Journal Pre-proof

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PII: S0040-4020(20)30057-0

DOI: https://doi.org/10.1016/j.tet.2020.130965

Reference: TET 130965

To appear in: *Tetrahedron*

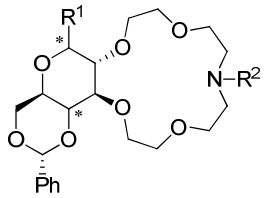
Received Date: 2 November 2019

Revised Date: 13 January 2020

Accepted Date: 17 January 2020

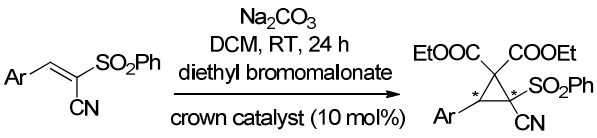
Please cite this article as: Nemcsok Tamá, Rapi Z, Bagi Pé, Guan YH, Orbán Istvá, Keglevich Gyö, Bakó Pé, Enantioselective cyclopropanation of conjugated cyanosulfones using carbohydrate-based crown ether catalysts, *Tetrahedron* (2020), doi: https://doi.org/10.1016/j.tet.2020.130965.

Applied catalysts:



D-glucose- and D-galactose-based crown ethers

Asymmetric MIRC reactions:



m- *p*-substituted products: 75-84% ee
o-substituted products: 0-12% ee
aryl or heteroryl derivatives: 40-85% ee

Enantioselective cyclopropanation of conjugated cyanosulfones using carbohydrate-based crown ether catalysts

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Abstract

A few new D-galactose- and D-glucose-based monoaza-15-crown-5 type lariat ethers have been synthesized. These macrocycles and their derivatives proved to be efficient catalysts in the cyclopropanation of (*E*)-3-phenyl-2-(phenylsulfonyl)acrylonitrile performed with diethyl bromomalonate under mild phase transfer conditions. Among the catalysts tested, the macrocycle having methyl α-D-galactopyranoside unit generated the highest asymmetric induction (80% ee). In the reactions of the aryl-substituted phenylsulfonyl-acrylonitrile derivatives, the cyclopropanation of the *meta*- and *para*-substituted starting materials took place with high ee values (75-84% ee). The cyclopropane derivatives synthesized from analogous α,β-unsaturated cyanosulfones containing naphthyl, pyridyl, furyl and thienyl groups were obtained with enantioselectivities up to 85%, and in excellent yields.

Keywords

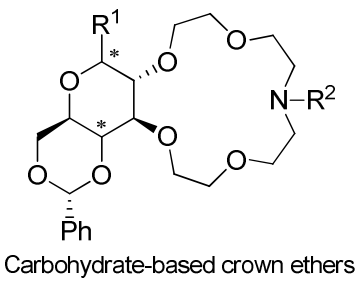
Phase transfer catalysis, Chiral crown ethers, Enantioselective cyclopropanation

1. Introduction

The chiral cyclopropane moiety is an important building block of numerous biologically active compounds and natural products.[1] Moreover, cyclopropane derivatives are considered important intermediates in organic synthesis, particularly if electron-donating and electron-withdrawing groups are introduced into the molecule in the appropriate position, since the easy ring cleavage of the three-membered ring.[2] The synthesis of optically active cyclopropanes have been intensively studied, especially applying the Simmons-Smith reaction[3] and the decomposition of diazoalkanes as carbene precursors in the presence of transition-metal complex catalysts.[4] The Michael-initiated ring closure (MIRC) reaction is another powerful method for the preparation of cyclopropanes, as it requires cheap and readily available reagents along with mild reaction conditions. In the last two decades, different chiral catalysts have been developed to perform MIRC reactions in an enantioselective manner.[5] Among them asymmetric phase transfer catalysis is an attractive

method to perform stereoselective MIRC reactions, as it offers several advantages, such as operational simplicity, mild reaction conditions, inexpensive and environmentally benign reagents and solvents, as well as suitability for large-scale syntheses.[6] However, the application of chiral phase transfer catalysts in enantioselective MIRC-type cyclopropanations has been limited to only a few examples.[7] Previously, in our group a few carbohydrate-based crown ethers proved to be highly enantioselective in several Michael additions and MIRC reactions.[8] Crown ethers with carbohydrate moieties form a special group of chiral macrocycles which can be used as phase transfer catalysts in asymmetric syntheses. Sugar-based chiral catalysts have several advantages: carbohydrates used as starting materials are, in most cases, inexpensive, and easily available commercial products; they are biocompatible; and available in enantiomerically pure form with known chiroptical properties. Carbohydrates have functionalities which can be used to establish secondary binding sites, as well as catalytic sites. Chiral crown ethers have been synthesized from various carbohydrates, *e.g.* from D-glucose[9], D-galactose[10], D-mannose[11], D-altrose[12], D- or L-xylose[13], L-arabinose[14], and sugar alcohols (such as D-mannitol or L-threitol).[15]

In our previous works the D-galactose- and D-glucose-based monoaza-15-crown-5 macrocycles with alkyl or aralkyl substituents on the *N*-atom proved to be the most efficient in a few asymmetric reactions.[16] In these molecules 4- and 6-hydroxy groups of the hexopyranosides are protected as benzylidene acetals (Figure 1), which lend some rigidity to the ring system. In the present work, this basic scaffold was preserved. Previously, the structure-activity studies revealed that the R^1 substituent on the C-1 atom of the sugar moiety, and the side arm (R^2) of the macrocycle have a significant impact on the asymmetric induction during Michael additions,[17,18] therefore the syntheses of a few new derivatives with α-OMe, β-OMe, β-OPh and β-*O*-naphthyl groups in the C-1 position of the sugar moiety with hydroxypropyl and methoxy substituted phenylethyl side arm on the *N*-atom of the crown ring was planned.



Carbohydrate-based crown ethers

Figure 1. The general structure of the most efficient catalysts so far

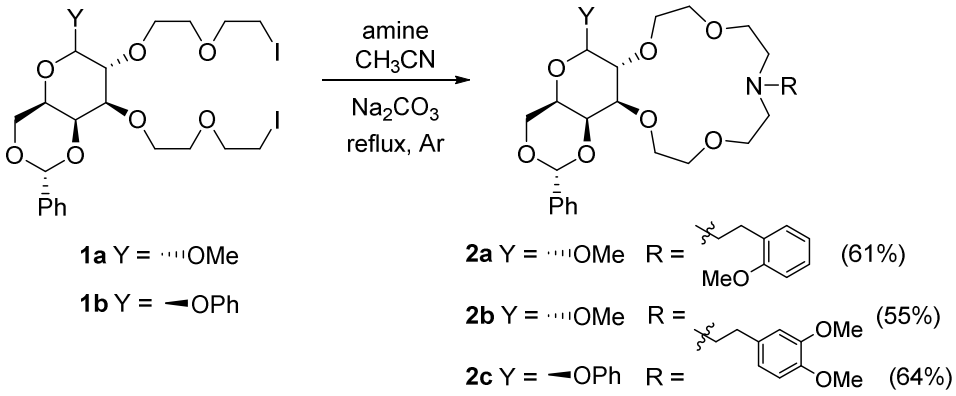
The asymmetric cyclopropanation of (*E*)-3-phenyl-2-(phenylsulfonyl)acrylonitrile, and its derivatives, is an important reaction, since the formed, highly functionalized enantiopure cyclopropanes can be further transformed to other siginifcant chiral products. Cobb *et al*. used a quinine-derived organocatalyst for the cyclopropanation of α,β-unsaturated cyanosulfones using dimethyl bromomalonate to afford chiral cyclopropanes in high yield, and in good enantioselectivities (58-82%).[19] Despite the good results, the applied methodology has the disadvantage of long reaction time (120 h), and not too robust reaction conditions (-10 °C). The authors also demonstrated the utility of the resulting cyclopropanes as synthetic intermediates, for instance in the synthesis of δ^3-amino acids. In this work, we intended to extend the application of carbohydrate-based crown ethers to the aformentioned MIRC reaction by using the new and the previously efficient catalysts of our group.

2. Results and discussion

2.1. Synthesis of the new monoaza crown ethers

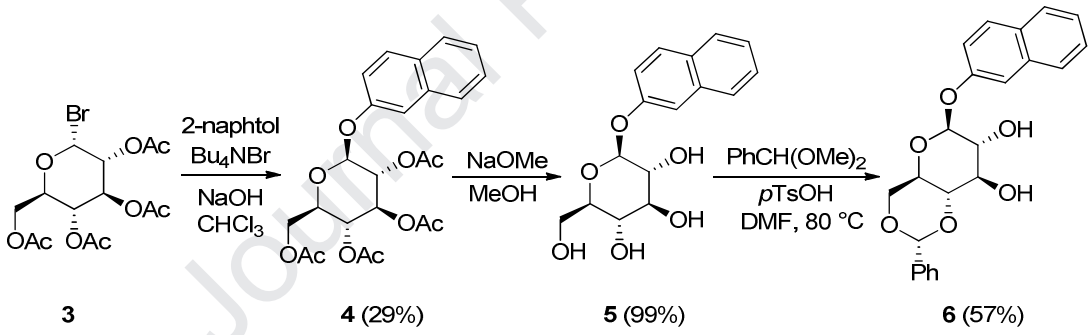
D-Galactose-based macrocycles have been synthesized only with hydroxypropyl and methoxypropyl side chain so far,[8b,8e] although other carbohydrate-based crown ethers with phenylethyl side arm also proved to be effective.[17] Thus, the syntheses of three new galactose-based macrocycle with methoxy-substituted phenylethyl side arm was targeted. The starting material for the syntheses of these crown compounds were the bisiodo podands **1a** and **1b** that were synthesized according to methods reported by our group.[8b,8e] The ring closures were performed by reaction with the appropriate primary amines in boiling acetonitrile in the presence of Na_2CO_3. Intermediate **1a** was cyclized with 2-(2-methoxyphenyl)ethylamine and 2-(3,4-dimethoxyphenyl)ethylamine, while bisiodo compound **1b** was reacted only with 2-(3,4-dimethoxyphenyl)ethylamine (Scheme 1). The D-galactopyranoside-based monoaza crown ethers **2a-c** were isolated in moderate yields (55-64%) after purification by chromatography.

The phenyl β-glucopyranoside-based macrocycles proved to be highly effective in a few Michael additions,[17] therefore we wished to study the effect of a more bulky aromatic substituent, such as 2-naphthyl, in the C-1 position of the glucose unit—on the enantioselectivity. The starting material for the 2-naphthyl-substituted crown ether was the 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (**3**), which was reacted with β-naphthol under phase transfer conditions applying the method of Sidhu *et al*. (Scheme 2.).[20] The β-anomer **4** was isolated in 29% yield after recrystallization.



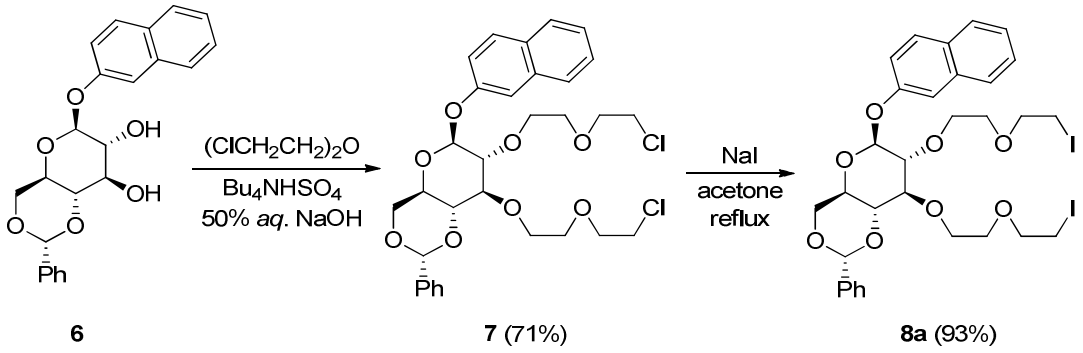
Scheme 1. Synthesis of the D-galactose-based crown ethers **2a-c**

Then, the acetyl groups were cleaved using the Zemplén deacetylation to afford intermediate **5** in a yield of 99%. The 4- and 6-hydroxy groups of the glucopyranoside moiety were protected with benzaldehyde dimethylacetal in DMF in the presence of *p*-toluenesulfonic acid as the catalyst, affording protected glucose derivative **6** in 57% yield after recrystallization from 2-propanol.



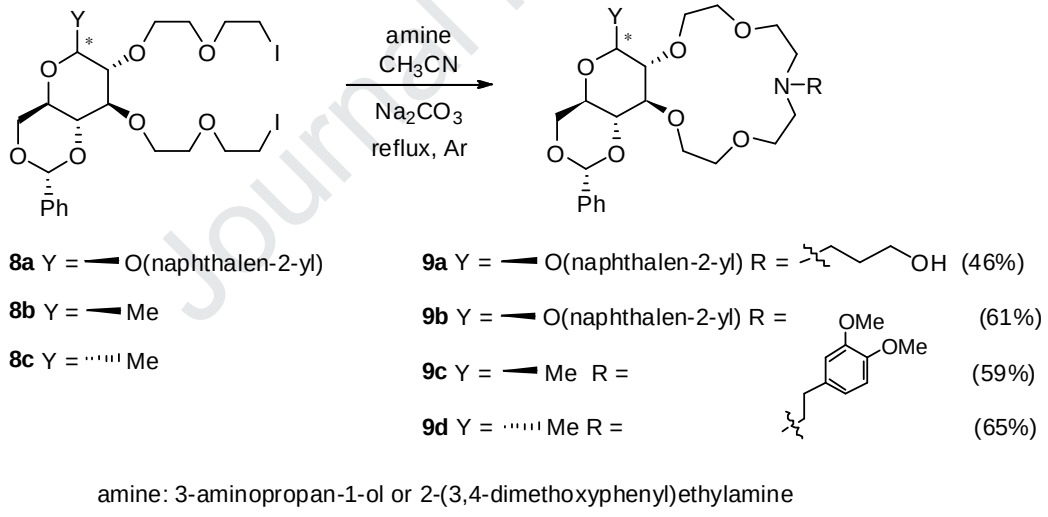
Scheme 2. The synthesis of 2-naphthyl 4,6-*O*-benzylidene-β-D-glucopyranoside (**6**)

The monoaza-15-crown ring was built on the free vicinal hydroxy groups of monosaccharide **6**, applying the method elaborated earlier (Scheme 3).[9b] The 2- and 3-hydroxy groups of **6** were alkylated with bis(2-chloroethyl)ether in the presence of 50% *aq.* NaOH and tetrabutylammonium hydrogensulfate, affording bischloro compound **7** in good yield (71%) after recrystallization from a mixture of EtOH-hexane. The exchange of chlorine to iodine in intermediate **7** was accomplished by reaction with NaI in boiling acetone to provide the bisiodo intermediate **8a** in excellent yield (93%).



Scheme 3. Synthesis of bisiodo podand **8a**

The ring closure reaction of bisiodo derivative **8a** was performed with two primary amines (3-aminopropan-1-ol and 2-(3,4-dimethoxyphenyl)ethylamine), selected on the basis of our previous experiments (Scheme 4).[17,21] The reactions took place in acetonitrile in the presence of Na_2CO_3, giving monoaza crown ethers **9a** and **9b** in moderate yields (46% and 61%, respectively) after purification by chromatography. The cyclization of the α-methyl and β-methyl substituted bisiodo compounds (**8b-c**) with 2-(3,4-dimethoxyphenyl)ethylamine was also realized under the same reaction conditions. The new crown compounds (**9c-d**) were isolated in 59% and 65% yields (Scheme 4).



Scheme 4. Synthesis of D-glucose-based crown ethers **9a-c**

2.2. Asymmetric MIRC reaction of α,β-unsaturated cyanosulfones

The utility of carbohydrate-based crown ethers in the asymmetric MIRC reaction of (*E*)-3-phenyl-2-(phenylsulfonyl)acrylonitrile (**10a**) with diethyl bromomalonate (**11**) was investigated. The catalysts applied for this cyclopropanation are presented in Figure 2. Beside testing the new macrocycles, a few previously synthesized D-glucose- and D-galactose-based lariat ethers (**2d**,[8b] **2e**,[8e] **2f**,[8e] **9e**[22]) were also used. The applied lariat ethers differ in the

configuration of the sugar unit, in the substituent at the C-1 position, and in the side chain on the nitrogen atom of the crown ring. We hoped that a better understanding of the structure-activity relationship may be achieved by using these differently substituted hexopyranoside-based monoaza crown ethers in the aforementioned MIRC reaction.

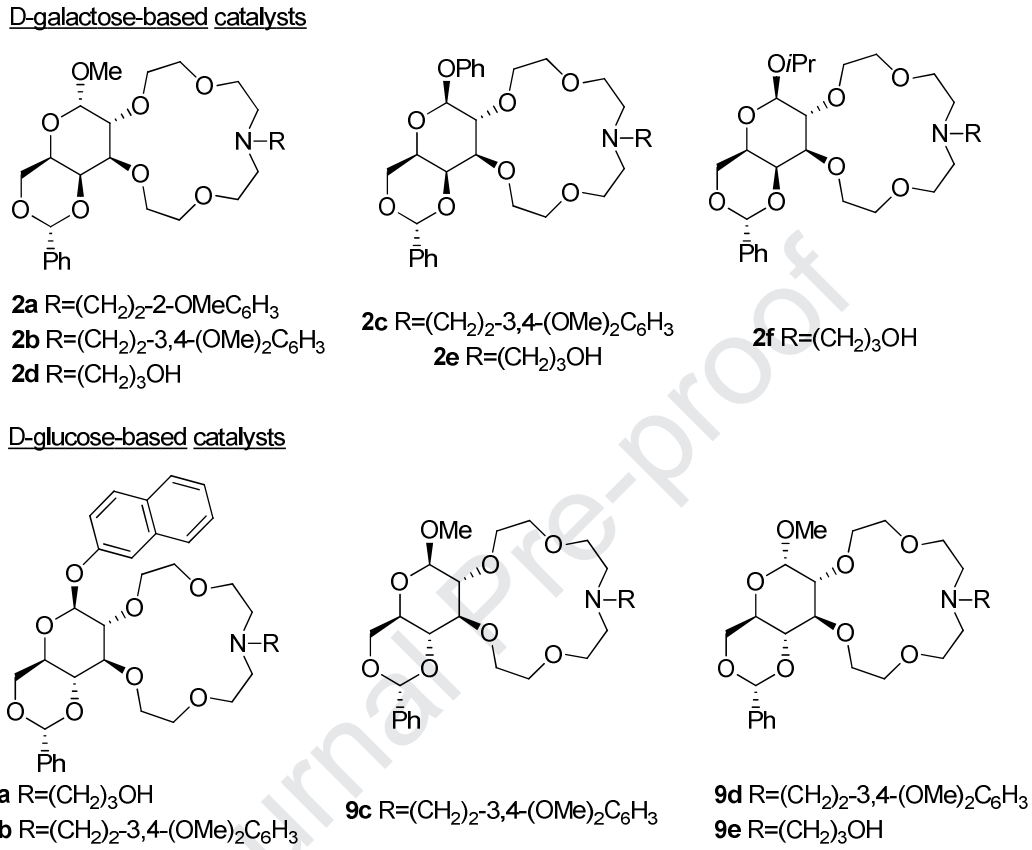


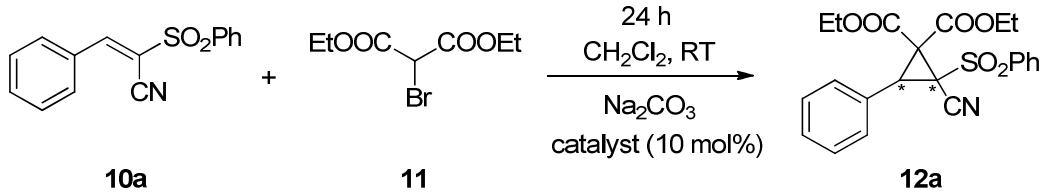
Figure 2. Catalysts applied in the asymmetric MIRC reaction of cyanosulfone **10a**

First, the screening of the catalysts was performed. The reactions of cyanosulfone **10a** with diethyl bromomalonate (1.5 equivalents) took place in dry dichloromethane, using 10 mol% crown ether as the catalyst, and 2 equivalents of Na_2CO_3 as the base. The crude products were purified by preparative TLC, and the enantiomeric purity was determined by chiral HPLC analysis. The results are summarized in Table 1. It can be seen from Table 1, that the chiral cyclopropane **12a** was isolated in good yields (85-94%), while the enantiomeric excesses altered between 18-80% depending on the nature of the catalyst. A single diastereomer was formed (as checked by NMR) in all cases. Relative configuration of the cyclopropane ring in phenyl-substituted **12a** and 2-naphthyl-substituted **12n** was evaluated by a series of NOE (Nuclear Overhauser Effect) measurements. Selective irradiation of the *ortho*-protons of the phenylsulfonyl group resulted in the increase in the intensity of the signal

of the CH group of the cyclopropane ring and that of the CH_2 group of one ethyl ester function. Hence the proximity of these three functions was proved suggesting that they are located on the same side of the cyclopropane ring. From this it follows that the sterically demanding phenylsulfonyl and phenyl or naphthyl substituenst are located in the opposite, *i.e.* in the *anti* (*trans*) disposition.The above explanation is only one of the two NOE measurements. However, the conclusion was also proved from the other way round, *i.e.* on irradiation of the CH signals, the intensity was increased on the signals of the *ortho* protons of the phenylsulfonyl moiety, and on irradiation of the *ortho* hydrogens of the naphthyl group, there was an intensity increase in the signals of the suitable protons of the ethyl ester.

Among the galactose-based lariat ethers (**2a**-**2f**), the highest enantioselectivity (80%) was observed using methyl α-D-galactopyranoside-based macrocycle **2b** having 2-(3,4-dimethoxyphenyl)ethyl side chain (Table 1, entry 2). Catalyst **2a** with 2-(2-methoxyphenyl)ethyl side chain generated approximately the same enantiomeric excess (76%), while the experiment with lariat ether **2d** with hydroxypropyl side arm resulted in a somewhat lower ee value (62%) (Table 1, entries 1 and 4). Using phenyl β-galactopyranoside-based crown ethers **2c** and **2e** the product (**12a**) was isolated in 72% ee and 43% ee, respectively (Table 1, entries 3 and 5). The β-isopropyl derivative **2f** generated an asymmetric induction of 61% (Table 1, entry 6). The reactions performed with D-glucose-based catalysts (**9a**-**e**) resulted with somewhat weaker selectivities (18-73% ee) (Table 1, entries 7-11). If we compare catalyst **9e** with **2d**, and **9d** with **2b**, differing only in the configuration of the sugar unit, it may be concluded that regarding the enantioselectivity the D-galactose-based crown ethers are somewhat more efficient than the D-glucose-based ones (**2d**: 62% ee, **9e**: 50% ee, **2b**: 80% ee, **9d**: 73% ee). The presence of the more bulky β-2-naphthyloxy substituent in position C-1 of the glucopyranoside-based catalysts **9a** and **9b** decreased drastically the observed ee values (18% and 35%, respectively), as compared to the β-methyl analogue **9c** (58% ee). One can draw the conclusion that catalysts with substituted phenylethyl side arms were more efficient in all cases, and that using D-galactose-based macrocycles, the product (**12a**) was formed in slightly higher ee values, than applying the D-glucose-based ones. The substituent of the C-1 position also had a significant impact on the selectivity. The alkyl derivatives were more efficient than the more bulky aromatic derivatives.

Table 1. Catalyst screening in the asymmetric MIRC reaction of cyanosulfone **10a**



10a **11** **12a**

Entry	Catalyst			Yield (%)	ee (%)[a]
	No.	Sugar unit	Side arm		
1	**2a**	Me-α-galactose	$(CH_2)_2$-2-$MeOC_6H_4$	95	76
2	**2b**	Me-α-galactose	$(CH_2)_2$-3,4-$(MeO)_2C_6H_3$	93	80
3	**2c**	Ph-ß-galactose	$(CH_2)_2$-3,4-$(MeO)_2C_6H_3$	90	72
4	**2d**	Me-α-galactose	$(CH_2)_3OH$	85	62
5	**2e**	Ph-ß-galactose	$(CH_2)_3OH$	91	43
6	**2f**	*i*Pr-β-galactose	$(CH_2)_3OH$	93	61
7	**9a**	(naphthalen-2-yl)-β-glucose	$(CH_2)_3OH$	88	18
8	**9b**	(naphthalen-2-yl)-β-glucose	$(CH_2)_2$-3,4-$(MeO)_2C_6H_3$	90	35
9	**9c**	Me-β-glucose	$(CH_2)_2$-3,4-$(MeO)_2C_6H_3$	91	58
10	**9d**	Me-α-glucose	$(CH_2)_2$-3,4-$(MeO)_2C_6H_3$	94	73
11	**9e**	Me-α-glucose	$(CH_2)_3OH$	89	50

[a]: based on chiral HPLC analysis

After screening the catalysts the influence of the solvent was investigated using macrocycle **2b**. It was found that applying CH_2Cl_2, $CHCl_3$, Et_2O, MTBE, toluene and EtOAc as the solvent, the yield of cyclopropane **12a** (86-95%) did not depend much on the medium used, however, the enantiomeric purity of the product showed a significant dependence (51-80% ee). It turned out that dichloromethane is the choice of solvent regarding the enantioselectivity (Table 2.).

Table 2. Solvent screening in the asymmetric MIRC reaction of cyanosulfone **10a**

Solvent	Time (h)	Yield (%)	ee (%)[a]
CH_2Cl_2	24	93	80
$CHCl_3$	24	91	75
Et_2O	48	95	69
MTBE	48	94	60
Toluene	24	86	67
EtOAc	48	87	51

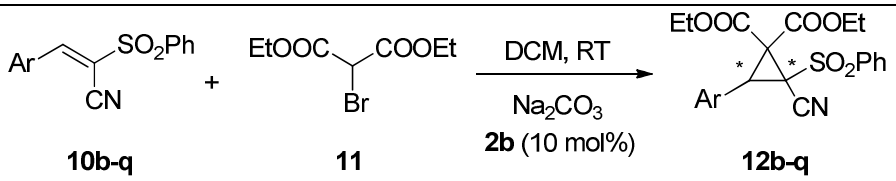
[a]: based on chiral HPLC

Next, the effect of the substituents in the aromatic ring of cyanosulfone **10a** on the enantioselectivity was studied in the presence of methyl α-galactopyranoside-based lariat

ether **2b**. The results of the experiments starting from chloro-, methyl-, nitro-, methoxy-substituted cyanosulfones (**10b-m**) and other analogues (**10n-q**, Ar = 2-naphthyl, 3-pyridyl, 2-furyl, 2-thienyl) are presented in Table 3. In the reaction of 2-Cl, 3-Cl and 4-Cl cyanosulfones (**10b**, **10c**, **10d**) with bromomalonate **11**, ee values of 2%, 84% and 81%, respectively, were detected (Table 3, entries 1-3), while with the 2-Me-, 3-Me- and 4-Me-substituted cyanosulfones (**10e**, **10f** and **10g**), the ee values were 3%, 81% and 78%, respectively (Table 3, entries 4-6). The 2-NO_2, 3-NO_2 and 4-NO_2 cyclopropane derivatives (**12h**, **12i**, and **12j**) were formed with ee values of 12%, 75% and 82%, respectively (Table 3, entries 7-9). In the case of 2-MeO, 3-MeO and 4-MeO substituents, the cyclopropane derivatives **12k**, **12l** and **12m** were obtained with 3%, 81% and 77% ee, respectively. If one regards the results obtained for substituted cyclopropanes **12b-m**, an interesting tendency can be observed (Table 3, entries 1-12). Within the above series, the maximum ee values were obtained with *meta*- and *para*-substituted cyanosulfones (Table 3, entries 2-3, 5-6, 8-9 and 11-12). At the same time, the *ortho*-substituents, which are closer to the reaction center, caused a significant decrease in the ee values (Table 3, entries 1, 4, 7 and 10), as in these cases almost racemic products were isolated (3-12% ee). The *meta*- and *para*-derivatives, with any kind of substituents were formed with approximately the same enantiomeric excess (75-84%). These values are very similar to that obtained in case of the unsubstituted cyclopropane **10a** (80% ee). The outcome seems to be almost independent of the nature of the substituent, no matter if it is an electron-withdrawing or an electron-donating one. The above phenomenon definitely refers to the importance of steric effect.

Cyclopropane derivatives **12n-q** were obtained with moderate to good enantioselectivities (40-85%), and in good yields (86-94%). The 2-naphthyl analogue **12n** was formed with the highest ee value (85% ee), while 3-pyridyl and 2-thienyl derivatives **12o** and **12q** were both isolated in an ee of 72%. The experiment giving cyclopropane **12p** (Ar = 2-furyl) resulted in the lowest enantioselectivity (40%).

Table 3. The asymmetric MIRC reaction of cyanosulfone derivatives **10b-q** catalyzed by crown catalyst **2b**



10b-q **11** **12b-q**

Entry	Ar	Time (h)	Yield (%)	ee (%)[a]
1	2-Cl-C_6H_4	72	**12b**: 83	2
2	3-Cl-C_6H_4	24	**12c**: 91	84
3	4-Cl-C_6H_4	24	**12d**: 94	81
4	2-Me-C_6H_4	48	**12e**: 95	1
5	3-Me-C_6H_4	24	**12f**: 90	81
6	4-Me-C_6H_4	24	**12g**: 87	78
7	2-NO_2-C_6H_4	24	**12h**: 91	12
8	3-NO_2-C_6H_4	24	**12i**: 91	75
9	4-NO_2-C_6H_4	24	**12j**: 87	82
10	2-MeO-C_6H_4	24	**12k**: 89	3
11	3-MeO-C_6H_4	24	**12l**: 95	81
12	4-MeO-C_6H_4	24	**12m**: 94	77
13	2-naphtyl	48	**12n**: 92	85
14	3-pyridyl	24	**12o**: 88	72
15	2-furyl	24	**12p**: 86	40
16	2-thienyl	24	**12q**: 94	72

[a]: based on chiral HPLC

3. Conclusions

An efficient method have been developed for the enantioselective synthesis of a series of highly substituted cyclopropane derivatives by the reaction of α,β-unsaturated cyanosulfones with diethyl bromomalonate in the presence of carbohydrate-based lariat ethers as the phase transfer catalysts under mild conditions. Comparing the sugar unit with two different configurations in the macrocycles, it can be established that regarding enantioselectivity, the D-galactose-based crown ethers are slightly more efficient than the D-glucose-based ones. Among the tested catalysts, a new methyl α-D-galactopyranoside-based macrocycle with a 2-(3,4-dimethoxyphenyl)ethyl side arm generated the highest asymmetric induction (80% ee). It was found that in the presence of this catalyst, the position of the substituents in the aromatic ring of 3-phenyl-2-(phenylsulfonyl)acrylonitrile had a significant impact on the yield and enantioselectivity. The *meta*- and *para*-substituted cyclopropane derivatives were isolated with high enantiomeric excesses (75-84%), while the *ortho*

analogues were formed almost as racemates (3-12% ee). This phenomenon refers to the role of steric effect on the asymmetric induction. The new cyclopropane derivatives prepared in our experiments can be important intermediates in other asymmetric syntheses.

4. Experimental

4.1. General

Melting points were determined by using a Stuart SMP10 apparatus and are uncorrected. The specific rotation was measured on a Perkin-Elmer 341LC polarimeter at 22°C. Nuclear magnetic resonance spectra were obtained on a Bruker (Billerica, MA) DRX-500 or Bruker-300 instrument in $CDCl_3$ with Me_4Si as an internal standard. The exact mass measurements were performed by using quadrupole time of flight mass spectrometer Premier mass spectrometer (Waters, Milford, MA) in positive electrospray ionization mode. Analytical and preparative thin-layer chromatography (TLC) was performed on silica gel plates (60 GF_{254}, Merck, Darmstadt, Germany). Chiral separation of the enantiomers was carried out on a PerkinElmer Series 200 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 254 nm.

4.2. Synthesis of bisiodo compound 8

4.2.1. 2-Naphthyl 4,6-*O*-benzylidene-β-D-glucopyranoside (6)

2-Naphthyl β-D-glucopyranoside (**5**) (9.04 g, 29.5 mmol) was dissolved in dry dimethylformamide (50 ml), then benzaldehyde dimethylacetal (8.90 ml, 59 mmol) and *p*TsOH (0.56 g, 3.0 mmol) were added. The mixture was stirred at 80 °C for 48 h under Ar. After cooling to room temperature, Et_3N was added, then the volatiles were removed by vacuum distillation. The residue was dissolved in $CHCl_3$, and the organic solution was washed with saturated $NaHCO_3$ solution. The organic layer was dried, filtered then concentrated in vacuum. The crude product was crystallized from 2-propanol.

Yield: 57% (6.65 g); white solid, mp 200-201 °C; $[\alpha]_D^{22}$ = -39.2 (*c* = 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$/TMS), δ (ppm): 7.80 (dd, *J* = 11.2, 7.6 Hz, 3H, Ar*H*), 7.58-7.36 (m, 8H, Ar*H*), 7.28 (dd, *J* = 8.9, 2.6 Hz, 1H, Ar*H*), 5.59 (s, 1H, ArC*H*); 5.20 (d, *J* = 7.5, 1H, H-1); 4.43 (dd, *J* = 10.4, 3.9 Hz, 1H, H-6a), 4.05-3.80 (m, 3H, H-6b, H-4, H-5), 3.94-3.79 (m, 2H, H-4, H-5), 3.74-3.61 (m, 2H, H-2, H-3), 3.01 (s, 1H, O*H*), 2.94 (s, 1H, O*H*).

4.2.2. 2-Naphthyl 4,6-*O*-benzylidene-2,3-bis-*O*-[(2-chloroethoxy)-ethyl)]-β-D-glucopyranoside (7)

To a mechanically stirred solution of 2-naphthyl 4,6-*O*-benzylidene-β-D-glucopyranoside (6.65 g, 16.9 mmol) in bis(2-chloroethyl)ether (60 ml, 0.51 mol), 50% *aq*. NaOH solution (60 ml) and equimolar amount of Bu_4NHSO_4 (5.73 g, 16.9 mmol) was added. The reaction mixture was stirred vigorously for 10 h at room temperature, then poured into a mixture of CH_2Cl_2 and water. The phases were separated, and the aqueous layer was extracted with CH_2Cl_2 three times. The combined organic layers were washed with water, dried and concentrated in vacuum. The excess of the bis(2-chloroethyl)ether was removed by vacuum distillation, and the crude product was purified by recrystallization from EtOH-hexane mixture.

Yield: 71% (7.31 g); yellowish white solid, mp 85-87 °C; $[\alpha]_D^{22}$ = -19.3 (*c* = 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$/TMS), δ (ppm): 7.83-7.73 (m, 3H, Ar*H*), 7.53-7.44 (m, 3H, Ar*H*), 7.40-7.37 (m, 5H, Ar*H*), 7.28 (dd, *J* = 8.9, 2.6 Hz, 1H, Ar*H*), 5.57 (s, 1H, ArC*H*), 5.21 (d, *J* = 7.6 Hz, 1H, H-1), 4.41 (dd, *J* = 10.6, 5.0 Hz, 1H, H-6a), 4.15-3.96 (m, 4H, H-2, H-4, H-5, H-6b), 3.82 (t, *J* = 10.3 Hz, 1H, H-3), 3.77-3.49 (m, 16H, 6 x OCH_2, 2 x CH_2Cl).

4.2.3. 2-Naphthyl 4,6-*O*-benzylidene-2,3-bis-*O*-[(2-iodoethoxy)-ethyl)]-β-D-glucopyranoside (8)

To the solution of bischloro compound **7** (7.30 g, 12.0 mmol) in dry acetone (120 ml), NaI (7.20g, 48.0 mmol) was added, and the solution was stirred at reflux temperature for 40 h. The mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was dissolved in $CHCl_3$, washed with water three times, and the aqueous phase was extracted with $CHCl_3$. The combined organic layer was dried and concentrated in vacuum.

Yield: 93% (8.82 g); white solid, mp 110-112 °C; $[\alpha]_D^{22}$ = -12.6 (*c* = 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$/TMS), δ (ppm): 7.78 (dd, *J* = 17.8, 8.4 Hz, 3H, Ar*H*), 7.54-7.44 (m, 3H, Ar*H*), 7.43-7.34 (m, 5H, Ar*H*), 7.29-7.25 (m, 1H, Ar*H*), 5.58 (s, 1H, ArC*H*), 5.21 (d, *J* = 7.6 Hz, 1H, H-1), 4.40 (dd, *J* = 10.6, 5.0 Hz, 1H, H-6a), 4.15-3.95 (m, 4H, H-2, H-4, H-5, H-6b), 3.82 (t, *J* = 10.3 Hz, 1H, H-3), 3.75-3.53 (m, 12H, 6 x OCH_2), 3.25-3.13 (m, 4H, 2 x CH_2I).

4.3. General procedure for the preparation of crown ethers

The appropriate bisiodo podand was dissolved in dry CH_3CN and anhydrous Na_2CO_3 (6 equivalents), and the appropriate amine (1 equivalent) was added under Ar. The mixture was refluxed for 50 hours. 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 (Na_2SO_4), then concentrated. The crude product was purified by column chromatography.

4.3.1. Methyl 4,6-*O*-benzylidene-2,3-dideoxy-α-D-galactopyranosido-[2,3h]-*N*-(2-(2-methoxyphenyl)ethyl)-1,4,7,10-tetraoxa-13-azacyclopentadecane (2a)

Bisiodo compound **1a** (3.39 g, 5.0 mmol); dry CH_3CN (50 mL), anhydrous Na_2CO_3 (3.18 g, 30.0 mmol); 2-(2-methoxyphenyl)ethylamine (0.76 g, 5.0 mmol). Eluent: $CHCl_3$:MeOH 100:2 → 100:8 (silica gel). Yield: 61% (1.75 g), brown oil; = +79.0 (*c* = 1, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$/TMS) δ (ppm): 7.52 (dd, *J* = 7.7, 1.5 Hz, 2H, Ar*H*), 7.37-7.31 (m, 3H, Ar*H*), 7.18-7.11 (m, 2H, Ar*H*), 6.86 (td, *J* = 7.4, 1.2 Hz, 1H, Ar*H*), 6.82 (dd, *J* = 8.2, 1.1 Hz, 1H, Ar*H*), 5.55 (s, 1H, PhC*H*), 4.96 (d, *J* = 3.4 Hz, 1H, H-1), 4.33 (s, 1H, H-3), 4.28 (dd, *J* = 12.4, 1.6 Hz, 1H, H-6a), 4.08 (dd, *J* = 12.5, 1.8 Hz, 1H, H-6b), 3.93 (dd, *J* = 10.0, 3.5 Hz, 1H, H-5), 3.79-3.53 (m, 17H, OCH_3, 6 x OCH_2, H-2, H-4), 3.43 (s, 3H, OCH_3), 2.96-2.69 (m, 8H, NCH_2, ArCH_2). ^{13}C NMR (75 MHz, $CDCl_3$/TMS) δ (ppm): 157.49, 137.88, 130.48, 128.91, 128.13, 127.44, 126.43, 126.32, 120.54, 110.29, 101.03, 98.66, 77.27, 75.72, 73.66, 73.63, 70.56, 70.24, 69.55, 62.51, 55.53, 55.29, 54.23.

4.3.2. Methyl 4,6-*O*-benzylidene-2,3-dideoxy-α-D-galactopyranosido-[2,3h]-*N*-(2-(3,4-dimethoxyphenyl)ethyl)-1,4,7,10-tetraoxa-13-azacyclopentadecane (2b)

Bisiodo compound **1a** (3.39 g, 5.0 mmol); dry CH_3CN (50 mL), anhydrous Na_2CO_3 (3.18 g, 30.0 mmol); 2-(3,4-dimethoxyphenyl)ethylamine (0.91 g, 5.0 mmol). Eluent: $CHCl_3$:MeOH 100:0 → 100:3 (silica gel). Yield: 55% (1.66 g), brown oil; = +92.4 (*c* = 1, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$/TMS) δ (ppm): 7.51 (dd, *J* = 7.8, 1.8 Hz, 2H, Ar*H*), 7.38-7.31 (m, 3H, Ar*H*), 6.77 (d, *J* = 8.2 Hz 1H, Ar*H*), 6.73-6.69 (m, 2H, Ar*H*), 5.54 (s, 1H, PhC*H*), 4.96 (d, *J* = 3.2 Hz, 1H, H-1), 4.34 (s, 1H, H-3), 4.28 (dd, *J* = 12.5, 1.5 Hz, 1H, H-6a), 4.08 (dd, *J* = 12.5, 1.9 Hz, 1H, H-6b), 3.95-3.90 (m, 1H, H-5), 3.89-3.53 (m, 21H, 2 x OCH_3, 6 x OCH_2, H-2, H-3, H-4), 3.43 (s, 3H, OCH_3), 3.11-2.68 (m, 8H, 3 x NCH_2, ArCH_2). ^{13}C NMR (75 MHz, $CDCl_3$/TMS) δ (ppm): 148.94, 137.37, 128.98, 128.25, 126.05, 126.02, 120.61, 112.11, 111.30, 101.33, 98.17, 82.32, 79.75, 77.94, 77.25, 72.55, 70.64, 70.40, 70.13, 69.05, 62.21, 55.93, 55.24.

4.3.3. Phenyl 4,6-*O*-benzylidene-2,3-dideoxy-β-D-galactopyranosido-[2,3h]-*N*-(2-(3,4-dimethoxyphenyl)ethyl)-1,4,7,10-tetraoxa-13-azacyclopentadecane (2c)

Bisiodo compound **1b** (3.70 g, 5.0 mmol); dry CH_3CN (50 mL), anhydrous Na_2CO_3 (3.18 g, 30.0 mmol); 2-(3,4-dimethoxyphenyl)ethylamine (0.91 g, 5.0 mmol). Eluent: $CHCl_3$:MeOH 100:0 → 100:3 (silica gel). Yield: 64% (2.12 g), brown oil; = -4.3 (*c* = 1, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$/TMS) δ (ppm): 7.57-7.49 (m, 2H, Ar*H*), 7.38-7.31 (m, 3H, Ar*H*), 7.30-7.26 (m, 2H, Ar*H*), 7.08-7.00 (m, 3H, Ar*H*), 6.79-6.67 (m, 3H, Ar*H*), 5.54 (s, 1H, PhC*H*), 4.98 (d, *J* = 7.8 Hz, 1H, H-1), 4.38-4.29 (m, 2H, H-3, H-6a), 4.12-3.96 (m, 3H, H-6b, OCH_2), 3.91-3.48 (m, 19H, 5 x OCH_2, 2 x OCH_3, H-2, H-4, H-5), 3.10-2.53 (m, 8H, 3 x NCH_2, ArCH_2). ^{13}C NMR (75 MHz, $CDCl_3$/TMS) δ (ppm): 157.53, 148.95, 137.77, 129.43, 129.01, 128.14, 126.48, 122.71, 120.65, 117.31, 112.22, 111.40, 102.15, 101.33, 79.52, 72.51, 70.74, 70.23, 69.27, 68.70, 66.58, 55.97.

4.3.4. 2-Naphthyl 4,6-*O*-benzylidene-2,3-dideoxy-β-D-glucopyranosido-[2,3h]-*N*-(3-hydroxypropyl)-1,4,7,10-tetraoxa-13-azacyclopentadecane (9a)

Bisiodo compound **8a** (3.30 g, 4.2 mmol); dry CH_3CN (50 mL), anhydrous Na_2CO_3 (2.66 g, 25.1 mmol); 3-aminopropan-1-ol (0.31 g, 4.2 mmol). Eluent: $CHCl_3$:MeOH 100:1 (Al_2O_3). Yield: 46% (1.17 g), white amorphous solid; = -26.6 (*c* = 1, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$/TMS) δ (ppm): 7.81-7.73 (m, 3H, Ar*H*), 7.51-7.43 (m, 3H, Ar*H*), 7.41-7.34 (m, 5H, Ar*H*), 7.22 (dd, *J* = 8.9, 2.5 Hz, 1H, Ar*H*), 5.56 (s, 1H, ArC*H*), 5.22 (d, *J* = 7.7 Hz, 1H, H-1), 4.39 (dd, *J* = 10.5, 5.0 Hz, 1H, H-6a), 4.14-4.97 (m, 4H, H-2, H-4, H-5, H-6b), 3.84-3.54 (m, 16H, H-3, 6 x OCH_2, CH_2OH, O*H*), 2.88-2.80 (m, 2H, NCH_2), 2.75-2.66 (m, 4H, 2 x NCH_2), 1.75-1.62 (m, 2H, CH_2CH$_2$OH). ^{13}C NMR (75 MHz, $CDCl_3$/TMS) δ 154.82, 137.26, 134.21, 130.05, 129.65, 129.01, 128.27, 127.67, 127.17, 126.53, 126.05, 124.54, 118.86, 111.54, 102.20, 101.24, 81.81, 81.46, 80.99, 77.23, 72.55, 72.35, 70.37, 70.26, 68.76, 66.19, 64.14, 56.53, 54.27, 54.22, 28.38.

4.3.5. 2-Naphthyl 4,6-*O*-benzylidene-2,3-dideoxy-β-D-glucopyranosido-[2,3h]-*N*-(2-(3,4-dimethoxyphenyl)ethyl)-1,4,7,10-tetraoxa-13-azacyclopentadecane (9b)

Bisiodo compound **8a** (3.30 g, 4.2 mmol); dry CH_3CN (50 mL), anhydrous Na_2CO_3 (2.66 g, 25.1 mmol); 2-(3,4-dimethoxyphenyl)ethylamine (0.76 g, 4.2 mmol). Eluent: $CHCl_3$:MeOH 100:0 → 100:3 (silica gel). Yield: 61% (1.82 g), white amorphous solid; = -19.7 (*c* = 1, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$/TMS) δ (ppm): 7.82-7.74 (m, 3H, Ar*H*); 7.51-7.44 (m, 3H, Ar*H*); 7.42-7.34 (m, 5H, Ar*H*); 7.23 (dd, *J* = 8.9, 2.5 Hz, 1H, Ar*H*); 6.80-6.76 (m, 1H, Ar*H*); 6.75-6.71 (m, 2H, Ar*H*), 5.57 (s, 1H, ArC*H*); 5.23 (d, *J* = 7.6 Hz, 1H, H-1); 4.40 (dd, *J*

= 10.6, 5.1 Hz, 1H, H-6a), 4.16-4.00 (m, 4H, H-2, H-4, H-5, H-6b); 3.87 (s, 3H, OCH_3); 3.84 (s, 3H, OCH_3); 3.82-3.54 (m, 13H, H-3, 6 x OCH_2); 3.16-2.60 (m, 8H, 3 x NCH_2, ArCH_2). ^{13}C NMR (75 MHz, $CDCl_3$/TMS) δ (ppm): 154.78, 148.85, 147.37, 137.23, 134.21, 130.06, 129.70, 129.10, 129.05, 128.29, 127.68, 127.16, 126.58, 126.04, 124.60, 120.57, 118.81, 112.10, 111.53, 111.26, 102.23, 101.26, 81.75, 81.55, 80.98, 72.55, 72.38, 70.54, 68.75, 66.19, 58.75, 55.93, 54.00.

4.3.6. Methyl 4,6-*O*-benzylidene-2,3-dideoxy-β-D-glucopyranosido-[2,3h]-*N*-(2-(3,4-dimethoxyphenyl)ethyl)-1,4,7,10-tetraoxa-13-azacyclopentadecane (9c)

Bisiodo compound **8b** (3.39 g, 5.0 mmol); dry CH_3CN (50 mL), anhydrous Na_2CO_3 (3.18 g, 30.0 mmol); 2-(3,4-dimethoxyphenylethyl)amine (0.91 g, 5.0 mmol). Eluent: $CHCl_3$:MeOH 100:0 → 100:6 (silica gel). Yield: 59% (1.78 g), brown oil; = -42.4 (*c* = 1, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$/TMS) δ (ppm): 7.48-7.44 (m, 2H, Ar*H*), 7.39-7.33 (m, 3H, Ar*H*), 6.80-6.77 (m, 1H, Ar*H*), 6.73 (dd, *J* = 5.9, 2.1 Hz, 2H, Ar*H*), 5.53 (s, 1H, PhC*H*), 4.38-4.31 (m, 2H, H-1, H-6a), 3.99-3.94 (m, 2H, H-4, H-5), 3.90 (dt, *J* = 10.6, 3.5 Hz, 1H, OCH_2), 3.87 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 3.79-3.67 (m, 3H, H-2, OCH_2), 3.58 (dd, *J* = 10.0, 5.7 Hz, 6H, 3 x OCH_2), 3.54 (s, 3H, OCH_3), 3.37 (td, *J* = 9.3, 4.9 Hz, 1H, OCH_2), 3.22 (t, *J* = 8.0 Hz, 1H, H-3), 2.98-2.67 (m, 8H, 3 x NCH_2, ArCH_2). ^{13}C NMR (125 MHz, $CDCl_3$/TMS) δ (ppm): 149.02, 147.51, 137.53, 129.16, 128.45, 126.20, 120.76, 112.32, 111.46, 105.37, 101.32, 82.08, 81.99, 81.20, 77.42, 72.47, 72.44, 70.67, 70.60, 68.99, 66.06, 57.60, 56.14, 56.06, 54.31, 54.23.

4.3.7. Methyl 4,6-*O*-benzylidene-2,3-dideoxy-α-D-glucopyranosido-[2,3h]-*N*-(2-(3,4-dimethoxyphenyl)ethyl)-1,4,7,10-tetraoxa-13-azacyclopentadecane (9d)

Bisiodo compound **8c** (2.03 g, 3.0 mmol); dry CH_3CN (30 mL), anhydrous Na_2CO_3 (1.91 g, 18.0 mmol); 2-(3,4-dimethoxyphenylethyl)amine (0.54 g, 3.0 mmol). Eluent: $CHCl_3$:MeOH 100:0 → 100:6 (silica gel). Yield: 59% (1.78 g), brown oil; = -42.4 (*c* = 1, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$/TMS) δ (ppm): 7.47 (dd, *J* = 7.4, 1.6 Hz, 2H, Ar*H*), 7.39-7.33 (m, 3H, Ar*H*), 6.80-6.76 (m, 1H, Ar*H*), 6.75-6.71 (m, 2H, Ar*H*), 5.53 (s, 1H, PhC*H*), 4.86 (d, *J* = 3.7 Hz, 1H, H-1), 4.28 (dd, *J* = 10.0, 4.6 Hz, 1H, H-6a), 4.00-3.90 (m, 2H, H-4, H-5), 3.87 (s, 3H. OCH_3), 3.85 (s, 3H, OCH_3), 3.82-3.54 (m, 14H, 6 x OCH_2, H-2, H-3), 3.49 (dd, *J* = 9.4, 3.6 Hz, 1H, H-6b), 3.43 (s, 3H, OCH_3), 2.95-2.64 (m, 8H, 3 x NCH_2, ArCH_2). ^{13}C NMR (125 MHz, $CDCl_3$/TMS) δ (ppm): 148.77, 137.40, 128.95, 128.24, 126.03, 120.57, 112.09, 111.24, 101.31, 98.32, 82.26, 79.87, 78.08, 77.22, 72.51, 70.57, 70.07, 69.07, 62.24, 55.92, 55.22, 54.46.

4.4. General procedure for the enantioselective MIRC reaction

Unsaturated cyanosulfone (0.5 mmol), diethyl bromomalonate (0.75 mmol), and the crown ether (0.05 mmol) were dissolved in dichloromethane, and dry Na_2CO_3 (0.12 g, 1.0 mmol) was added. The reaction mixture was stirred at room temperature. After completion of the reaction (followed by TLC), the mixture was filtered, then concentrated in vacuum. The crude product was purified by preparative TLC (silica gel) with hexane - EtOAc (5:1) as eluent. Enantioselectivity was determined by chiral HPLC analysis by using 5AmyCoat or Lux 5u cellulose-1 column with hexane - EtOH mixture as eluent, in comparison with authentic racemic materials.

4.4.1. Diethyl 2-cyano-3-phenyl-2-(phenylsulfonyl)cyclopropane-1,1-dicarboxylate (12a)

Yield: 93%; mp 58-59 °C, = +18.5 (*c* = 1, $CHCl_3$); 80% ee, 5AmyCoat column, Hexane:EtOH 85:15, major enantiomer t_r = 18.6 min, minor enantiomer t_r = 14.2 min. ^{1}H NMR (500 MHz, $CDCl_3$/TMS) δ (ppm): 8.13 (dd, *J* = 8.5, 1.3 Hz, 2H, Ar*H*), 7.81 (tt, *J* = 7.5, 1.2 Hz, 1H, Ar*H*), 7.68 (t, *J* = 7.9 Hz, 2H, Ar*H*), 7.31 (dd, *J* = 4.9, 2.0 Hz, 3H, Ar*H*), 7.17-7.11 (m, 2H, Ar*H*), 4.50-4.37 (m, 2H, OCH_2), 4.16 (s, 1H, PhC*H*), 4.13 (qd, *J* = 7.1, 2.6 Hz, 2H, OCH_2), 1.42 (t, *J* = 7.1 Hz, 3H, CH_3), 1.10 (t, *J* = 7.1 Hz, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$/TMS) δ (ppm): 162.94, 162.06, 136.12, 135.59, 130.13, 129.59, 128.98, 128.94, 128.65, 128.27, 111.52, 63.55, 63.46, 48.24, 47.58, 36.95, 13.82, 13.60. HRMS calcd for $C_{22}H_{21}NO_6S$ 427.1090; found 427.1095.

4.4.2. Diethyl 3-(2-chlorophenyl)-2-cyano-2-(phenylsulfonyl)cyclopropane-1,1-dicarboxylate (12b)

Yield: 83%; mp 121-122 °C, = +0.4 (*c* = 1, $CHCl_3$); 2% ee, Lux 5u cellulose-1 column, Hexane:EtOH 85:15, major enantiomer t_r = 9.3 min, minor enantiomer t_r = 10.1 min. ^{1}H NMR (500 MHz, $CDCl_3$/TMS) δ (ppm): 8.13 (dd, *J* = 7.7, 1.1 Hz, 2H Ar*H*), 7.80 (tt, *J* = 7.5, 1.3 Hz, 1H, Ar*H*), 7.66 (t, *J* = 8.1 Hz, 2H, Ar*H*), 7.36 (dd, *J* = 8.0, 1.3 Hz, 1H, Ar*H*), 7.30-7.25 (m, 1H, Ar*H*), 7.20 (td, *J* = 7.6, 1.4 Hz, 1H, Ar*H*), 7.09 (dt, *J* = 7.7, 1.3 Hz, 1H, Ar*H*), 4.49-4.38 (m, 2H, OCH_2), 4.12 (q, *J* = 7.2 Hz, 2H, OCH_2), 4.08 (s, 1H, ArC*H*), 1.42 (t, *J* = 7.1 Hz, 3H, CH_3), 1.11 (t, *J* = 7.1 Hz, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$/TMS) δ (ppm): 162.48, 162.20, 136.03, 135.63, 134.60, 130.32, 130.12, 130.11, 129.84, 129.54, 127.18, 127.11, 111.53, 63.45, 63.29, 48.44, 47.09, 36.09, 13.77, 13.46. HRMS calcd for $C_{22}H_{20}ClNO_6S$ 461.0700; found 461.0704.

4.4.3. Diethyl 3-(3-chlorophenyl)-2-cyano-2-(phenylsulfonyl)cyclopropane-1,1-dicarboxylate (12c)

Yield: 91%; oil, = +14.0 (*c* = 1, $CHCl_3$); 84% ee, 5AmyCoat column, Hexane:EtOH 85:15, major enantiomer t_r = 15.4 min, minor enantiomer t_r = 12.6 min. ^{1}H NMR (500 MHz, $CDCl_3$/TMS) δ (ppm): 8.15 (d, *J* = 7.8 Hz, 2H, Ar*H*), 7.84 (t, *J* = 7.4 Hz, 1H, Ar*H*), 7.70 (t, *J* = 7.7 Hz, 2H, Ar*H*), 7.36-7.23 (m, 2H, Ar*H*), 7.16 (s, 1H, Ar*H*), 7.06 (d, *J* = 7.3 Hz, 1H, Ar*H*), 4.55-4.36 (m, 2H, OCH_2), 4.27-4.14 (m, 2H, OCH_2), 4.12 (s, 1H, ArC*H*), 1.44 (t, *J* = 7.1 Hz, 3H, CH_3), 1.18 (t, *J* = 7.1 Hz, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.65, 161.83, 135.87, 135.73, 134.86, 130.59, 130.36, 130.16, 129.64, 129.28, 128.55, 126.58, 111.23, 63.71, 48.17, 47.47, 36.01, 13.82, 13.71. HRMS calcd for $C_{22}H_{20}ClNO_6S$ 461.0700; found 461.0707.

4.4.4. Diethyl 3-(4-chlorophenyl)-2-cyano-2-(phenylsulfonyl)cyclopropane-1,1-dicarboxylate (12d)

Yield: 94%; oil, = +30.0 (*c* = 1, $CHCl_3$); 81% ee, Lux 5u cellulose-1 column, Hexane:EtOH 85:15, major enantiomer t_r = 9.2 min, minor enantiomer t_r = 8.5 min. ^{1}H NMR (500 MHz, $CDCl_3$/TMS) δ (ppm): 8.12 (dd, *J* = 8.5, 1.3 Hz, 2H, Ar*H*), 7.82 (tt, *J* = 7.5, 1.7 Hz, 1H, Ar*H*), 7.68 (t, *J* = 7.9 Hz, 2H, Ar*H*), 7.30 (d, *J* = 8.5 Hz, 2H, Ar*H*), 7.09 (d, *J* = 7.6 Hz, 2H, Ar*H*), 4.49-4.38 (m, 2H, OCH_2), 4.15 (q, *J* = 7.2 Hz, 2H, OCH_2), 4.09 (d, *J* = 1.0 Hz, 1H, ArC*H*), 1.42 (t, *J* = 7.2 Hz, 3H, CH_3), 1.14 (t, *J* = 7.1 Hz, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$/TMS) δ (ppm): 162.71, 161.88, 135.93, 135.71, 135.18, 130.14, 129.70, 129.64, 129.29, 127.17, 111.35, 77.26, 63.66, 48.23, 47.54, 36.14, 13.82, 13.69. HRMS calcd for $C_{22}H_{20}ClNO_6S$ 461.0700; found 461.0709.

4.4.5. Diethyl 2-cyano-3-(2-methylphenyl)-2-(phenylsulfonyl)cyclopropane-1,1-dicarboxylate (12e)

Yield: 95%; mp 128-130 °C, $[\alpha]_D^{22}$ = +0.3 (*c* = 1, $CHCl_3$); 1% ee, Lux 5u cellulose-1 column, Hexane:EtOH 85:15, major enantiomer t_r = 8.1 min, minor enantiomer t_r = 8.6 min. ^{1}H NMR (500 MHz, $CDCl_3$/TMS) δ (ppm): 8.16 (dd, *J* = 8.1, 1.4 Hz, 2H, Ar*H*), 7.81 (tt, *J* = 7.5, 1.2 Hz, 1H, Ar*H*), 7.68 (t, *J* = 7.8 Hz, 2H, Ar*H*), 7.27-7.17 (m, 2H, Ar*H*), 7.11 (td, *J* = 7.3, 1.9 Hz, 1H, Ar*H*), 7.03 (d, *J* = 7.7 Hz, 1H, Ar*H*), 4.47 (qd, *J* = 7.2, 5.2 Hz, 2H, OCH_2), 4.17-4.02 (m, 3H, OCH_2, ArC*H*), 2.41 (s, ArCH_3), 1.45 (t, *J* = 7.1 Hz, 3H, CH_2CH_3), 1.05 (t, *J* = 7.1 Hz, 3H, CH_2CH_3). ^{13}C NMR (75 MHz, $CDCl_3$/TMS) δ (ppm): 163.03, 162.29, 137.85, 136.21,

135.55, 130.69, 130.16, 129.54, 128.85, 128.01, 127.02, 126.13, 111.93, 63.39, 63.30, 48.06, 47.04, 36.87, 19.27, 13.75, 13.40. HRMS calcd for $C_{23}H_{23}NO_6S$ 441.1246; found 441.1240.

4.4.6. Diethyl 2-cyano-3-(3-methylphenyl)-2-(phenylsulfonyl)cyclopropane-1,1-dicarboxylate (12f)

Yield: 90%; mp 90-92 °C, = +16.0 (*c* = 1, $CHCl_3$); 81% ee, Lux 5u cellulose-1 column, Hexane:EtOH 85:15, major enantiomer t_r = 8.7 min, minor enantiomer t_r = 7.8 min. ^{1}H NMR (500 MHz, $CDCl_3$/TMS) δ (ppm): 8.15 (dd, *J* = 7.6, 1.3 Hz, 2H, Ar*H*), 7.83 (tt, *J* = 7.5, 1.3 Hz, 1H, Ar*H*), 7.69 (t, *J* = 7.7 Hz, 2H, Ar*H*), 7.25-7.09 (m, 2H, Ar*H*), 7.00-6.86 (m, 2H, Ar*H*), 4.53-4.37 (m, 2H, OCH_2), 4.24-4.08 (m, 3H, OCH_2, ArC*H*), 1.44 (t, *J* = 7.1 Hz, 3H, CH_2CH_3), 1.14 (t, *J* = 7.1 Hz, 3H, CH_2CH_3). ^{13}C NMR (75 MHz, $CDCl_3$/TMS) δ (ppm): 163.00, 162.10, 138.77, 136.14, 135.54, 130.14, 129.71, 129.56, 128.94, 128.88, 128.47, 125.24, 111.53, 63.54, 63.41, 48.27, 47.58, 36.91, 21.30, 13.82, 13.66. HRMS calcd for $C_{23}H_{23}NO_6S$ 441.1246; found 441.1243.

4.4.7. Diethyl 2-cyano-3-(4-methylphenyl)-2-(phenylsulfonyl)cyclopropane-1,1-dicarboxylate (12g)

Yield: 87%; mp 100-101 °C, = +20.0 (*c* = 1, CH_2Cl_2); 78% ee, Lux 5u cellulose-1 column, Hexane:EtOH 85:15, major enantiomer t_r = 8.7 min, minor enantiomer t_r = 8.1 min. ^{1}H NMR (500 MHz, $CDCl_3$/TMS) δ (ppm): 8.13 (dd, *J* = 8.4, 1.3 Hz, 2H, Ar*H*), 7.80 (tt, *J* = 7.5, 1.6 Hz, 1H, Ar*H*), 7.67 (t, *J* = 8.3 Hz, 1H, Ar*H*), 7.11 (d, *J* = 8.0 Hz, 2H, Ar*H*), 7.01 (d, *J* = 7.8 Hz, 2H, Ar*H*), 4.50-4.37 (m, 2H, OCH_2), 4.14 (qd, *J* = 7.2, 1.6 Hz, 2H, OCH_2), 4.11 (s, 1H, ArC*H*), 2.30 (s, 3H, ArCH_3), 1.41 (t, *J* = 7.1 Hz, 3H, CH_2CH_3), 1.13 (t, *J* = 7.1 Hz, 3H, CH_2CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.00, 162.09, 138.90, 136.20, 135.53, 130.10, 129.67, 129.56, 128.12, 125.49, 111.57, 63.51, 63.42, 48.32, 47.65, 36.87, 21.21, 13.82, 13.66. HRMS calcd for $C_{23}H_{23}NO_6S$ 441.1246; found 441.1248.

4.4.8. Diethyl 2-cyano-3-(2-nitrophenyl)-2-(phenylsulfonyl)cyclopropane-1,1-dicarboxylate (12h)

Yield: 91%; mp 165-167 °C, = +6.6 (*c* = 1, $CHCl_3$); 12% ee, Lux 5u cellulose-1 column, Hexane:EtOH 85:15, major enantiomer t_r = 15.9 min, minor enantiomer t_r = 13.8 min. ^{1}H NMR (500 MHz, $CDCl_3$/TMS) δ (ppm): 8.17 (dd, *J* = 8.0, 1.4 Hz, 2H, Ar*H*), 8.07 (dd, *J* = 8.2, 1.4 Hz, 1H, Ar*H*), 7.83 (tt, *J* = 7.5, 1.3 Hz, 1H, Ar*H*), 7.70 (t, *J* = 7.8 Hz, 2H, Ar*H*), 7.66 (td, *J* = 7.6, 1.4 Hz, 1H, Ar*H*), 7.55 (t, *J* = 7.8 Hz, 1H, Ar*H*), 7.42 (d, *J* = 7.8 Hz, 1H, Ar*H*), 4.52 (s, 1H, ArC*H*), 4.51-4.39 (m, 2H, OCH_2), 4.09 (q, *J* = 7.2 Hz, 2H, OCH_2), 1.45 (t, *J* = 7.1

Hz, 3H, C*H*$_3$), 1.15 (t, *J* = 7.1 Hz, 3H, C*H*$_3$). ^{13}C NMR (75 MHz, CDCl$_3$/TMS) δ (ppm): 162.27, 161.84, 148.69, 135.79, 135.70, 133.89, 132.14, 130.45, 129.96, 129.58, 125.05, 124.61, 111.54, 63.99, 63.53, 49.65, 47.37, 36.00, 13.81, 13.49. HRMS calcd for $C_{22}H_{20}N_2O_8S$ 472.0940; found 472.0945.

4.4.9. Diethyl 2-cyano-3-(3-nitrophenyl)-2-(phenylsulfonyl)cyclopropane-1,1-dicarboxylate (12i)

Yield: 91%; mp 118 °C, = +22.2 (*c* = 1, CHCl$_3$); 75% ee, 5AmyCoat column, Hexane:EtOH 50:50 major enantiomer t$_r$ = 9.8 min, minor enantiomer t$_r$ = 7.8 min. ^{1}H NMR (500 MHz, CDCl$_3$/TMS) δ (ppm): 8.22 (dt, *J* = 8.0, 1.2 Hz, 1H, Ar*H*), 8.15 (dd, *J* = 7.7, 1.3 Hz, 2H, Ar*H*), 7.99 (s, 1H, Ar*H*), 7.86 (tt, *J* = 7.6, 1.0 Hz, 1H, Ar*H*), 7.72 (t, *J* = 8.1 Hz, 2H, Ar*H*), 7.60-7.51 (m, 2H, Ar*H*), 4.54-4.40 (m, 2H, OC*H*$_2$), 4.27-4.15 (m, 3H, OC*H*$_2$, ArC*H*), 1.45 (t, *J* = 7.1 Hz, 3H, C*H*$_3$), 1.22 (t, *J* = 7.1 Hz, 3H, C*H*$_3$). ^{13}C NMR (75 MHz, CDCl$_3$/TMS) δ (ppm): 162.33, 161.73, 148.38, 135.94, 135.64, 134.68, 130.84, 130.32, 130.17, 129.74, 124.01, 123.61, 110.99, 64.07, 63.88, 48.34, 47.48, 35.70, 13.83, 13.75. HRMS calcd for $C_{22}H_{20}N_2O_8S$ 472.0940; found 472.0948.

4.4.10. Diethyl 2-cyano-3-(4-nitrophenyl)-2-(phenylsulfonyl)cyclopropane-1,1-dicarboxylate (12j)

Yield: 87%; mp 98-99 °C, = +40.1 (*c* = 1, CHCl$_3$); 82% ee, Lux 5u cellulose-1 column, Hexane:EtOH 85:15, major enantiomer t$_r$ = 17.2 min, minor enantiomer t$_r$ = 19.7 min. ^{1}H NMR (500 MHz, CDCl$_3$/TMS) δ (ppm): 8.21 (d, *J* = 8.8 Hz, 2H, Ar*H*), 8.14 (dd, *J* = 8.3, 1.3 Hz, 2H, Ar*H*), 7.85 (tt, *J* = 7.5, 1.2 Hz, 1H, Ar*H*), 7.71 (t, *J* = 7.8 Hz, 2H, Ar*H*), 7.36 (d, *J* = 8.2 Hz, 2H, Ar*H*), 4.53-4.40 (m, 2H, OC*H*$_2$), 4.23-4.12 (m, 3H, OC*H*$_2$, ArC*H*), 1.44 (t, *J* = 7.1 Hz, 3H, C*H*$_3$), 1.17 (t, *J* = 7.2 Hz, 3H, C*H*$_3$). ^{13}C NMR (75 MHz, CDCl$_3$) δ (ppm): 162.35, 161.70, 148.17, 135.94, 135.88, 135.65, 130.20, 129.73, 129.59, 124.18, 111.07, 63.93, 63.87, 48.17, 47.42, 35.92, 13.83, 13.73. HRMS calcd for $C_{22}H_{20}N_2O_8S$ 472.0940; found 472.0942.

4.4.11. Diethyl 2-cyano-3-(2-methoxyphenyl)-2-(phenylsulfonyl)cyclopropane-1,1-dicarboxylate (12k)

Yield: 89%; mp 138-139 °C, = +0.3 (*c* = 1, CHCl$_3$); 3% ee, Lux 5u cellulose-1 column, Hexane:EtOH 85:15, major enantiomer t$_r$ = 10.1 min, minor enantiomer t$_r$ = 11.9 min. ^{1}H NMR (500 MHz, CDCl$_3$/TMS) δ (ppm): 8.13 (dd, *J* = 8.4, 1.3 Hz, 2H, Ar*H*), 7.79 (tt, *J* = 7.6, 1.3 Hz, 1H, Ar*H*), 7.66 (t, *J* = 7.7 Hz, 2H, Ar*H*), 7.30-7.25 (m, 1H, Ar*H*), 6.96 (dt, *J* = 7.5, 1.4 Hz, 1H, Ar*H*), 6.86 (td, *J* = 7.5, 0.7 Hz, 1H, Ar*H*), 6.80 (d, *J* = 8.5 Hz, 1H, Ar*H*), 4.42 (qd, *J* =

7.1, 5.0 Hz, 2H, OCH_2), 4.14 (q, *J* = 7.1, 2H, OCH_2), 3.94 (s, 1H, ArC*H*), 3.48 (s, 3H, OCH_3), 1.40 (t, *J* = 7.1 Hz, 3H, CH_2CH_3), 1.12 (t, *J* = 7.2 Hz, 3H, CH_2CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 163.18, 162.62, 157.78, 136.71, 135.26, 130.47, 130.32, 129.50, 129.37, 120.72, 116.88, 111.85, 110.79, 63.19, 63.12, 55.02, 48.39, 46.86, 34.47, 13.84, 13.63. HRMS calcd for $C_{23}H_{23}NO_7S$ 457.1195; found 457.1190.

4.4.12. Diethyl 2-cyano-3-(3-methoxyphenyl)-2-(phenylsulfonyl)cyclopropane-1,1-dicarboxylate (12l)

Yield: 95%; oil, = +18.9 (*c* = 1, $CHCl_3$); 81% ee, Lux 5u cellulose-1 column, Hexane:EtOH 85:15, major enantiomer t_r = 10.6 min, minor enantiomer t_r = 9.6 min. ^{1}H NMR (500 MHz, $CDCl_3$/TMS) δ (ppm): 8.13 (dd, *J* = 7.8, 1.3 Hz, 2H, Ar*H*), 7.81 (tt, *J* = 7.5, 1.1 Hz, 1H, Ar*H*), 7.68 (t, *J* = 7.8 Hz, 2H, Ar*H*), 7.21 (t, *J* = 8.0 Hz, 1H, Ar*H*), 6.84 (dd, *J* = 8.2, 2.5 Hz, 1H, Ar*H*), 6.70 (d, *J* = 7.6 Hz, 1H, Ar*H*), 6.64-6.60 (m, 1H, Ar*H*), 4.49-4.37 (m, 2H, OCH_2), 4.19-4.10 (m, 3H, OCH_2, ArC*H*), 3.71 (s, 3H, OCH_3), 1.42 (t, *J* = 7.2 Hz, 3H, CH_2CH_3), 1.13 (t, *J* = 7.1 Hz, 3H, CH_2CH_3). ^{13}C NMR (75 MHz, $CDCl_3$/TMS) δ (ppm): 162.90, 162.02, 159.85, 136.14, 135.56, 130.14, 130.08, 129.91, 129.58, 120.39, 114.80, 113.72, 111.54, 63.55, 63.48, 55.25, 48.20, 47.60, 36.98, 13.82, 13.65. HRMS calcd for $C_{23}H_{23}NO_7S$ 457.1195; found 457.1198

4.4.13. Diethyl 2-cyano-3-(4-methoxyphenyl)-2-(phenylsulfonyl)cyclopropane-1,1-dicarboxylate (12m)

Yield: 94%; oil, = +24.4 (*c* = 1, $CHCl_3$); 77% ee, Lux 5u cellulose-1 column, Hexane:EtOH 85:15, major enantiomer t_r = 11.8 min, minor enantiomer t_r = 10.6 min. ^{1}H NMR (500 MHz, $CDCl_3$/TMS) δ (ppm): 8.12 (dd, *J* = 8.2, 0.8 Hz, 2H, Ar*H*), 7.81 (tt, *J* = 7.5, 1.2 Hz, 1H, Ar*H*), 7.68 (t, *J* = 7.8 Hz, 2H, Ar*H*), 7.05 (d, *J* = 8.4 Hz, 2H, Ar*H*), 6.82 (d, *J* = 8.8 Hz, 2H, Ar*H*), 4.49-4.36 (m, 2H, OCH_2), 4.15 (q, *J* = 7.1 Hz, 2H, OCH_2), 4.10 (s, 1H, ArC*H*), 3.77 (s, 3H, OCH_3), 1.41 (t, *J* = 7.2 Hz, 3H, CH_2CH_3), 1.14 (t, *J* = 7.2 Hz, 3H, CH_2CH_3). ^{13}C NMR (75 MHz, $CDCl_3$/TMS) δ (ppm): 162.94, 162.05, 159.92, 136.16, 135.50, 130.05, 129.53, 129.50, 120.29, 114.40, 111.57, 63.48, 63.40, 55.27, 48.37, 47.72, 36.55, 13.78, 13.66. HRMS calcd for $C_{23}H_{23}NO_7S$ 457.1195; found 457.1194.

4.4.14. Diethyl 2-cyano-3-(naphthalen-2-yl)-2-(phenylsulfonyl)cyclopropane-1,1-dicarboxylate (12n)

Yield: 92%; oil, = +49.1 (*c* = 1, $CHCl_3$); 85% ee, 5AmyCoat column, Hexane:EtOH 50:50, major enantiomer t_r = 13.6 min, minor enantiomer t_r = 10.2 min. ^{1}H NMR (500 MHz,

$CDCl_3$/TMS) δ (ppm): 8.17 (dd, *J* = 8.4, 1.3 Hz, 2H, Ar*H*), 7.84-7.77 (m, 3H, Ar*H*), 7.74-7.66 (m, 3H, Ar*H*), 7.62 (s, 1H, Ar*H*), 7.51-7.44 (m, 2H, Ar*H*), 7.20 (dd, *J* = 8.6, 1.8 Hz, 1H, Ar*H*), 4.53-4.40 (m, 2H, OCH_2), 4.31 (s, 1H, ArC*H*), 4.17-4.06 (m, 2H, OCH_2), 1.44 (t, *J* = 7.1 Hz, 3H, CH_2CH_3), 1.07 (t, *J* = 7.1 Hz, 3H, CH_2CH_3). ^{13}C NMR (75 MHz, $CDCl_3$/TMS) δ (ppm): 162.99, 162.08, 136.14, 135.61, 133.13, 133.04, 130.19, 129.62, 128.99, 127.92, 127.79, 126.91, 126.77, 125.93, 125.28, 111.57, 63.63, 63.52, 48.39, 47.74, 37.02, 13.86, 13.67. HRMS calcd for $C_{26}H_{23}NO_6S$ 477.1246; found 477.1239.

4.4.15. Diethyl 2-cyano-2-(phenylsulfonyl)-3-(pyridin-3-yl)cyclopropane-1,1-dicarboxylate (12o)

Yield: 88%; oil, = +15.0 (*c* = 1, $CHCl_3$); 72% ee, Lux 5u cellulose-1 column, Hexane:EtOH 85:15, major enantiomer t_r = 14.6 min, minor enantiomer t_r = 15.5 min. ^{1}H NMR (500 MHz, $CDCl_3$/TMS) δ (ppm): 8.59 (d, *J* = 5.0 Hz, 1H, Ar*H*), 8.40 (d, *J* = 2.4 Hz, 1H, Ar*H*), 8.17 (dd, *J* = 8.2, 1.4 Hz, 2H, Ar*H*), 7.82 (tt, *J* = 7.6, 1.2 1H, Ar*H*), 7.69 (t, *J* = 7.9 Hz 2H, Ar*H*), 7.58-7.51 (m, 1H, Ar*H*), 7.30 (dd, *J* = *J* = 8.0, 4.9 Hz, 1H, Ar*H*), 4.51-4.39 (m, 2H, OCH_2), 4.17 (q, *J* = 7.1 Hz, 2H, OCH_2), 4.10 (s, 1H, ArC*H*), 1.42 (t, *J* = 7.2 Hz, 3H, CH_3), 1.15 (t, *J* = 7.2 Hz, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$/TMS) δ (ppm): 162.38, 161.72, 149.71, 149.23, 136.27, 135.83, 135.74, 130.11, 129.67, 125.31, 123.71, 111.08, 63.86, 63.76, 47.90, 47.25, 34.29, 13.78, 13.65. HRMS calcd for $C_{21}H_{20}N_2O_6S$ 428.1042; found 428.1046.

4.4.16. Diethyl 2-cyano-3-(furan-2-yl)-2-(phenylsulfonyl)cyclopropane-1,1-dicarboxylate (12p)

Yield: 86%; oil, = -10.3 (*c* = 1, $CHCl_3$); 40% ee, Lux 5u cellulose-1 column, Hexane:EtOH 85:15, major enantiomer t_r = 10.1 min, minor enantiomer t_r = 9.5 min. ^{1}H NMR (500 MHz, $CDCl_3$/TMS) δ (ppm): 8.07 (dd, *J* = 8.6, 1.1 Hz, 2H, Ar*H*), 7.77 (tt, *J* = 7.5, 1.2 Hz, 1H, Ar*H*), 7.64 (t, *J* = 7.9 Hz, 2H, Ar*H*), 7.35 (d, *J* = 1.8 Hz, 1H, Ar*H*), 6.39 (d, *J* = 3.4 Hz, 1H, Ar*H*), 6.33 (dd, *J* = 3.4, 1.9 Hz, 1H, Ar*H*), 4.44-4.35 (m, 2H, OCH_2), 4.22 (qd, *J* = 7.1, 5.3 Hz, 2H, OCH_2), 4.08 (s, 1H, ArC*H*), 1.39 (t, *J* = 7.2 Hz, 3H, CH_2CH_3), 1.20 (t, *J* = 7.1 Hz, 3H, CH_2CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.06, 161.46, 143.69, 142.19, 136.03, 135.61, 129.93, 129.58, 111.19, 111.06, 110.86, 63.79, 63.68, 47.41, 46.98, 31.21, 13.78, 13.67. HRMS calcd for $C_{20}H_{19}NO_7S$ 417.0882; found 417.0884.

4.4.17. Diethyl 2-cyano-2-(phenylsulfonyl)-3-(thiophen-2-yl)cyclopropane-1,1-dicarboxylate (12q)

Yield: 94%; oil, = -7.5 (*c* = 1, $CHCl_3$); 72% ee, 5AmyCoat column, Hexane:EtOH 85:15, major enantiomer t_r = 23.6 min, minor enantiomer t_r = 16.8 min. ^{1}H NMR (500 MHz, $CDCl_3$/TMS) δ (ppm): 8.09 (dd, *J* = 7.4, 1.2 Hz, 2H, Ar*H*), 7.79 (tt, *J* = 7.5, 1.2 Hz, 1H, Ar*H*), 7.65 (t, *J* = 7.9 Hz, 2H, Ar*H*), 7.26 (dd, *J* = 5.1, 1.3 Hz, 1H, Ar*H*), 6.96 (dt, *J* = 2.7, 1.3 Hz, 1H, Ar*H*), 6.93 (dd, *J* = 5.1, 3.6 Hz, 1H, Ar*H*), 4.47-4.35 (m, 2H, OCH_2), 4.27-4.13 (m, 3H, OCH_2, ArC*H*), 1.40 (t, *J* = 7.1 Hz, 3H, CH_2CH_3), 1.18 (t, *J* = 7.1 Hz, 3H, CH_2CH_3). ^{13}C NMR (75 MHz, $CDCl_3$/TMS) δ (ppm): 161.28, 160.51, 135.05, 134.58, 128.91, 128.58, 127.17, 126.32, 126.02, 110.26, 62.67, 47.82, 47.29, 31.96, 12.74, 12.62.
HRMS calcd for $C_{20}H_{19}NO_6S_2$ 433.0654; found 433.0660.

5. Acknowledgement

The research reported in this paper has been supported by the National Research Development and Innovation Fund (TUDFO/51757/2019-ITM, Thematic Excellence Program). We thank Dr. Tibor Bakó for his help with the NOE NMR measurements.

Supplementary data

Supplementary data related to this article can be found on this article's webpage.

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Highlights

- New D-glucose- and D-galactose-based crown ethers have been synthesized.
- A new D-galactose-based macrocycle induced significant enantioselectivity (up to 85%) in the MIRC reaction of some α,β-unsaturated cyanosulfones.
- The *m*- and *p*-substituted products were formed with higher enantioselectivity (75-84%), than the *o*-substituted cyclopropanes (0-12%).
- The new chiral cyclopropanes may be important intermediates in asymmetric syntheses.

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: