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The Synthesis of Hydrobenzoin-Based Monoaza Crown Ethers and Their Application as Recyclable Enantioselective Catalysts

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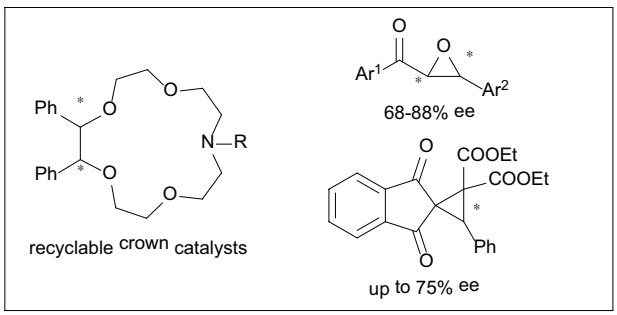
Abstract
New recyclable monoaza-15-crown ethers have been synthesized starting from (*R*,*R*)-(+)- and (*S*,*S*)-(−)-hydrobenzoin. These macrocycles proved to be efficient and reusable phase transfer catalysts in a few asymmetric reactions under mild conditions. The asymmetric epoxidation of *trans*-chalcone took place with up to 81% ee, while using other chalcone derivatives, the products were formed with 68–88% ee. The hydrobenzoin-based lariat ethers were also tested in the cyclopropanation of a few electron deficient olefins using diethyl bromomalonate to afford the product with good enantioselectivities (54–75% ee). The catalysts were recovered by salt formation, followed by extraction, and were reused without the loss of the activity and effect on the enantioselectivity.

Graphic Abstract
The synthesis of hydrobenzoin-based monaza crown ethers and their application as recyclable enantioselective catalysts.



1 Introduction

Asymmetric phase transfer catalysis has become a topic of great scientific interest in the last 30 years. A great number of chiral catalysts have been synthesized and used with excellent enantioselectivities in different reactions [1–8]. Despite all advantages, most of the applied methods have the shortcomings that the recovery of the catalyst is not solved, or cumbersome purification (e.g. chromatography) has to be used. Recently, in response to economy and sustainability concerns, an increasing attention has been paid to process intensification, elimination of harmful substances, waste reduction, and recycling of the solvents and catalysts. Therefore, the design of recyclable chiral phase transfer catalyst is a challenging area in current organic chemistry. For this purpose, several polymer-supported chiral ammonium salt-type catalysts derived mostly from cinchona alkaloids have been synthesized [9–16]. However, the enantioselectivity achieved by most of these catalysts decreased as compared to the nonsupported derivatives. To avoid this decrease in the selectivity, a few recyclable homogenous catalysts have also been developed. A binaphthyl-based fluorous phase transfer catalyst has been used

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by Maruoka et al. in the synthesis of a few amino acids with high enantioselectivities [17]. This fluorinated catalyst was regenerated by extraction with a fluorous solvent, however, the scale up of this method is problematic due to the high price of the fluorinated reagents and solvents. Nájera et al. applied a cinchona-derived dimeric ammonium salt that provided a good enantioselectivity, and it was possible to recover the catalyst almost quantitatively by precipitation in ether [18].

Chiral crown ethers have also been used in enantioselective syntheses as phase transfer catalysts [19]. Macrocycles derived from binaphtol, [20, 21] carbohydrates, [22–26] spirobiindane [27] and other chiral diols [28–31] have all been used efficiently in different asymmetric reactions. In our group, monoaza-15-crown-5-type lariat ethers incorporating a carbohydrate unit were synthesized [32, 33]. These macrocycles generated high asymmetric induction in certain model reactions [34–37]. Although chiral crown compounds have been widely used as phase transfer catalysts, to the best of our knowledge, none of these catalysts were reusable. Monoaza crown ethers have the advantage that they can be regenerated by salt formation, followed by extraction. This recovery technique is known for achiral monoaza crown ethers [38]. Our most efficient monoaza-type catalysts all had acid sensitive functional groups, therefore, this type of recovery attempt has not been successful so far. We intended to develop new chiral crown ether catalysts, which can be recovered by the simple method mentioned.

Herein, we wish to report the synthesis and application of a few recyclable hydrobenzoin-based monoaza-15-crown-5 ethers. Enantiopure (*R*,*R*)- and (*S*,*S*)-hydrobenzoin have been extensively used in asymmetric syntheses as chiral ligands, auxiliaries, and chiral building blocks because of their easy availability and relatively low price, as compared to other chiral diols [39] We assumed that a diol with bulky aromatic groups would be the best choice as a starting material, since both steric and π-π interactions may enhance the enantioselectivity of the catalyst. Crown ethers derived from hydrobenzoin have already been reported [40]. These macrocycles generated good enantioselectivites in the asymmetric reduction of aromatic ketones with ammonia-borane complexes [30, 31], but only moderate results were obtained in a Michael addition [29]. As monoaza-type crown ethers starting from hydrobenzoin have not been prepared so far, we intended to synthesize a few such derivatives, with various side arms, and test their catalytic effect, and also their reusability.

2 Results and Discussion

2.1 Synthesis of Hydrobenzoin-Based Lariat Ethers

The synthesis of monoaza-15-crown ethers was performed according to the protocol elaborated earlier, starting from (*R*,*R*)- and (*S*,*S*)-hydrobenzoin (Scheme 1) [41, 42]. The vicinal hydroxy groups of diol **1** were alkylated with bis(2-chloroethyl) ether in the presence of 50% *aq*. NaOH and tetrabutylammonium hydrogensulphate to give intermediates (*R*,*R*)-**2** and (*S*,*S*)-**2** in 64% and 68% yield after chromatography. The exchange of chlorine to iodine in bischloro compounds (*R*,*R*)-**2** and (*S*,*S*)-**2** was accomplished by reaction with NaI in boiling acetone in excellent yields (93% and 95%, respectively). Bisiodo compound (*R*,*R*)-**3** was then cyclized with four different amines (3-aminopropan-1-ol, 3-methoxypropylamine, 2-(2-methoxyphenyl)ethylamine and 2-(3,4-diethoxyphenyl)ethylamine, respectively) in boiling acetonitrile in the presence of Na_2CO_3 to afford azacrown ethers (*R*,*R*)-**4a-d** after chromatography in yields of 52–68%. Previously, these side arms proved to be efficient in terms of enantioelectivity when they were attached to carbohydrate-based monoaza crown ethers [43, 44]. The (*S*,*S*)-**3** intermediate was reacted only with 3-aminopropan-1-ol and 2-(3,4-diethoxyphenyl)ethylamine, because these two side chains proved to be the most effective according to experiments with macrocycles (*R*,*R*)-**4a-d**. Thus, six new hydrobenzoin-based monoaza crown ethers have been synthesized, of which (*S*,*S*)-**4a** and (*R*,*R*)-**4a** and also (*S*,*S*)-**4c** and (*R*,*R*)-**4c** are pairs of enantiomers, therefore the outcome of the asymmetric reactions may be influenced by choosing the proper enantiomer of the catalyst.

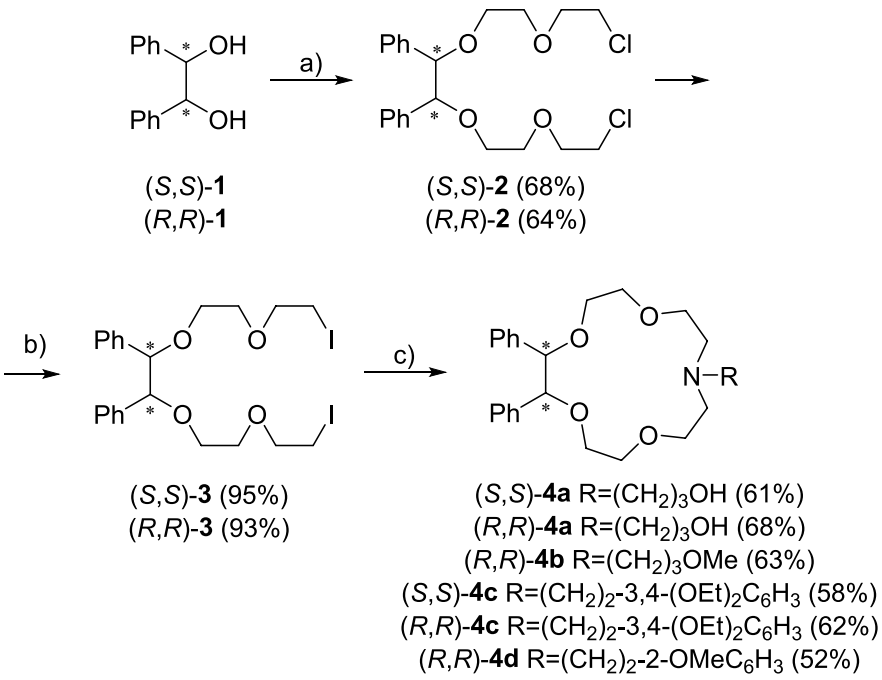
2.2 Asymmetric Reactions Catalyzed by Lariat Ethers

The new hydrobenzoin-based catalysts were applied in a few asymmetric reactions to test their ability to induce enantioselectivity. Besides synthesizing the products in high optical purity, we also tried to turn these model reactions more eco-friendly by choosing green solvents, using minimum amounts of the reagents and catalyst, and by recycling the catalyst after the reactions. The crude products were purified by preparative TLC. Enantiomeric excess of the products was determined by chiral HPLC analysis.

One of the model reactions was the asymmetric epoxidation of *trans*-chalcone (**5a**) and its derivatives. Chiral epoxides are useful intermediates in organic synthesis, prone to react with a variety of nucleophilic reagents affording intermediates and precursors in the preparation of enantiomerically pure bioactive compounds [45–48]. Although the asymmetric synthesis of epoxides **6** was reported applying different catalysts [49, 50], only a part of these methods used a recyclable catalyst [51–54], and even less examples can be found, when the activity of the catalyst did not decrease after the recyclings [55–57].

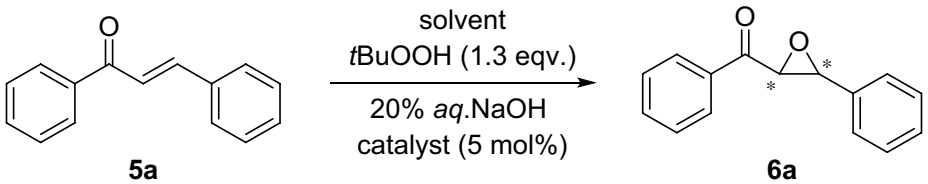
First, we tested the new hydrobenzoin-based catalysts (*R*,*R*)-**4a-d** under the reaction conditions reported by our group using carbohydrate-based crown ethers [58] with

Scheme 1 The synthesis of hydrobenzoin-based crown ethers ((*R*,*R*)-**4a–d**, (*S*,*S*)-**4a** and (*S*,*S*)-**4c**)



some modifications (Table 1, entries 1–4). Less catalyst (5 mol%), and only 1.3 equivalents of the oxidizing agent (*tert*-butylhydroperoxide) were used in a toluene—20% *aq*. NaOH two phase system. Other oxidizing agents such as H_2O_2, NaOCl and *m*CPBA were tested earlier, however, the enantioselectivities and/or the yields were significantly lower as compared to *t*BuOOH. Among catalysts (*R*,*R*)-**4a–d**, only crown ether (*R*,*R*)-**4a** with hydroxypropyl side arm generated a significant asymmetric induction (80% ee). Using the other three derivatives ((*R*,*R*)-**4b–d**), product **6a**

Table 1 Optimization of the reaction conditions and screening the catalyst in the asymmetric epoxidation of *trans*-chalcone (**5a**)



Entry	Catalyst	Time (h)	Solvent	T (°C)	Yield (%)	ee (%)[a]
1	(*R*,*R*)-**4a**	4	Toluene	25	89	80 (2*S*,3*R*)
2	(*R*,*R*)-**4b**	4	Toluene	25	81	15 (2*S*,3*R*)
3	(*R*,*R*)-**4c**	5	Toluene	25	90	8 (2*S*,3*R*)
4	(*R*,*R*)-**4d**	6	Toluene	25	85	6 (2*S*,3*R*)
5	(*R*,*R*)-**4a**	5	CH_2Cl_2	25	81	56 (2*S*,3*R*)
6	(*R*,*R*)-**4a**	5	Et_2O	25	83	77 (2*S*,3*R*)
7	(*R*,*R*)-**4a**	4	MTBE	25	88	81 (2*S*,3*R*)
8	(*R*,*R*)-**4a**	10	MTBE	0	83	81 (2*S*,3*R*)
9	(*S*,*S*)-**4a**	4	MTBE	25	90	79 (2*R*,3*S*)

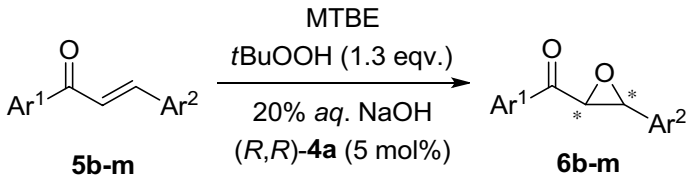
[a]Based on chiral HPLC, the absolute configuration was assigned by comparison of the specific rotations with literature data [59]

was obtained with low enantioselectivities (6–15%). In all cases complete diastereoselectivity was observed. The significant difference between the catalytic activities is currently unclear. Similar phenomenon has been observed earlier in the case of other crown compounds when catalysts with hydroxypropyl side chain performed better than their methoxypropyl analogues [33, 37, 43].

Thereafter, we tested the influence of different solvents using catalyst (*R*,*R*)-**4a** (Table 1, entries 5–7). In dichloromethane, the enantioselectivity was lower (56%), while the experiments carried out in diethyl ether or methyl *tert*-butyl ether (MTBE) led to similar results (77% ee and 81% ee, respectively) obtained in toluene (80% ee). The yield of epoxyketone **6a** was not significantly influenced by the solvent. Considering the green chemical principles, MTBE was chosen as the solvent in the next experiments. Finally, we investigated the effect of the temperature on the course of the reaction (Table 1, entry 8). When the reaction was performed at 0 °C, an increased reaction time of 10 h (instead of 4 h) was needed, but this change did not increase the enantioselecivity (81%). Using the other enantiomer (*S*,*S*) of catalyst **4a,** almost the same enantiomeric excess (79%) was observed, but, as expected, this occasion the other enantiomer (2*R*,3*S*) of the product was formed (Table 1, entry 9).

After exploring the optimized protocol for the enantioselective epoxidation, we investigated the generality and the scope of this methodology. The oxidation of a variety of chalcone derivatives with different substituents (Ar^1 or Ar^2) in the aromatic rings (**5b–k**) were studied (Table 2). It can be concluded from Table 2 that neither the yield (71–93%), nor the enantioselectivity (68–88% ee) changed drastically, and in a few cases even slightly better results were obtained as compared to those observed with the unsubstituted chalcone (88% yield, 81% ee). The chloro-substituted products were formed in good yields and with 70–88% ee (Table 2, entries 1–5). The degree of asymmetric induction was slightly influenced by the position of the chlorine atom in the phenyl ring (Ar^2). When the Cl atom was in *ortho* position, the enantioselectivity was somewhat lower (**6b**: 75% ee, **6e**: 70% ee) as compared to the *meta* and *para* substituted derivatives (**6c**: 85% ee, **6d**: 83% ee). The highest enantioselectivity (88% ee) was observed in case of product **6f**, when the Cl atom was in the other phenyl ring (Ar^1) in *para* position. The methyl group did not have an influence on the outcome of the reaction (Table 2, entries 6, 7). Product **6g** (Ar^1 = Ph, Ar^2 = 3-Me-C_6H_4) and **6h** (Ar^1 = 4-Me-C_6H_4, Ar^2 = Ph) were both formed with 79% ee. The experiment with *para* nitro substituted chalcone **5i** (Ar^2 = 4-NO_2–C_6H_4) resulted with an ee value of 74% (Table 2, entry 8). Somewhat weaker enantioselectivity (68%) was observed in case of chalcone **5j** (Ar^1 = Ph, Ar^2 = piperonyl) (Table 2, entry 9). The enantioselective epoxidation catalyzed by (*R*,*R*)-**4a** was also performed with the structurally similar, but cyclic 2-benzylidene-1-indanone (**5k**) and 2-benzylidene-1-tetralone (**5l**). High enantiomeric excess (86%) was observed in case of the oxidation of 2-benzylidene-1-tetralone (**5l**), while the experiment with 2-benzylidene-1-indanone (**5k**) led to

Table 2 Generality of catalyst (*R*,*R*)-**4a** in the asymmetric epoxidation of chalcone derivatives (**5b–m**)



Entry	Ar^1	Ar^2	Time (h)	Yield (%)	ee (%)[a]
1	C_6H_5	2-Cl-C_6H_4	10	**6b:** 76	75 (2*S*,3*R*)
2	C_6H_5	3-Cl-C_6H_4	7	**6c:** 88	85 (2*S*,3*R*)
3	C_6H_5	4-Cl-C_6H_4	5	**6d:** 93	83 (2*S*,3*R*)
4	C_6H_5	2,6-diCl-C_6H_3	3	**6e:** 85	70 (−)
5	4-Cl-C_6H_4	C_6H_5	5	**6f:** 89	88 (2*S*,3*R*)
6	C_6H_5	3-Me-C_6H_4	6	**6g:** 79	79 (2*S*,3*R*)
7	4-Me-C_6H_4	C_6H_5	8	**6h:** 86	79 (2*S*,3*R*)
8	C_6H_5	4-NO_2-C_6H_4	24	**6i:** 80	74 (2*S*,3*R*)
9	C_6H_5	Piperonyl	10	**6j:** 86	68 (+)
10	2-benzylidene-1-indanone		24	**6k:** 71	76 (+)
11	2-benzylidene-1-tetralone		24	**6l:** 75	86 (2*S*,3′*R*)

[a]Based on chiral HPLC, the absolute configurations were assigned by comparison of the specific rotations with literature data [60–62]

somewhat lower selectivity (76% ee) (Table 2, entries 11, 12).

The reusability of catalyst (*R*,*R*)-**4a** was also investigated in the epoxidation of chalcone **5a**. The recovery technique was summarized in Scheme 2. After completion of the reactions, the monoaza crown ether (*R*,*R*)-**4a** was transformed to its hydrochloride salt with 10% *aq*. HCl, and extracted several times with HCl solution. Then, sodium hydroxide was added to the aqueous layer until the pH turned basic (pH 8–9), and the liberated azacrown ether was extracted with MTBE. Finally, the organic layer was concentrated, and the catalyst was dried in a desiccator for 24 h. The recovered catalyst was then reused in the next experiment.

The results of the repeated uses are summarized in Table 3, from which one can see that neither the enantioselectivity (78–81%) nor the yields (86–90%) changed much even after the fifth cycle. Applying the above-mentioned method, catalyst (*R*,*R*)-**4a** was recovered with good yields (95–98%) and high purity (checked by ^{1}H NMR). The slight loss of the catalyst was compensated with the addition of unused (*R*,*R*)-**4a**.

Thereafter, the hydrobenzoin-based crown compounds (**4**) were tested in some MIRC (Michael-initiated ring closure) reactions, in which an electron deficient olefin reacts with diethyl bromomalonate (**8**) affording cyclopropane derivatives. Chiral cyclopropanes are prevalent in natural products and bioactive compounds [63–66]. Moreover, they can be easily transformed to other important optically active compounds as the consequence of the easy ring cleavage of the strained cyclopropane moiety [67–69]. Recently, much attention was payed to the enantioselective synthesis of cyclopropanes, [70–72] however, only a few of the reported methods applied chiral phase transfer catalysts [73–77].

First, the reaction conditions were optimized, and the effect of catalysts was evaluated. The MIRC reaction of 2-benzylidene-1,3-indandione (**7**) and diethyl bromomalonate (**8**) was chosen as the model reaction to test the utility of catalysts (*R*,*R*)-**4a–d** (Table 4, entries 1–4) [78, 79]. The reactions took place in diethyl ether using Na_2CO_3 as the base, and 5 mol % of the catalyst in 1–2 h. In this instance, the side arm of lariat ethers (*R*,*R*)-**4a–d** did not have a significant effect on the enantioselectivity as compared to the above-mentioned epoxidation. Product **9**, with

Table 3 Recycling of catalyst (*R*,*R*)-**4a** in the asymmetric epoxidation of *trans*-chalcone (**5a**)

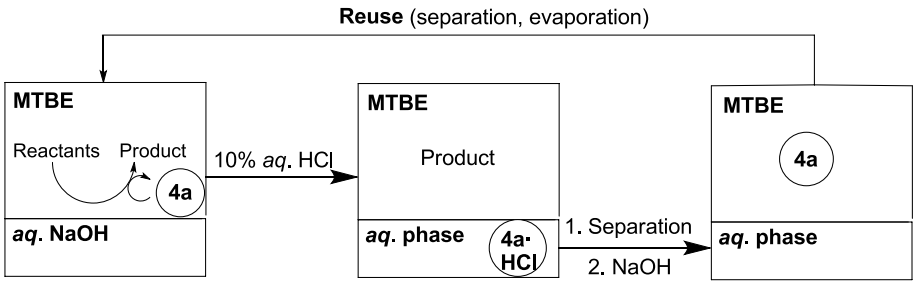
Number of uses	1	2	3	4	5
Yield (%)	87	89	88	90	86
ee (%)[a]	80	81	81	78	81

[a]Based on chiral HPLC

S configuration in all cases, was formed with moderate enantioselectivities (55–63%), and in good yields (74–83%) regardless of the side chain. The best result was obtained using crown ether (*R*,*R*)-**4c** with a 3,4-diethoxyphenethyl side arm (Table 4, entry 3), therefore the further experiments were carried out with this catalyst. Next, the effect of the solvent was investigated (Table 4, entry 5–9). After testing six different solvents, it may be concluded that the nature of the solvent has a strong influence on the asymmetric induction. Ether type solvents (Et_2O and MTBE) proved to be the best (63% and 64% ee), whereas in dichloromethane, hexane or ethyl acetate, the enantioselectivities were much lower (30%, 40% and 44%, respectively). However, the yield of cyclopropane **9** did not depend much on the different solvents (78–86%). Again, considering green chemical principles, MTBE was chosen for further investigations.

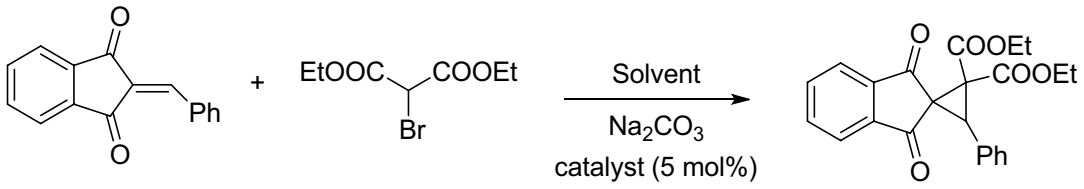
Eventually, the reaction was performed at 0 °C (Table 4, entry 10), resulting in spiro compound **9** with a better enantiomeric excess (75%). Carrying out the reaction at − 20 °C the conversion remained incomplete (Table 4, entry 11). While in the presence of lariat ether (*R*,*R*)-**4c** the *S* isomer of cyclopropane derivative **9** was formed in 75% ee, catalyst (*S*,*S*)-**4c** induced the formation of the opposite *R* isomer with almost the same enantiomeric excess (72%). This methodology seems to be superior as compared to the previously reported synthetic method of compound **9**, [77–79] since less catalyst was used (5 mol % instead of 10 mol % and 50 mol %), slightly better ee values were observed, and the recovery of the catalyst may be solved.

After the cyclopropanation of starting material **7**, the recovery of catalyst **4c** was also investigated using the above described method. The experiment was repeated five times with the recovered catalyst (the loss was compensated), and the results confirmed that macrocycle **4c** can



Scheme 2 Recovery of catalyst (*R*,*R*)-**4a** by salt formation followed by extraction

Table 4 Optimization of the reaction conditions and screening the catalyst in the asymmetric MIRC reaction of 2-benzylidene-1,3-indandione (**7**) and diethyl bromomalonate (**8**)



7 **8** **9**

Entry	Catalyst	Solvent	T (°C)	Time (h)	Yield (%)	ee (%)[a]
1	(*R*,*R*)-**4a**	Et_2O	25	2	83	58 (*S*)
2	(*R*,*R*)-**4b**	Et_2O	25	2	81	55 (*S*)
3	(*R*,*R*)-**4c**	Et_2O	25	1	80	63 (*S*)
4	(*R*,*R*)-**4d**	Et_2O	25	1	74	58 (*S*)
5	(*R*,*R*)-**4c**	CH_2Cl_2	25	2	81	30 (*S*)
6	(*R*,*R*)-**4c**	toluene	25	3	78	55 (*S*)
7	(*R*,*R*)-**4c**	EtOAc	25	2	86	44 (*S*)
8	(*R*,*R*)-**4c**	hexane	25	6	78	40 (*S*)
9	(*R*,*R*)-**4c**	MTBE	25	1	82	64 (*S*)
10	(*R*,*R*)-**4c**	MTBE	0	3	83	75 (*S*)
11	(*R*,*R*)-**4c**	MTBE	−20	24	28	78 (*S*)
12	(*S*,*S*)-**4c**	MTBE	0	3	81	72 (*R*)

[a]Based on chiral HPLC, the absolute configuration was assigned by comparison of the specific rotations with literature data [78]

be reused without any decrease in its activity or selectivity. Product **9** was obtained in a yield of 75–84% and with an ee of 71–75%. At the same time, the yield of the recovery was somewhat lower (73–83%) for catalyst **4c** as compared to species **4a**, that can be explained by the higher lipophilicity of macrocycle **4c.**

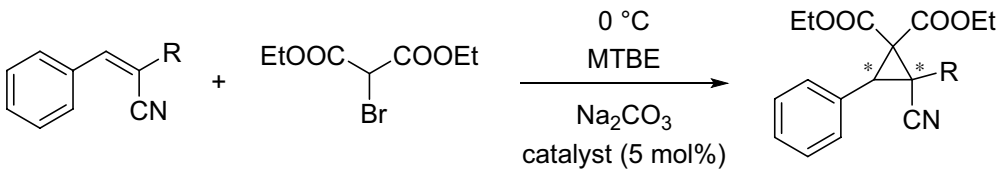
Having the optimized reaction conditions in hand, additional, less studied MIRC reactions were performed [77, 80, 81]. Electron deficient olefins **10a–c** were reacted with diethyl bromomalonate (**8**) using both enantiomers of catalyst **4c** to afford chiral cyclopropanes **11a–c** (Table 5). The reactions were complete within one day (5–24 h), and the products were isolated in good yields (86–94%) and with moderate enantioselectivities (54–72%). The best result (72% ee) was achieved in the cyclopropanation of ethyl (*E*)-2-cyano-3-phenylacrylate (**10b**) (Table 5, entries 2 and 5). The corresponding product (**11b**) was obtained in a somewhat lower enantiomeric excess (72%) than reported by Feng et al. (89% ee) [81], however, in our method less catalyst was used (5 mol % instead of 10 mol %), furthermore, the hydrobenzoin-based catalyst may be recycled, thus, this methodology is more robust.

Slightly lower enantioselectivities were observed in the reaction of benzylidenemalononitrile (**10a**) and (*E*)-3-phenyl-2-(phenylsulfonyl)acrylonitrile (**10c**) (59% and 54%, respectively). Both lower and higher enantioselectivities were reported earlier for the preparation of compound **11a** [36, 77]. A 80% ee was described by Cobb et al. for the synthesis of the dimethyl analogue of product **11c** [80]. However, in these cases, the catalyst could not be reused; moreover, halogenated solvents, or solvent mixtures were used, that make these methods less valuable from the point of view of scaling up. Using the appropriate catalyst ((*S*,*S*)-**4c** or (*R*,*R*)-**4c**), the desired enantiomer of the product could be prepared with approximately the same enantiomeric excess and yield.

3 Conclusions

In conclusion, new hydrobenzoin-based monoaza-15-crown-5 ethers with various side arms have been synthesized, and applied as recyclable phase transfer catalysts in a few asymmetric reactions. To the best of our knowledge, this is the first time that a chiral crown ether phase transfer catalyst was reused in an efficient way. For the epoxidation of *trans*-chalcone, a scalable and green method was elaborated using recyclable catalyst **4a** and MTBE as the solvent. The product was formed with good yield (90%) and enantiomeric excess (81%). Macrocycle **4a** was reused five times without any decrease in

Table 5 Asymmetric MIRC reaction of electron deficient olefins **10a–c** and diethyl bromomalonate (**8**) using catalyst **4c**



10a-c **8** **11a-c**

Entry	Catalyst	R	Time (h)	Yield (%)	ee (%)[a]
1	(*S*,*S*)-**4c**	CN	5	**11a**: 86	59 (*R*)
2	(*S*,*S*)-**4c**	COOEt	24	**11b**: 90	72 (2*S*,3*S*)
3	(*S*,*S*)-**4c**	SO_2Ph	24	**11c**: 93	54 (2*S*,3*R*)
4	(*R*,*R*)-**4c**	CN	5	**11a**: 89	56 (*S*)
5	(*R*,*R*)-**4c**	COOEt	24	**11b**: 88	72 (2*R*,3*R*)
6	(*R*,*R*)-**4c**	SO_2Ph	24	**11c**: 94	51 (2*R*,3*S*)

[a]Based on chiral HPLC, the absolute configuration was assigned by comparison of the specific rotations with literature data [77, 81] The absolute configuration of **11c** was determined based on analogy with the dimethyl analogue [80]

the yield and enantioselectivity. The method developed has a general value, as it could be extended also to other chalcone derivatives. Neither the yield (71–93%), nor the enantiomeric excess (68–86%) of the products decreased drastically by the effect of the substituents in the aromatic ring of the chalcone. In the asymmetric MIRC reaction of 2-benzylidene-1,3-indandione, crown ether **4c** with a 3,4-diethoxyphenylethyl side arm generated the highest enantiomeric excess (75%). The experiments with benzylidenemalonitrile, ethyl (*E*)-2-cyano-3-phenylacrylate, (*E*)-3-phenyl-2-(phenylsulfonyl)acrylonitrile resulted in good yields (85–94%) and moderate ee values (54–72%). This methodology for the synthesis of these chiral cyclopropanes seems to be superior from the point of view green chemistry and scaling up, as compared to previously reported methods. These promising results encourage us to perform further investigations with the hydrobenzoin-based crown ethers by substituting the aromatic ring of hydrobenzoin. We hope that these modifications will improve the selectivity of our catalysts, and even enantiopure products may be obtained. We believe that the applied recovery technique can help to expand the sphere of application of chiral monoaza crown ethers in asymmetric catalysis by eliminating the drawback regarding the high price and poor recyclability.

4 Experimental

4.1 General Procedure for Preparation of Bischloro Compounds (*R*,*R*)-2 and (*S*,*S*)-2

A solution of hydrobenzoin (*R*,*R*-**1** or *S*,*S*-**1**) and tetrabutylammonium hydrogensulphate in bis(2-chloroethyl)ether was vigorously stirred with 50% *aq*. NaOH solution at room temperature for 10 h. Then, the mixture was poured on a mixture of CH_2Cl_2 and water 1:1 (3 times the volume of the reaction mixture), and the phases were separated. The water layer was extracted twice with CH_2Cl_2, the combined organic layer was washed with water, and dried (Na_2SO_4), then the solvent was evaporated. The remaining bis(2-chloroethyl)ether was removed by vacuum distillation. The crude product was purified by column chromatography on silica gel to give the pure product.

4.2 General Procedure for Preparation of Bisiodo Compounds (*R*,*R*)-3 and (*S*,*S*)-3

A mixture of bischloro compound and NaI (4 equivalent) in dry acetone was stirred under reflux for 40 h. After cooling, the precipitate was filtered, and washed with acetone. The combined acetone solutions were evaporated in vacuum. The residue was dissolved in a mixture of $CHCl_3$ and water (1:1), the layers were separated, and the organic phase was washed with water and dried (Na_2SO_4). Evaporation of the solvent afforded the products.

4.3 General Procedure for the Preparation of Crown Ethers 4a–d

Bisiodo podand (*R*,*R*)-**3** or (*S*,*S*)-**3** was dissolved in dry CH_3CN and anhydrous Na_2CO_3 (6 equivalent), and the appropriate amine (1 equivalent) was added under Ar. The mixture was refluxed for 50 h. Then, the solvent was removed, the residue was dissolved in a mixture of $CHCl_3$ and water, the layers were separated, and the organic phase

was washed with water, dried, then concentrated. The crude product was purified by column chromatography.

4.4 General Procedure for the Asymmetric Epoxidations

trans-Chalcone derivative (0.5 mmol) and crown catalyst (5 mol %) were dissolved in MTBE (3 ml), then 0.12 ml (1.3 equivalent) *tert*-butylhydroperoxide (5.5 M in decane) and 20% *aq*. NaOH solution (1 ml) were added. The mixture was stirred at room temperature. The reactions were monitored by TLC (hexane–ethyl-acetate 10:2). After completion, the mixture was diluted with MTBE (7 ml) and water (3 ml), and the phases were separated. The organic layer was washed with 10% *aq*. HCl solution (3×10 ml), dried (Na_2CO_3 and Na_2SO_4), filtered and concentrated in vacuum. The crude products were purified by preparative TLC (hexane–ethyl-acetate). Enantioselectivity was determined by chiral high performance liquid chromatography (HPLC), in comparison with authentic racemic materials.

4.5 General Procedure for Asymmetric Michael Initiated Ring Closure Reactions

Unsaturated compound (0.5 mmol), bromomalonate (0.6 mmol), and the crown ether (5 mol %) were dissolved in MTBE, and dry Na_2CO_3 (0.11 g, 1 mmol) was added. The reaction mixture was stirred at 0 °C (ice bath). The reaction was monitored by TLC (hexane–ethyl-acetate 4:1). After completion of the reaction, the mixture was filtered, then concentrated. The crude product was purified on silica gel by preparative TLC with hexane:EtOAc (5:1) as eluent. Enantioselectivity was determined by chiral high performance liquid chromatography (HPLC), in comparison with authentic racemic materials.

4.6 General Procedure for the Catalyst Recycling

After the reactions were complete, 7 ml MTBE and 3 ml water was added to the reaction mixture and the phases were separated. Then the catalyst was extracted with 5×10 ml *aq*. HCl solution (10 w/w %). Solid sodium hydroxide was added to the combined aqueous layers until the pH turned slightly basic (pH 8–9). The liberated crown catalyst was extracted with MTBE (5×10 ml) and the combined organic layers were dried (Na_2CO_3), filtered then concentrated. The residue was dried in a desiccator.

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