased by 25%–30% in the scaled-up recycling reactions. At the same time, the asymmetric induction did not change significantly after regeneration, which was performed with a 48%–71% recovery yield, slightly better than in the case of **3a**. ^{1}H NMR measurement showed that the recovered crown **2a** was reasonably pure, it contained only small amounts of aromatic and aliphatic impurities after the third cycle.

Catalysts **5a** and **5b** are analogues of previously effective and successfully reused hydrobenzoin-based macrocycles.[11d] The recoverability of crown ethers **5a** and **5b** was tested in the solid–liquid phase cyclopropanation of benzylidene malononitrile (**25**) (Scheme 8). During the experiments, a decreasing enantioselectivity was measured with both catalysts, while their recoverability was not adequate (Figure 3, 39%–61% for **5a**, and 30%–34% for **5b**). Based on the ^{1}H NMR measurements of crown ethers regenerated after the third cycle, reduced selectivity may be related to catalyst contamination: the recovered material consisted of the cyclopropane product **27**, paraffins, and only the traces of **5a** or **5b**. Although crown ethers **6a–c** also have an analogous structure, their reusability was not investigated because they were barely recoverable after the first use (15%–30%, see Table S6).

3. Conclusion

The effect of a total of 18 crown ethers derived from threitol or tartaric acid was investigated in five types of asymmetric phase transfer reactions. The chiral unit, the applied protecting groups, and the *N*-substituents affected the enantioselectivity differently depending on the reaction. In liquid–liquid systems, hydroxypropyl side chain proved to be the most effective, assumably because of a hydrogen bond. In the absence of the OH group, lower enantiomeric excess was usually measured both in the Darzens condensation and in the epoxidation of chalcone. The results pointed out the significant role of lipophilicity in the latter case: higher logP values are associated with lower enantiomeric excess. In solid–liquid phase reactions the *N*-substituent had a less decisive effect. In general, the hydroxypropyl substituent still proved to be the most efficient in the Michael addition, but similar or better ee values were measured in the cyclopropanations using aromatic side chains, while the catalyst structure was otherwise unchanged. In some cases, we gave a possible explanation for the differences occurring during complex formation, which may be due to lipophilicity, hydrogen bonds, π–π interactions, and steric effects. These connections show trends rather than correlations, but can provide clues for further experiments and computations. Examining the recoverability of the catalysts, the positive impact of polar groups can be assumed. When the model reactions were upscaled, in a few cases, the enantioselectivity changed. These results pointed out that unexpected effects can occur in the design of catalysts, some of which can only be detected experimentally. However, the catalysts investigated proved to be reusable in three cycles without the total loss of their asymmetric induction. As it was demonstrated previously regarding the selectivity, both the enantiomeric excess and the recovery yields could be increased by the careful optimization of the conditions (solvent, amount of reagents and catalyst, etc.)—that was not the aim of this study.[16] Using the collected experiences, we will conduct further experiments to prepare more efficient reusable chiral crown ethers and to explore the background of the surprising results.

4. Experimental Section

4.1. General

Reagent-grade chemicals were purchased from Merck KGaA. (Darmstadt, Germany) and used without further purification. Analytical and preparative thin-layer chromatography (TLC) was performed on silica gel plates (60 F_{254}, Merck KGaA, Darmstadt, Germany), while column chromatography was carried out using 70–230 mesh silica gel and Brockman II neutral aluminum oxide. Visualization of compounds on the TLC plates was performed with 254 nm UV light

or 5 v/v% sulfuric acid/ethanol stain. Melting points were determined using a Stuart SMP10 apparatus and are uncorrected. The specific rotation was measured on a Perkin-Elmer 341LC polarimeter at 22 °C. NMR spectra were recorded on a Bruker (Billerica, MA, USA) DRX-500 or Bruker-300 instrument. The enantiomeric excess was determined either on a ThermoFinnigan Surveyor (reversed-phase) or a PerkinElmer Series 200 (normal-phase) liquid chromatography system using different columns. In all cases, isocratic elution was applied with a mobile phase flow rate of 0.8 mL/min. The temperature was 20 °C, and the wavelength of the detector was 222 nm. HRMS measurements were performed on a Xevo G2-XS Q-Tof mass spectrometer, with the default ESI ionization method.

The structures of the synthesized intermediates and catalysts were confirmed by NMR spectroscopy. Additionally, HRMS analysis of the dichloro podands and crown ethers was in good agreement with their expected molar masses.

Compounds **1a,b**;[14] **2a,b**;[14] **3a,b**;[14] **7a–c**,[14] **8a–c**,[14] **9a–c**,[14] **10**,[15] **11**,[15] **12**,[15] **13a**[15] were synthesized following the methods described in the literature or in our previous work.

4.2. Synthesis of Vicinal Diols 9a–d

4.2.1. 1,4-Di-O-methyl-l-threitol (9a), 1,4-Di-O-butyl-l-threitol (9b), and 1,4-Di-O-benzyl-l-threitol (9c)

See in the literature.[14]

4.2.2. 2,3-O-Isopropylidene-1,4-di-O-(2-methoxyethyl)-l-threitol (8)

2,3-*O*-Isopropylidene-L-threitol (**7**) (10.0 g, 62 mmol) was dissolved in THF (120 mL) under argon, then sodium hydride (7.44 g, 310 mmol) was added in small portions. The mixture was diluted with an additional 80 mL of THF. A solution of 2-methoxyethyl tosylate (38.49 g, 167 mmol) in THF (80 mL) was subsequently added dropwise. The reaction mixture was stirred for 6 h at room temperature, followed by 1 h of reflux, and the reaction was monitored by TLC (toluene–acetone 5:1). After full conversion, the precipitate was filtered, and the filtrate was concentrated in vacuum. The residue was dissolved in ethyl acetate (120 mL) and was washed with water (3 × 30 mL). The combined aqueous layers were extracted with ethyl acetate (20 mL), then the organic layers were combined, dried on Na_2SO_4, and concentrated. The crude product was roughly purified by column chromatography on silica gel with hexane-acetone (6:1) eluent. This was followed by a finer purification on silica gel using a gradient elution (toluene-acetone 100:5–20). Yield: 51% (8.74 g), pale yellow oil.

$[\alpha]_D^{22} = -10.2$ ($c = 1.0$, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, δ): 4.00–3.95 (m, 2H, 2 × OC*H*), 3.70–3.60 (m, 8H, 4 × OCH_2), 3.59–3.49 (m, 4H, 2 × OCH_2), 3.36 (s, 6H, 2 × OCH_3), 1.39 (s, 6H, 2 × CCH_3); ^{13}C NMR (126 MHz, $CDCl_3$, δ): 109.75, 77.48, 72.14, 71.90, 70.98, 59.05, 27.03.

4.2.3. 1,4-Di-O-(2-methoxyethyl)-l-threitol (9d)

2,3-*O*-Isopropylidene-1,4-di-*O*-(2-methoxyethyl)-L-threitol (**8**) (8.74 g, 31 mmol) was dissolved in methanol (50 mL), then hydrochloric acid (5 mL, 0.5 M) was added. The mixture was stirred for 2 h at room temperature, while the reaction was monitored by TLC (hexane- EtOAc 1:1). After full conversion, the reaction mixture was concentrated by distillation at atmospheric pressure. The crude product was used in the next step without purification. Yield: 97% (7.17 g), pale yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$, δ): 3.88–3.81 (m, 2H, 2 × OC*H*), 3.73–3.58 (m, 8H, 4 × OCH_2), 3.54 (t, $J = 4.6$ Hz, 4H, 2 × OCH_2), 3.37 (s, 6H, 2 × OCH_3), 2.74 (br, 2H, 2 × O*H*); ^{13}C NMR (126 MHz, $CDCl_3$, δ): 73.22, 71.82, 70.77, 70.42, 59.01.

4.3. Synthesis of vicinal diols 15a and 15b

4.3.1. 2,3-O-Isopropylidene-l-threitol-1,4-dimethanesulfonate (12), L-threitol-1,4-dimethanesulfonate (13), (2S,2′S)-2,2′-bioxirane (14), (2S,3S)-1,4-diphenylbutane-2,3-diol (15a)

See in the literature.[15]

4.3.2. (2S,3S)-1,4-Di(naphtalene-1-yl)butane-2,3-diol (15b)

A suspension of copper(I) iodide (3.43 g, 18.0 mmol) in dry THF (30 mL) was cooled down to −30 °C under argon atmosphere, then a 1 M slurry of 1-naphthylmagnesium bromide (41.6 g, 180 mmol) in dry THF (170 mL) was added in small portions. After 10 min of stirring, a solution of (2*S*,2′*S*)-2,2′-bioxirane (**14**) (5.16 g, 60 mmol) in dry THF (20 mL) was slowly introduced dropwise. The suspension was stirred for 10 min at −30 °C, then it was let to warm up to 0 °C. After 2.5 h at 0 °C, the mixture was quenched with saturated NH_4Cl solution (100 mL), and it was stirred for 15 min without the cooling bath. After that, the phases were separated, and the aqueous layer was extracted with dichloromethane (4 × 50 mL). The combined organic phase was dried over $MgSO_4$ and subsequently concentrated in vacuum. The crude product was recrystallized from toluene, and then from EtOAc-hexane mixture. Yield: 46% (9.43 g), white solid.

M.p. 141 °C (lit. 139 °C–141 °C);[19] $[\alpha]_D^{22} = +14.1$ ($c = 1.0$, $CHCl_3$) (lit. $[\alpha]_D^{23} = +29$ ($c = 0.98$, $CHCl_3$));[19] ^{1}H NMR (500 MHz, $CDCl_3$, δ): 8.08–7.96 (m, 2H, Ar*H*), 7.93–7.82 (m, 2H, Ar*H*), 7.77 (dd, $J = 7.2$, 2.2 Hz, 2H, Ar*H*), 7.57–7.46 (m, 4H, Ar*H*), 7.46–7.33 (m, 4H, Ar*H*), 4.12–4.00 (m, 2H, 2 × OC*H*), 3.44 (dd, $J = 14.0$, 4.5 Hz, 2H, 2 × ArCH$_a$CH$_b$), 3.34 (dd, $J = 14.1$, 8.3 Hz, 2H, 2 × ArCH$_a$C*H*$_b$), 2.12 (d, $J = 4.8$ Hz, 2H, 2 × O*H*); ^{13}C NMR (126 MHz, $CDCl_3$, δ): 134.24, 134.05, 132.23, 128.88, 127.64, 127.48, 126.11, 125.71, 125.52, 123.76, 73.49, 37.39.

4.4. General Procedure for the Preparation of the Dichloro Compounds

Vicinal diol was dissolved in bis(2-chloroethyl) ether (30 equiv) in a two-necked round-bottom flask fitted with a mechanical stirrer. Tetrabutylammonium hydrogensulfate (1 equiv) and 50 m/m% NaOH solution (67 equiv) were added to the mixture. After stirring at room temperature for 16 h, the emulsion was poured into a 1:1 mixture of dichloromethane and water. The phases were separated, and the aqueous layer was extracted with dichloromethane. The combined organic phase was then washed with water, dried over Na_2SO_4, and concentrated. Excess bis(2-chloroethyl) ether was removed by vacuum distillation. The crude product was roughly purified by column chromatography on silica gel using a gradient elution ($CHCl_3$–CH_3OH).

4.4.1. (7S,8S)-1,14-Dichloro-7,8-bis(methoxymethyl)-3,6,9,12-tetraoxatetradecane (10a), (7S,8S)-7,8-Bis(butoxymethyl)-1,14-dichloro-3,6,9,12-tetraoxatetradecane (10b), and (7S,8S)-7,8-Bis((benzyloxy)methyl)-1,14-dichloro-3,6,9,12-tetraoxatetradecane (10c)

See in the literature.[14]

4.4.2. (7S,8S)-14-Chloro-7-(2-(2-chloroethoxy)ethoxy)-8-((2-methoxyethoxy)methyl)-2,5,9,12-tetraoxatetradecane (10d)

Yield: 47% (6.31 g), yellow oil.

$[\alpha]_D^{22} = +4.8$ ($c = 1.0$, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, δ): 3.87–3.49 (m, 30H, 2 x OC*H*, 12 × OCH_2, 2 × CH_2Cl), 3.37 (s, 6H, 2 × OCH_3); ^{13}C NMR (126 MHz, $CDCl_3$, δ): 79.14, 71.98, 71.27, 70.87, 70.83, 70.77, 70.69, 59.05, 42.87; HRMS (ESI/Q-TOF) *m/z*: $[M+Na]^+$ calcd for $C_{18}H_{36}Cl_2O_8$ 473.1679; found 473.1744.

4.4.3. (7S,8S)-7,8-Dibenzyl-1,14-dichloro-3,6,9,12-tetraoxatetradecane (16a)

Yield: 76% (14.14 g), pale turquoise oil.

$[\alpha]_D^{22} = -22.7$ ($c = 1.0$, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.31–7.22 (m, 8H, Ar*H*), 7.22–7.16 (m, 2H, Ar*H*), 3.66–3.40 (m, 18H, 2 × OC*H*, 6 × OCH_2, 2 × CH_2Cl), 2.98 (dd, $J = 13.8$, 3.4 Hz, 2H, 2 × $PhCH_aH_b$), 2.82–2.73 (m, 2H, 2 × $PhCH_aH_b$); ^{13}C NMR (126 MHz, $CDCl_3$, δ): 139.62, 129.46, 128.25, 126.06, 82.51, 71.21, 70.86, 70.21, 42.78, 36.41; HRMS (ESI/Q-TOF) *m/z*: $[M+Na]^+$ calcd for $C_{24}H_{32}Cl_2O_4$ 477.1570; found 477.1634.

4.4.4. (7S,8S)-1,14-Dichloro-7,8-bis(naphthalen-1-ylmethyl)-3,6,9,12-tetraoxatetradecane (16b)

Yield: 46% (6.86 g), yellow oil.

$[\alpha]_D^{22} = -4.8$ ($c = 1.0$, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, δ): 8.19 (dd, $J = 7.9$, 1.8 Hz, 2H, Ar*H*), 7.88 (dd, $J = 7.4$, 2.0 Hz, 2H, Ar*H*), 7.77 (d, $J = 8.1$ Hz, 2H, Ar*H*), 7.55–7.46 (m, 6H, Ar*H*), 7.46–7.40 (m, 2H, Ar*H*), 3.93–3.87 (m, 2H, 2 × OC*H*), 3.72 (dd, $J = 14.1$, 2.0 Hz, 2H, 2 × $ArCH_aCH_b$), 3.61–3.53 (m, 2H, OCH_2), 3.49–3.24 (m, 14H, 5 × OCH_2, 2 × CH_2Cl), 3.21 (dd, $J = 13.9$, 9.2 Hz, 2H, 2 × $ArCH_aCH_b$); ^{13}C NMR (126 MHz, $CDCl_3$, δ): 136.01, 133.96, 132.22, 128.77, 127.93, 126.93, 125.77, 125.46, 125.44, 124.20, 82.01, 71.11, 71.00, 70.37, 42.59, 33.38; HRMS (ESI/Q-TOF) *m/z*: $[M+Na]^+$ calcd for $C_{32}H_{36}Cl_2O_4$ 577.1883; found 577.1947.

4.5. General Procedure for the Preparation of Diiodo Compounds

To a 0.15 M solution of the dichloro compound in dry acetone, anhydrous sodium iodide (4.0 equiv) was added. After refluxing for 24 h, the solvent was removed in vacuum. The residue was dissolved in dichloromethane followed by the filtration of the precipitate. The filtrate was washed with water. The organic layer was then dried over Na_2SO_4, evaporated in vacuum, and the residue was dried in a desiccator. The crude product was used in the next step without purification.

4.5.1. (7S,8S)-1,14-Diiodo-7,8-bis(methoxymethyl)-3,6,9,12-tetraoxatetradecane (11a), (7S,8S)-7,8-Bis(butoxymethyl)-1,14-diiodo-3,6,9,12-tetraoxatetradecane (11b), and (7S,8S)-7,8-Bis((benzyloxy)methyl)-1,14-diiodo-3,6,9,12-tetraoxatetradecane (11c)

See in the literature.[14]

4.5.2. (7S,8S)-14-Iodo-7-(2-(2-iodoethoxy)ethoxy)-8-((2-methoxyethoxy)methyl)-2,5,9,12-tetraoxatetradecane (11d)

Yield: 94% (8.34 g), yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$, δ): 3.87–3.78 (m, 2H, 2 × OC*H*), 3.76–3.56 (m, 20H, 10 × OCH_2), 3.55–3.51 (m, 4H, 2 × OCH_2), 3.37 (s, 6H, 2 × OCH_3), 3.25 (t, $J = 6.9$ Hz, 4H, 2 × CH_2I); ^{13}C NMR (126 MHz, $CDCl_3$, δ): 79.26, 72.12, 72.00, 70.98, 70.90, 70.83, 70.59, 59.20, 3.23.

4.5.3. (7S,8S)-7,8-Dibenzyl-1,14-diiodo-3,6,9,12-tetraoxatetradecane (17a)

Yield: 93% (18.20 g), yellow oil.

$[\alpha]_D^{22} = -18.1$ ($c = 1.0$, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.30–7.23 (m, 8H, Ar*H*), 7.22–7.17 (m, 2H, Ar*H*), 3.67–3.53 (m, 8H, 4 × OCH_2), 3.52–3.41 (m, 6H, 2 × OC*H*, 2 × OCH_2), 3.17 (t, $J = 6.9$ Hz, 4H, CH_2I), 2.99 (dd, $J = 13.8$, 3.4 Hz, 2H, 2 × $PhCH_aH_b$), 2.77 (dd, $J = 13.8$, 8.3 Hz, 2H, 2 × $PhCH_aH_b$); ^{13}C NMR (126 MHz, $CDCl_3$, δ): 139.59, 129.46, 128.25, 126.07, 82.51, 71.80, 70.46, 70.22, 36.44, 2.99.

4.5.4. (7S,8S)-1,14-Diiodo-7,8-bis(naphthalen-1-ylmethyl)-3,6,9,12-tetraoxatetradecane (17b)

Yield: 92% (8.34 g), yellowish oil.

^{1}H NMR (500 MHz, $CDCl_3$, δ): 8.21–8.16 (m, 2H, Ar*H*), 7.88 (dd, $J = 7.2$, 2.2 Hz, 2H, Ar*H*), 7.77 (d, $J = 8.1$ Hz, 2H, Ar*H*), 7.54–7.46 (m, 6H, Ar*H*), 7.46–7.40 (m, 2H, Ar*H*), 3.93–3.87 (m, 2H, 2 × OC*H*), 3.71 (dd, $J = 13.9$, 1.9 Hz, 2H, 2 × $ArCH_aCH_b$), 3.61–3.54 (m, 2H, OCH_2), 3.49–3.40 (m, 2H, OCH_2), 3.40–3.24 (m, 8H, 4 × OCH_2), 3.21 (dd, $J = 14.0$, 9.2 Hz, 2H, 2 × $ArCH_aCH_b$), 2.99 (t, $J = 6.9$ Hz, 4H, 2 × CH_2I); ^{13}C NMR (126 MHz, $CDCl_3$, δ): 136.14, 134.09, 132.35, 128.94, 128.07, 127.09, 125.92, 125.60, 125.58, 124.34, 82.12, 71.87, 70.71, 70.47, 33.53, 2.93.

4.6. General Procedure for the Ring Closure of Diiodo Compounds with Primary Amines

To a 0.07 M solution of the diiodo compound in dry acetonitrile, dry sodium carbonate (6.0 equiv) then the primary amine (1.0 equiv) were added under argon. Following 30–50 h of reflux, the suspension was filtered, and the filtrate was evaporated in vacuum. The residue was then dissolved in dichloromethane and washed with water. The organic phase was dried over Na_2SO_4, and the solvent was removed in vacuum. The crude product was purified by column chromatography.

4.6.1. 3-[(5S,6S)-5,6-Bis(methoxymethyl)-1,4,7,10-tetraoxa-13-azacyclopentadecan-13-yl]propan-1-Ol (1a), (5S,6S)-5,6-Bis(methoxymethyl)-13-(3-methoxypropyl)-1,4,7,10-tetraoxa-13-azacyclopentadecane (1b)

See in the literature.[14]

4.6.2. (5S,6S)-5,6-Bis(methoxymethyl)-13-(2-methoxyphenethyl)-1,4,7,10-tetraoxa-13-azacyclopentadecane (1c)

Yield: 80% (2.96 g), maroon oil.

$[\alpha]_D^{22} = +9.2$ ($c = 1.0$, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$, δ): 7.31–7.14 (m, 2H, Ar*H*), 6.94–6.83 (m, 2H, Ar*H*), 4.27–3.26 (m, 29H, ArCH_2, 2 × O*CH*, 8 × OCH_2, 3 × OCH_3), 3.24–2.63 (m, 6H, 3 × NCH_2); ^{13}C NMR (126 MHz, $CDCl_3$, δ): 157.35, 131.08, 121.17, 110.50, 79.67, 71.74, 71.34, 70.82, 70.34, 70.09, 69.66, 64.97, 64.03, 60.24, 59.95, 59.30, 55.49, 53.51; HRMS (ESI/Q-TOF) *m/z*: $[M+H]^+$ calcd for $C_{23}H_{39}NO_7$ 442.2799; found 442.2865.

4.6.3. (5S,6S)-13-(3,4-Diethoxyphenethyl)-5,6-bis(methoxymethyl)-1,4,7,10-tetraoxa-13-azacyclopentadecane (1d)

Yield: 77% (3.13 g), maroon oil.

$[\alpha]_D^{22} = +15.2$ ($c = 1.0$, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$, δ): 6.95–6.86 (m, 1H, Ar*H*), 6.83–6.71 (m, 2H, Ar*H*), 4.11 (q, $J = 7.1$ Hz, 2H, ArOCH_2), 4.05 (q, $J = 7.0$ Hz, 2H, ArOCH_2), 4.01–3.91 (m, 2H, 2 × O*CH*), 3.87–3.47 (m, 18H, ArCH_2, 8 × OCH_2), 3.36 (s, 6H, 2 × OCH_3), 3.19–2.51 (m, 6H, 3 × NCH_2), 1.42 (m, 6H, 2 × CH_2CH_3); ^{13}C NMR (126 MHz, $CDCl_3$, δ): 132.74, 120.73, 114.62, 114.10, 69.67, 67.14, 64.80, 64.69, 59.32, 55.93, 30.80, 14.90; HRMS (ESI/Q-TOF) *m/z*: $[M+H]^+$ calcd for $C_{26}H_{45}NO_8$ 500.3218; found 500.3290.

4.6.4. 3-[(5S,6S)-5,6-Bis(butoxymethyl)-1,4,7,10-tetraoxa-13-azacyclopentadecan-13-yl]propan-1-Ol (2a), (5S,6S)-5,6-Bis(butoxymethyl)-13-(3-methoxypropyl)-1,4,7,10-tetraoxa-13-azacyclopentadecane (2b)

See in the literature.[14]

4.6.5. 3-[(5S,6S)-5,6-Bis((benzyloxy)methyl)-1,4,7,10-tetraoxa-13-azacyclopentadecan-13-yl]propan-1-Ol (3a), and (5S,6S)-5,6-Bis((benzyloxy)methyl)-13-(3-methoxypropyl)-1,4,7,10-tetraoxa-13-azacyclopentadecane (3b)

See in the literature.[14]

4.6.6. 3-((5S,6S)-5,6-Bis((2-methoxyethoxy)methyl)-1,4,7,10-tetraoxa-13-azacyclopentadecan-13-yl)propan-1-ol (4a)

Yield: 44% (0.80 g), brown oil.

$[\alpha]_D^{22} = -1.0$ ($c = 1.0$, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$, δ): 3.82–3.70 (m, 6H, 2 × O*CH*, 2 × OCH_2), 3.70–3.53 (m, 16H, 8 × OCH_2), 3.53–3.47 (m, 6H, 3 × OCH_2), 3.35 (s, 6H, 2 × OCH_3), 2.87–2.58 (m, 6H, 3 × NCH_2), 1.72–1.59 (m, 2H, CH_2CH_2OH); ^{13}C NMR (126 MHz, $CDCl_3$, δ): 79.81, 72.08, 71.15, 71.00, 70.78, 70.53, 69.23, 64.21, 59.13, 56.37, 54.47, 28.54; HRMS (ESI/Q-TOF) *m/z*: $[M+H]^+$ calcd for $C_{21}H_{43}NO_9$ 454.3011; found 454.3078.

4.6.7. (5S,6S)-5,6-Bis((2-methoxyethoxy)methyl)-13-(3-methoxypropyl)-1,4,7,10-tetraoxa-13-azacyclopentadecane (4b)

Yield: 20% (0.47 g), brown oil.

$[\alpha]_D^{22} = +18.3$ ($c = 0.5$, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$, δ): 3.95–3.23 (m, 37H), 3.00–2.79 (m, 2H), 2.75–2.64 (m, 1H), 2.55–2.47 (m, 1H), 2.39–2.24 (m, 2H), 1.95 (br, 2H); ^{13}C NMR (126 MHz, $CDCl_3$, δ): 79.72, 71.94, 71.80, 71.24, 70.72, 70.62, 70.25, 67.17, 59.01, 58.79, 29.70; HRMS (ESI/Q-TOF) *m/z*: $[M+H]^+$ calcd for $C_{22}H_{45}NO_9$ 468.3167, found 468.3232.

4.6.8. (5S,6S)-5,6-Bis((2-methoxyethoxy)methyl)-13-(2-methoxyphenethyl)-1,4,7,10-tetraoxa-13-azacyclopentadecane (4c)

Yield: 52% (1.10 g), brown oil.

$[\alpha]_D^{22} = +3.6$ ($c = 1.0$, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$, δ): 7.20 (t, $J = 8.1$ Hz, 1H, Ar*H*), 7.11 (d, $J = 7.3$ Hz, 1H, Ar*H*), 6.92–6.82 (m, 2H, Ar*H*), 3.90–3.45 (m, 31H, 2 × O*CH*, 12 × OCH_2, ArOCH_3, ArCH_2), 3.35 (s, 6H, 2 × CH_2OCH_3), 2.94–2.65 (m, 6H, 3 × NCH_2); ^{13}C NMR (126 MHz, $CDCl_3$, δ): 157.41, 130.47, 127.95, 120.91, 110.55, 72.03, 71.75, 70.85, 70.34, 70.07, 67.47, 59.11, 58.98, 55.50, 53.88, 51.38, 26.79.; HRMS (ESI/Q-TOF) *m/z*: $[M+H]^+$ calcd for $C_{27}H_{47}NO_9$ 530.3324; found 530.3408.

4.6.9. 3-((5S,6S)-5,6-Dibenzyl-1,4,7,10-tetraoxa-13-azacyclopentadecan-13-yl)propan-1-ol (5a)

Yield: 64% (1,46 g), yellow oil.

$[\alpha]_D^{22} = -41.4$ ($c = 1.0$, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$, δ): 7.33–7.25 (m, 8H, Ar*H*), 7.25–7.18 (m, 2H, Ar*H*), 3.82–3.72 (m, 2H, 2 × O*CH*), 3.70–3.63 (m, 4H, 2 × OCH_2), 3.60–3.55 (m, 2H, OCH_2), 3.54–3.48 (m, 4H, 2 × OCH_2), 3.41–3.29 (m, 4H, 2 × OCH_2), 2.99 (dd, $J = 13.7$, 1.7 Hz, 2H, 2 × PhCH_aH_b), 2.84–2.75 (m, 2H, 2 × PhCH_aH_b), 2.72–2.58 (m, 6H, 3 × NCH_2), 1.75–1.58 (m, 2H, CH_2CH_2OH); ^{13}C NMR (126 MHz, $CDCl_3$, δ): 139.49, 129.57, 128.11, 125.98, 83.41, 71.23, 70.62, 68.62, 64.21, 56.10, 53.80, 37.27, 28.28; HRMS (ESI/Q-TOF) *m/z*: $[M+H]^+$ calcd for $C_{27}H_{39}NO_5$ 458.2901; found 458.2988.

4.6.10. (5S,6S)-5,6-Dibenzyl-13-(3-methoxypropyl)-1,4,7,10-tetraoxa-13-azacyclopentadecane (5b)

Yield: 59% (1.40 g), orange oil.

$[\alpha]_D^{22} = -48.1$ ($c = 1.0$, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$, δ): 7.24–7.07 (m, 10H, Ar*H*), 3.64–3.17 (m, 16H, 2 × O*CH*, 7 × OCH_2), 3.23 (s, 3H, OCH_3), 2.94–2.85 (m, 2H, 2 × PhCH_aH_b), 2.74–2.65 (m, 2H, 2 × PhCH_aH_b), 2.63–2.54 (m, 4H, 2 × NCH_2), 2.45 (t, $J = 7.4$ Hz, 2H, NCH_2), 1.65–1.57 (m, 2H, $CH_2CH_2OCH_3$); ^{13}C NMR (126 MHz, $CDCl_3$, δ): 139.36, 129.56, 128.14, 126.02, 83.52, 70.94, 70.92, 70.65, 69.33, 58.58, 53.93, 53.03, 37.45, 27.68; HRMS (ESI/Q-TOF) *m/z*: $[M+H]^+$ calcd for $C_{28}H_{41}NO_5$ 472.3057; found 472.3123.

4.6.11. (5S,6S)-5,6-Dibenzyl-13-(2-methoxyphenethyl)-1,4,7,10-tetraoxa-13-azacyclopentadecane (5c)

Yield: 30% (0.81 g), maroon oil.

$[\alpha]_D^{22} = -26.3$ ($c = 1.0$, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$, δ): 7.22–7.01 (m, 12H, Ar*H*), 6.79 (t, $J = 7.4$ Hz, 1H, Ar*H*), 6.75 (d, $J = 8.2$ Hz, 1H, Ar*H*), 3.72 (s, 3H, OCH_3), 3.62–3.30 (m, 10H, 2 × O*CH*, 4 × OCH_2), 3.30–3.20 (m, 4H, 2 × OCH_2), 2.90 (dd, $J = 13.7$, 2.0 Hz, 2H, 2 × PhCH_aH_b), 2.84–2.60 (m, 8H, ArCH_2, 3 × NCH_2), 2.60 (dd, $J = 13.6$, 8.6 Hz, 2H, 2 × PhCH_aH_b); ^{13}C NMR (126 MHz, $CDCl_3$, δ): 157.47, 139.40, 130.36, 129.56, 128.14, 127.34, 126.01, 120.45, 110.23, 83.44, 71.03, 70.60, 55.22, 53.96, 53.63, 53.42, 37.36, 29.71; HRMS (ESI/Q-TOF) *m/z*: $[M+H]^+$ calcd for $C_{33}H_{43}NO_5$ 534.3214; found 534.3290.

4.6.12. (5S,6S)-5,6-Dibenzyl-13-(3,4-diethoxyphenethyl)-1,4,7,10-tetraoxa-13-azacyclopentadecane (5d)

Yield: 45% (1.34 g), amber oil.

$[\alpha]_D^{22} = -23.0$ ($c = 1.0$, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$, δ): 7.30–7.14 (m, 10H, Ar*H*), 6.78 (d, $J = 8.1$ Hz, 1H, Ar*H*), 6.71–6.64 (m, 2H, Ar*H*), 4.10–4.00 (m, 4H, 2 × ArOCH_2), 3.71–3.25 (m, 14H, 2 × OC*H*, 6 × OCH_2), 2.98 (dd, $J = 13.7$, 2.5 Hz, 2H, 2 × PhCH_aH$_b$), 2.92–2.60 (m, 10H, 2 × PhCH$_a$$H_b$, ArC$H_2$, 3 × NC$H_2$), 1.46–1.39 (m, 6H, 2 × CH_3); ^{13}C NMR (126 MHz, $CDCl_3$, δ): 148.79, 139.45, 133.31, 129.70, 128.30, 126.18, 120.91, 114.55, 113.90, 83.60, 71.11, 70.72, 69.44, 64.82, 64.69, 54.15, 53.89, 37.55, 32.07, 15.05; HRMS (ESI/Q-TOF) *m/z*: $[M+H]^+$ calcd for $C_{36}H_{49}NO_6$ 592.3633; found 592.3723.

4.6.13. 3-((5S,6S)-5,6-Bis(naphthalen-1-ylmethyl)-1,4,7,10-tetraoxa-13-azacyclopentadecan-13-yl)propan-1-ol (6a)

Yield: 48% (1.07 g), colorless oil.

$[\alpha]_D^{22} = -36.2$ ($c = 1.0$, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$, δ): 8.23–8.16 (m, 2H, Ar*H*), 7.89–7.83 (m, 2H, Ar*H*), 7.76 (d, $J = 8.1$ Hz, 2H, Ar*H*), 7.53–7.40 (m, 8H, Ar*H*), 4.10–4.04 (m, 2H, 2 × OC*H*), 3.74–3.68 (m, 2H, 2 × ArCH_aH$_b$), 3.63 (t, $J = 5.1$ Hz, 2H, CH_2OH), 3.46–3.37 (m, 2H, OCH_2), 3.36–3.24 (m, 6H, 3 × OCH_2*), 3.18–3.03 (m, 6H, 2 × ArCH$_a$$H_b$*, 2 × OC$H_2$), 2.55–2.42 (m, 4H, 2 × NCH_2), 2.37–2.28 (m, 2H, NCH_2), 1.59–1.45 (m, 2H, CH_2CH$_2$OH); ^{13}C NMR (126 MHz, $CDCl_3$, δ): 136.26, 134.06, 132.39, 128.81, 128.09, 126.95, 125.79, 125.55, 125.49, 124.54, 83.30, 71.95, 71.10, 68.61, 64.29, 55.64, 53.27, 34.32, 28.15; HRMS (ESI/Q-TOF) *m/z*: $[M+H]^+$ calcd for $C_{35}H_{43}NO_5$ 558.3214; found 558.3305.

4.6.14. (5S,6S)-13-(3-Methoxypropyl)-5,6-bis(naphthalen-1-ylmethyl)-1,4,7,10-tetraoxa-13-azacyclopentadecane (6b)

Yield: 66% (1.28 g), yellow oil.

$[\alpha]_D^{22} = -10.3$ ($c = 1.0$, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$, δ): 8.18–8.11 (m, 1H, Ar*H*), 8.06–8.01 (m, 1H, Ar*H*), 7.91–7.85 (m, 2H, Ar*H*), 7.80–7.74 (m, 2H, Ar*H*), 7.54–7.36 (m, 8H, Ar*H*), 4.07–3.87 (m, 2H, 2 × OC*H*), 3.73 (dd, $J = 13.9$, 1.6 Hz, 2H, 2 × ArCH_aH$_b$), 3.68–2.81 (m, 25H, 2 × ArCH$_a$$H_b$, 7 × OC$H_2$, OC$H_3$, 3 × NC$H_2$), 1.89 (s, 2H, NCH$_2CH_2$); ^{13}C NMR (126 MHz, $CDCl_3$, δ): 135.80, 133.86, 131.94, 128.79, 127.85, 126.90, 125.54, 125.41, 123.99, 82.93, 82.76, 73.06, 72.82, 70.20, 68.20, 64.96, 64.70, 59.60, 59.14, 58.73, 57.80, 34.11, 29.57; HRMS (ESI/Q-TOF) *m/z*: $[M+H]^+$ calcd for $C_{36}H_{45}NO_5$ 572.3371; found 572.3414.

4.6.15. (5S,6S)-13-(2-Methoxyphenethyl)-5,6-bis(naphthalen-1-ylmethyl)-1,4,7,10-tetraoxa-13-azacyclopentadecane (6c)

Yield: 68% (1.72 g), brown oil.

$[\alpha]_D^{22} = -9.1$ ($c = 1.0$, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$, δ): 8.19–8.09 (m, 2H, Ar*H*), 7.94–7.84 (m, 2H, Ar*H*), 7.83–7.74 (m, 2H, Ar*H*), 7.55–7.38 (m, 8H, Ar*H*), 7.11 (dd, $J = 7.3$, 1.7 Hz, 1H, Ar*H*), 7.05 (td, $J = 7.8$, 1.7 Hz, 1H, Ar*H*), 6.74 (m, 2H, Ar*H*), 4.12–3.68 (m, 9H, 2 × OC*H*, 2 × NaphCH_aH$_b$, OCH_2, OCH_3), 3.57–3.31 (m, 8H, 4 × OCH_2), 3.27–2.93 (m, 12H, 2 × NaphCH$_a$$H_b$, OC$H_2$, ArC$H_2$, 3 × NC$H_2$); ^{13}C NMR (126 MHz, $CDCl_3$, δ): 157.20, 136.25, 136.03, 134.00, 132.04, 131.06, 128.97, 128.12, 127.90, 127.10, 126.94, 125.75, 125.59, 124.30, 123.98, 123.39, 121.12, 110.39, 84.67, 82.97, 73.54, 72.76, 72.15, 69.74, 64.60, 63.89, 55.31, 53.13, 52.76, 51.09, 33.99, 25.87; HRMS (ESI/Q-TOF) *m/z*: $[M+H]^+$ calcd for $C_{41}H_{47}NO_5$ 634.3527; found 634.3608.

4.7. Asymmetric Reactions

The model reactions of the catalyst screening were carried out following the recipes described earlier in our publications.[17,20] For the enantiomeric excesses of each reaction, see Tables 1–5, and the experimental details (reaction times, yields, enantiomeric excess) can be found in the Supporting Information, Tables S1–S5.

In those cases, when the crown ethers were recovered during the screening, the organic phase was extracted with 10% hydrochloric acid three times (3 × 10 mL). After the pH of the aqueous phase was set to **10** and **11** with the addition of 20% aq. NaOH, it was extracted with dichloromethane (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, then evaporated in vacuum, then the residue was dried in a desiccator. For the respective recovery yields, see the Supporting Information, Table S6.

4.8. General Procedure for the Catalyst Recovery Experiments

The catalyst recovery experiments were performed on a 2 mmol scale. After the completion of the reactions, the base was separated (separatory funnel or filtration), and the organic phase was diluted to 30 mL (when the solvent was Et_2O-THF, it was changed to dichloromethane first). The monoaza-15-crown-5 ethers were separated as HCl salts by extraction with 10% hydrochloric acid (5 × 30 mL), then the combined aqueous phase was treated with 20% aq. NaOH until pH = 9 and 10 was reached. The neutralized macrocycles were extracted with dichloromethane (5 × 30 mL), the combined organic layers were dried over Na_2SO_4, and the solvent was removed. The regenerated catalysts were dried in a desiccator before the next cycle. For the respective experimental details and recovery yields, see Table S7.

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Conflict of Interests

The authors declare no conflict of interest

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Carbohydrates · Catalyst recovery · Chiral crown ethers · Enantioselectivity · Phase transfer catalysis

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