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ORIGINAL ARTICLE

Enantioselective cyclopropanations: a study on the catalytic effects of methyl-α-D-mannopyranoside-based lariat ethers

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Abstract

Novel monoaza-15-crown-5 ethers have been synthesized with an α-D-mannopyranoside backbone. These chiral catalysts contain different heteroaromatic side chains, which have never been incorporated in sugar-based crown ethers before. The novel macrocycles together with a few previously synthesized mannose-based crown ethers were examined in four asymmetric phase-transfer cyclopropanations. The reactions proceeded mainly with excellent yields (up to 99%), while enantiomeric excesses ranged from 1 to 44%, proving the mannose-based lariat ethers to be moderate enantioselective catalysts in these reactions. The distance between the crown ring and the functional group of the side chain proved to be important in terms of enantioselectivity, the propylene moiety was more favorable than the ethylene bridge. The type of heteroaromatic ring also affected the catalytic activity of the mannose-based macrocycles, using lariat ethers containing a pyrrole unit, higher enantiomeric excess was measured.

Keywords Crown ethers · Chirality · Phase-transfer catalysis · Enantioselectivity

Introduction

Catalytic asymmetric induction, the process by which a chiral environment provided by a catalyst influences the stereochemical outcome of a reaction, is a fundamental technique among enantioselective synthetic methods. It has been becoming more and more widespread in recent decades due to the great amount of research performed in the topic worldwide [1–4]. Phase-transfer catalysis is one of the methods by which enantioselective synthesis can be performed. Among the many types of phase-transfer catalysts (PTCs), crown ethers, known for their selective cation complexation ability, have been adapted for asymmetric induction by incorporating chiral moieties into their structure. This can be performed multiple ways, one of which is by utilizing carbohydrates as a cheap and readily accessible source of chirality. Since these compounds already contain stereogenic centers, they may possess the ability to trigger asymmetric induction [5].

The synthesis and application of carbohydrate-based crown ethers have been extensively studied in our research group. So far, most research on macrocycles derived from sugars has focused on crown ethers containing a d-glucose [6, 7] or a d-galactose [8–9] unit; their catalytic activity was tested in asymmetric phase-transfer reactions. Using a different, also easily accessible aldohexose, α-D-mannopyranoside-based lariat ethers were also synthesized and tested by members of our research group [10]. The investigated macrocycles (Fig. 1 and a-e) generated moderate to high enantiomeric excess, up to 92% ee, in biphasic Michael addition, Darzens condensation and epoxidation reactions. Since glucose-based crown ethers have proven to be good enantioselective catalysts in several cases [11, 12], and glucose and mannose differ only in the C-2 configuration, it was aimed to further explore the effect-structure relationships by expanding the previous work.

In recent years, several asymmetric cyclopropanation reactions were performed in the presence of chiral crown ethers [13, 14]. In these reactions, the effect of previously synthesized mannose-based macrocycles has not been investigated before. Thus, in this study we report the results of four different cyclopropanation reactions catalyzed by

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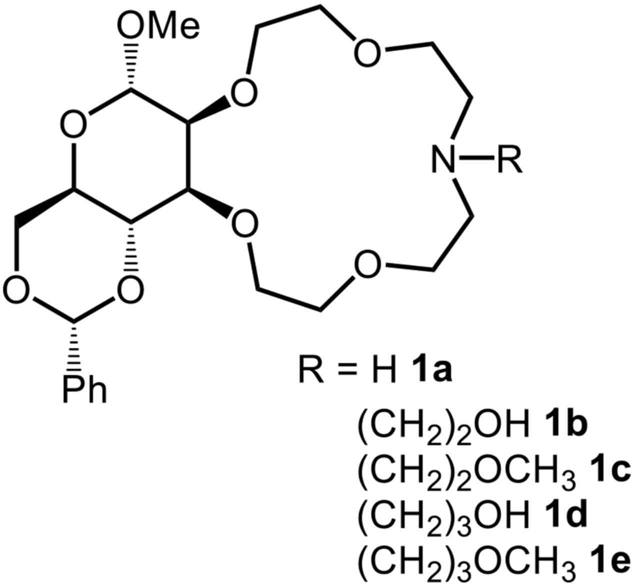

Fig. 1 Structure of previously synthesized d-mannose-based crown ethers **1a-e**

lariat ethers derived from mannose. Furthermore, novel mannose-based lariat ethers containing different heterocycles in their side arm were synthesized and tested as chiral phase-transfer catalysts. The side chain of carbohydrate-based lariat ethers heavily affects the catalytic activity, thus also the enantioselectivity [15]. We have synthesized new macrocycles derived from mannose that retain the monoaza-15-crown-5 structure and contain a heteroaromatic ring. This type of substituent has not been tested yet.

Synthesis of macrocycles

Monoaza 15-crown-5 ethers **1a-e** derived from mannose were prepared previously in our research group [10]. The key compound of their syntheses was methyl-4,6-*O*-benzylidene α-D-mannopyranoside (**4**). A characteristic property of methyl-α-D-mannopyranoside (**2**) is that it tends to form acetals in both the 4,6 and 2,3 positions. The formation of the latter unit is made possible by the axial-equatorial position of the OH groups on C-2 and C-3. During the synthesis of macrocycles **1a-e**, benzylidene mannopyranoside **4** was prepared from methyl mannopyranoside **2** using kinetic control [10], since the acetal is formed faster in the 4,6 positions than in the 2,3 positions. The disadvantage of the method is that a lower yield can be achieved, and the conditions must be set and maintained very precisely.

In the synthesis of novel macrocycles **7a-d**, the starting material was also methyl-α-D-mannopyranoside (**2**), which was prepared according to literature [16]. But for the aforementioned reasons, we looked for an alternative method to obtain mannoside **4**. From compound **2**, double acetal derivative **3** was prepared by transacetalation, using benzaldehyde dimethyl acetal in dry DMF [17]. The newly formed 1,3-dioxane and 1,3-dioxolane rings in compound **3** possess different reactivities, the dioxolane unit is less stable. Thus, mannopyranoside **3** was subjected to transfer hydrogenation with ammonium formate in methanol [18], where the ring opening only occurred to the dioxolane unit, thereby freeing the vicinal OH groups in positions 2 and 3 for further functionalization (Fig. 2).

The first step of the formation of the macroring was *O*-alkylation, which was performed using bis(2-chloroethyl ether), tetrabutylammonium hydrogensulfate and 50 m/m% aqueous NaOH under phase-transfer conditions. The resulting crude dichloro podant **5** was purified by column chromatography on silica gel. Next, the exchange of chlorine atoms to iodine was performed for further activation in the subsequent macrocyclization. Diiodo podant **6** was obtained with 89% yield. Mannose-based compound **6** was the last intermediate in the synthesis of macrocycles **7a-d**; diiodo derivative **6** was used to double *N*-alkylate primary amines in a dilute solution of dry acetonitrile (reflux, 48–55 h). After work-up, the crude crown ethers **7a-d** were subjected to column chromatography on Al_2O_3, which provided the pure macrocycles in 41–83% yield (Fig. 3).

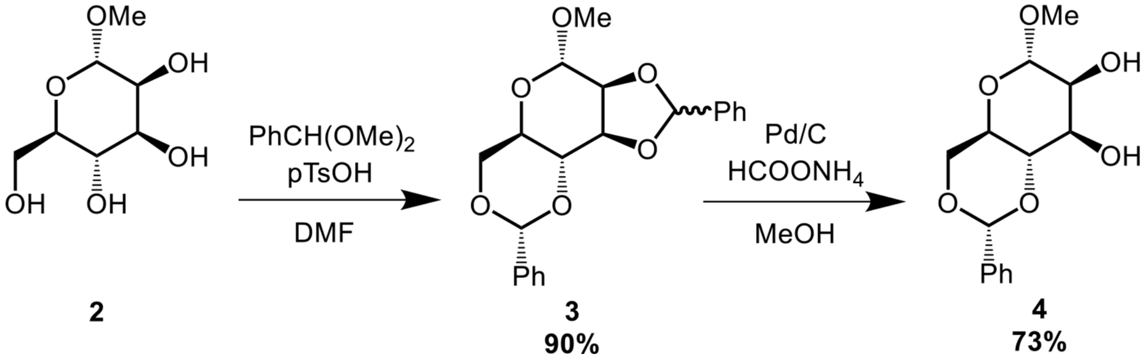

Fig. 2 Synthesis of methyl-4,6-*O*-benzylidene-α-D-mannopyranoside (**4**)

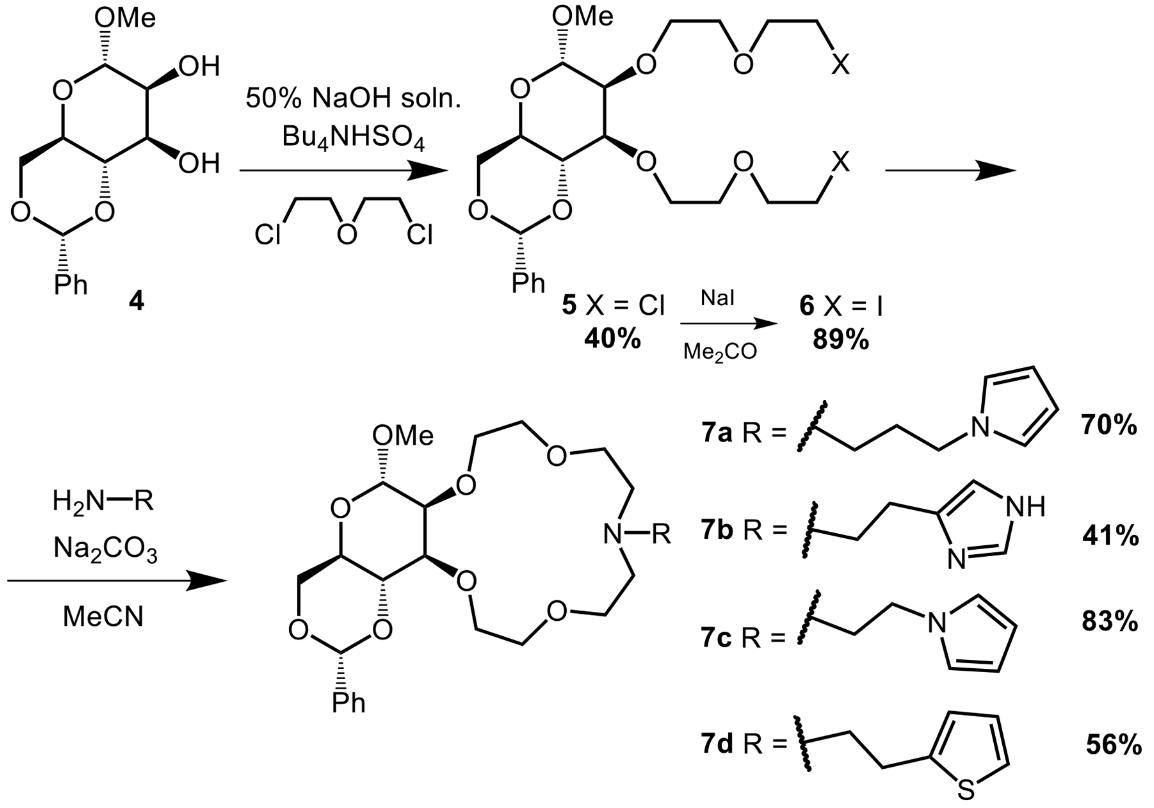

Fig. 3 Synthesis of methyl-α-D-mannopyranoside-based crown ethers (**7a-d**)

Two primary amines, *3-(1H-pyrrol-1-yl)-1-propanamine* and *2-(1H-pyrrol-1-yl)-1-ethanamine* were prepared according to a literature method [19]. Purification of the two amines was carried out differently than in the literature method, as these two compounds could easily be purified by vacuum distillation at 9 Hgmm. Histamine dihydrochloride and 2-thiopheneethylamine were purchased.

Side chains containing a five-membered, heteroaromatic ring have not yet been used in carbohydrate-based macrocycles. The pyrrole, imidazole and thiophene units were chosen because they can be used to examine whether the heteroatom has an effect on the enantioselectivity, or whether the electron system of the heteroaromatic ring is more dominant. In addition, crown ethers **7a** and **7c** can be used to investigate whether the distance between the nitrogen and the heterocycle influences the catalytic activity.

Enantioselective reactions

Crown ethers **1a-e** and **7a-d** were utilized as catalysts in four different solid-liquid biphasic cyclopropanation reactions, in which different carbohydrate-based macrocycles were previously investigated by our research group, however, mannose-based catalysts mentioned herein have not been applied yet. In terms of mechanism, all the examined reactions are so-called Michael-initiated ring closure (MIRC) reactions, since a conjugate addition occurs in the first step. In all cases, after complete conversion of the unsaturated compound, the products were isolated by preparative TLC after the appropriate work-up. The enantiomeric excess values were determined by chiral HPLC.

Previously, the amount of crown catalyst used in a solid-liquid phase cyclopropanation was investigated [20]. It was observed that the amount of crown ether can be reduced to 2.5% without loss of enantioselectivity, however, the reaction time was significantly prolonged. The use of only 1% macrocycle resulted in lower enantioselectivity. This investigation was performed with a glucose-based crown compound, however, due to structural similarity, it can be assumed that mannose-based lariat ethers exhibit similar behavior. Considering the above, and based on previous experience, 10 mol% catalyst was used in all cases.

The first reaction to be discussed is the reaction between 2-benzylidenemalononitrile (**8**) and diethyl bromomalonate (**9**) (Fig. 4). Sodium carbonate was used as a base, while the reaction proceeded in dichloromethane at room temperature.

In the presence of mannose-based macrocycles, the yield of product **10** was above 80% in every case, while the longest reaction time was measured to be 72 h (Table 1, *entry 1*). Cyclopropane derivative **10** was obtained with excellent yields (76–99%) in every case, while a greater difference

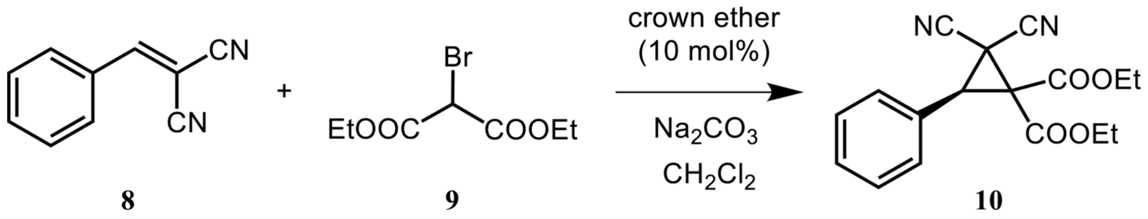

Fig. 4 Cyclopropanation of 2-benzylidenemalononitrile (**8**)

Table 1 Effect of mannose-based macrocycles **1a-e** and **7a-d** (applied in 10 mol%) in the MIRC reaction of **8**

Entry	Catalyst	Side chain properties		Time, h	Yield, %	ee, %
		Linker atoms	Functional group			
1	**1a**	0	NH	72	89	29
2	**1b**	2	OH	22	76	9
3	**1c**	2	OMe	22	79	14
4	**1d**	3	OH	22	83	21
5	**1e**	3	OMe	22	80	26
6	**7a**	3	pyrrole	72	95	25
7	**7b**	2	imidazole	45	93	6
8	**7c**	2	pyrrole	24	99	11
9	**7d**	2	thiophene	24	96	11

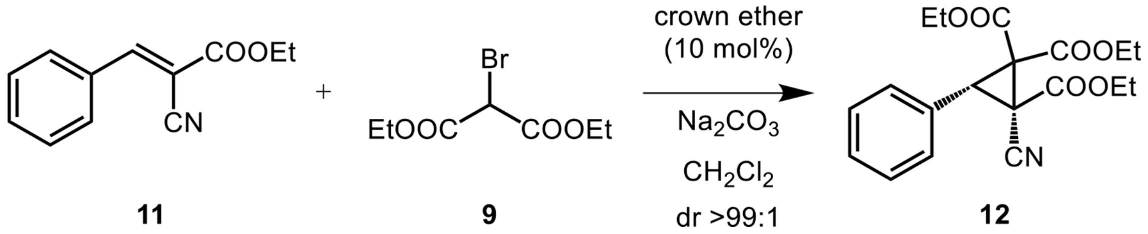

Fig. 5 Cyclopropanation of (*E*)-benzylidenecyanoacetic acid ethyl ester (**11**)

was observed in the enantiomeric excess values. The lowest ee values (9% and 6%, Table 1, *entries 2 and 7*) were measured in the presence of macrocycles **1b** and **7b**, bearing their corresponding functional groups at the end of an ethylene side chain.

It seems that in this reaction, higher ee values could be obtained when the side arm was containing a propyl chain −21–26% ee (Table 1, *entries 2 and 7*) - or when there was no side arm present in the catalyst at all. Catalyst **1a**, possessing an unfunctionalized monoaza-15-crown-5 structure generated the highest ee in this reaction −29% (Table 1, *entry 1*).

Macrocycle **7a** with a (pyrrol-1-yl)-propyl side chain generated very similar enantiomeric excess to crown **1a** (25% ee, Table 1, *entry 6*). As can be seen from Table 1, the mannose-based crown ethers were barely effective in this reaction in terms of enantioselectivity, however, as phase-transfer catalysts they performed far better (high yields were obtained).

The next cyclopropanation was performed using an analogue of dinitrile **8** as the substrate (Fig. 5). In compound **11** one of the nitrile groups has been substituted for an ester group. One might assume that this exchange in functional groups is inconsequential, it was found previously however, that it gives the compound vastly different properties in terms of reactivity. We have demonstrated the effect of a multitude of different crown ethers in the cyclopropanation of ethyl benzylidenecyanoacetate (**11**) in a previous publication [20]. In our experiments, the formation of only one pair of enantiomers was observed.

In the case of substrate **11**, the cyclopropanations required 48–168 h to reach full conversion in the presence of catalysts derived from mannose - on average, reaction times were elongated compared to the previous reaction. Surprisingly, macrocycle **1a** was just as effective in this reaction, as in the previous one (Table 2, *entry 1*), however the highest ee value this time was generated by crown ether **1d** −43% - with a yield of 82% (Table 2, *entry 4*). It seems that in this reaction, the three carbon atoms distance in the side chain between the nitrogen and the functional group was better to achieve enantioselectivity, just as in the previous cyclopropanation. In the presence of the novel mannose-based catalysts **7a-d** bearing a heterocyclic side arm, superior yields were measured (89–99%), while in the case

Table 2 Effect of mannose-based macrocycles **1a-e** and **7a-d** (applied in 10 mol%) in the MIRC reaction of **11**

Entry	Catalyst	Side chain properties		Time, h	Yield, %	ee, %
		Linker atoms	Functional group			
1	**1a**	0	NH	168	74	29
2	**1b**	2	OH	168	79	19
3	**1c**	2	OMe	168	79	22
4	**1d**	3	OH	168	82	43
5	**1e**	3	OMe	168	73	20
6	**7a**	3	pyrrole	48	96	32
7	**7b**	2	imidazole	120	99	9
8	**7c**	2	pyrrole	120	97	33
9	**7d**	2	thiophene	48	89	14

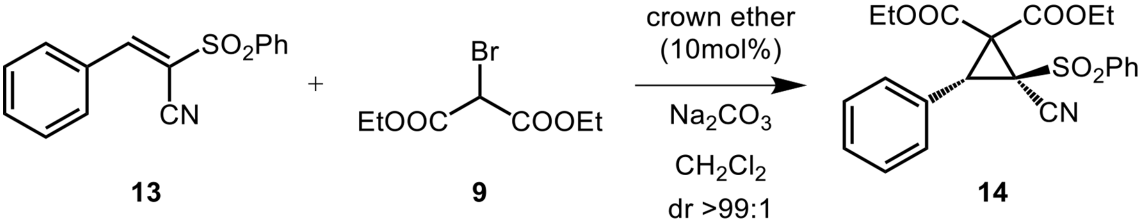

Fig. 6 Cyclopropanation of (*E*)-3-phenyl-2-(phenylsulfonyl)acrylonitrile (**13**)

Table 3 Effect of mannose-based macrocycles **1a-e** and **7a-d** (applied in 10 mol%) in the MIRC reaction of **13**

Entry	Catalyst	Side chain properties		Time, h	Yield, %	ee, %
		Linker atoms	Functional group			
1	**1a**	0	NH	96	82	3
2	**1b**	2	OH	72	85	3
3	**1c**	2	OMe	192	86	9
4	**1d**	3	OH	51	81	3
5	**1e**	3	OMe	30	85	1
6	**7a**	3	pyrrole	92	99	10
7	**7b**	2	imidazole	84	91	1
8	**7c**	2	pyrrole	72	80	10
9	**7d**	2	thiophene	72	89	6

of lariat ether **7a**, the level of selectivity achieved was 32% ee (Table 2, *entry 6*). This is comparable to the ee value generated by macrocycle **1d** (43%), which also contains three linker atoms in the side arm. This seems to be a significant property in the stereochemical outcome of the reactions. It is worth noting that the effect of catalysts **7a** and **7c** was completely identical (32% ee and 33% ee, Table 2, *entries 6 and 8*), despite the fact that the distance of the pyrrole unit from the crown ring is different in the two compounds.

Next, (*E*)-3-phenyl-2-(phenylsulfonyl)acrylonitrile (**13**) and diethyl bromomalonate (**9**) were reacted in the presence of mannose-based crown ethers **1a-e** and **7a-d** under the same conditions as described in the previous two cases (Fig. 6). This MIRC reaction was also extensively studied in a previous publication using d-galactose and d-glucose-based crown ethers [21]. The reaction was diastereoselective in the presence of the mannose-based crown ethers as it was in the presence of other carbohydrate-based lariat ethers.

Unfortunately, in this reaction enantioselectivity was poor at best, basically all crown ethers were unable to generate asymmetric induction. Reaction times were quite variable (30–192 h), while yields were excellent with each catalyst tested (80–99%). The highest ee values in this MIRC reaction were achieved using pyrrole-containing macrocycles **7a** and **7c** (only 10% ee in both cases) (Table 3, *entries 6 and 8*). It seems that the presence of the bulky phenylsulfonyl group had a detrimental effect on the enantioselectivity, as none of the examined mannose-based catalysts were able to generate considerable enantiomeric excess. Compared to the results obtained in the previous reactions, it can be assumed that the presence of two nitrile or a nitrile and an ester group is necessary for these catalysts to be effective in this type of cyclopropanation.

Finally, the MIRC reaction of 2-benzylidene-indane-1,3-dione (**15**) was investigated, with reagents and conditions similar to previous experiments (Fig. 7). The yields, ee values and reaction times were comparable to those

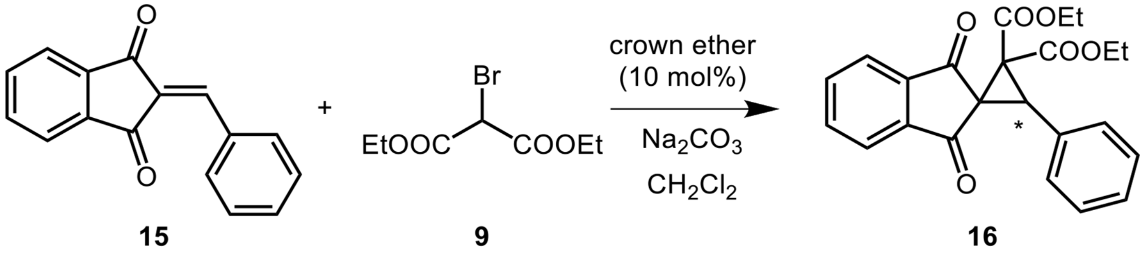

Fig. 7 Cyclopropanation of 2-benzylidene-indane-1,3-dione (**15**)

Table 4 Effect of mannose-based macrocycles **1a-e** and **7a-d** (applied in 10 mol%) in the MIRC reaction of **15**

Entry	Catalyst	Side chain properties		Time, h	Yield, %	ee, %
		Linker atoms	Functional group			
1	**1a**	0	NH	72	79	44
2	**1b**	2	OH	43	72	20
3	**1c**	2	OMe	45	64	19
4	**1d**	3	OH	21	67	43
5	**1e**	3	OMe	21	62	27
6	**7a**	3	pyrrole	68	95	37
7	**7b**	2	imidazole	72	96	20
8	**7c**	2	pyrrole	72	94	33
9	**7d**	2	thiophene	24	96	19

measured in the reaction of compound **11**. Yields were again excellent in the presence of the heterocyclic side chain-bearing crown ethers **7a-d** (94–96%) (Table 4, *entries 6–9*). Using catalysts **1a-e** a trend was observed. The highest ee value was measured in presence of crown compound **1a** (44% ee) (Table 4, *entry 1*). Enantioselectivity then decreased with crown ethers **1b** and **1c** (20% and 19% respectively) (Table 4, *entries 2–3*), showing that the length of the side chain was not ideal for higher selectivity to occur in these two cases. Then, in the case of crown ether **1d**, bearing a hydroxypropyl side chain, enantiomeric excess rose again to 43% (Table 4, *entry 4*).

This means that in this reaction the presence of an adequately positioned H-donor group is mandatory if higher enantioselectivity is to be achieved. This occurred in the case of macrocycle **1d**, where the side chain of the lariat ether was long enough, thus, the OH group was able to reach and influence the reaction center. In the case of crown ether **1a** which, despite having no side chain at all, possesses a free NH group in the macroring, which can act as a H-donor in the transition complex. Using macrocycle **1e** weaker results were observed −27% ee - as there were no H-donor groups present (Table 4, *entry 5*). Among crown ethers **7a-d**, the macrocycles containing a pyrrole unit turned out to be most selective, with enantiomeric excesses 33% and 37% (Table 4, *entries 6 and 8*).

The role of a crown ether in a solid-liquid phase cyclopropanation reaction has already been explained in one of our previous works [7]. The lariat ether forms a complex with Na^+, then the complex enters the organic phase accompanied by a carbonate ion. Then diethyl bromomalonate is deprotonated by an unsolvated carbonate anion resulting in a crown ether– nucleophile complex (Fig. 8). Since this supramolecular associate is chiral, the structure of this associate determines the enantioselectivity in the reaction.

Conclusion

In summary, four novel chiral macrocycles derived from mannose were synthesized with different heteroaromatic side chains. A total of nine mannose-based crown ethers, which differ only in their side chains, were tested as asymmetric phase-transfer catalysts in MIRC reactions. The corresponding cyclopropane derivatives were formed in mostly good yields (up to 99%), which indicates that the lariat ether examined are good phase-transfer catalysts. However, the enantioselectivity remained low, the highest enantiomeric excess was 44%.

Substrates **8**, **11** and **13** used in the test reactions differ from each other in only one functional group, despite their similarity we obtained different results in the cyclopropanation reactions. It is particularly striking that in the presence of the space-demanding phenylsulfonyl group, none of the catalysts caused significant asymmetric induction. In this case, due to the occurrence of steric hindrance, the energy difference between the complexes leading to individual enantiomers may have decreased.

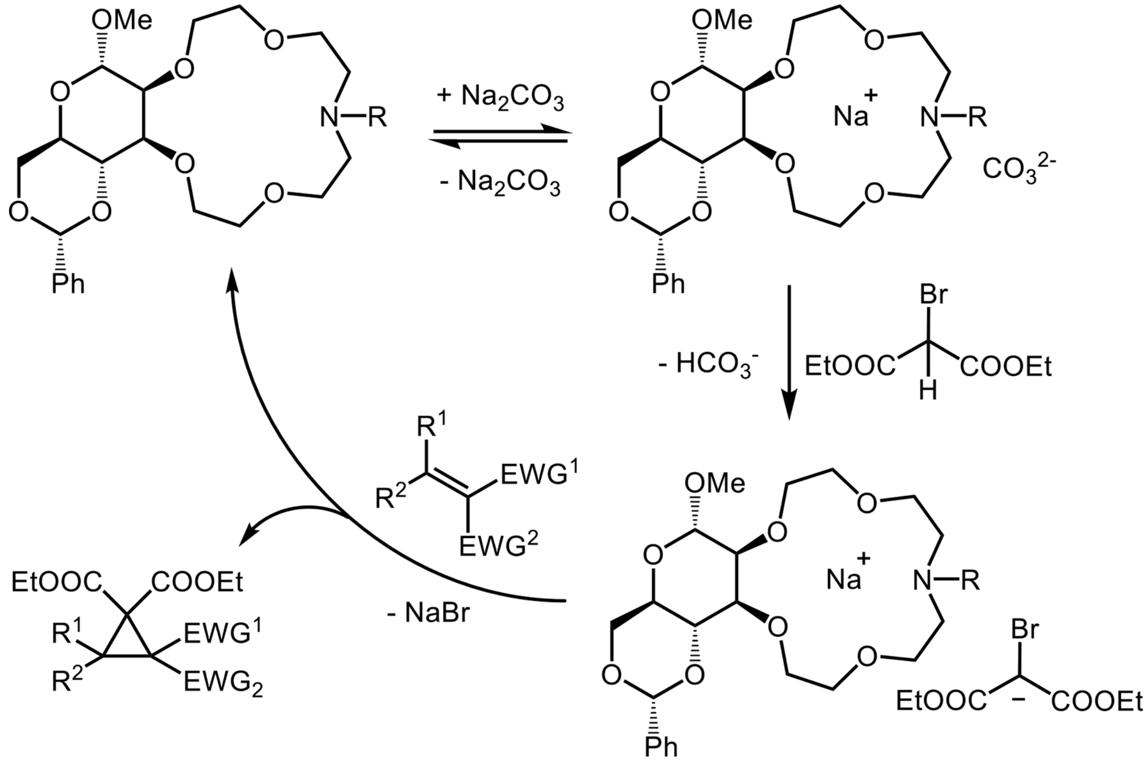

Fig. 8 The role of the crown catalyst in the solid-liquid phase transfer cyclopropanation

Regarding the side chains, the results show that a propylene bridge between the nitrogen of the ring and the functional group of the side chain is more favorable than an ethylene moiety. The imidazole, thiophene and pyrrole units, despite their similarity, had different effects on asymmetric induction. It should be noted that the thiophene and imidazole units were attached to the chain through a carbon atom (C-2), while pyrrole was attached through the nitrogen. For this reason, pyrrole moiety was mostly able to form π-π interactions, while thiophene and imidazole units could also form second-order bonds on heteroatoms. In all cases, the presence of the pyrrole ring proved to be better, which shows that the location of the heteroatoms is an additional influencing factor of the catalytic activity.

Glucose and mannose are C-2 epimers of each other. The enantiomeric excesses achieved with the crown ether **1d** were lower in all cases compared to the results previously achieved with the glucose-containing analogue. While the macroring is attached to the glucose unit in an equatorial-equatorial position, it is axial-equatorial in the case of the mannose unit. This configurational difference appears to be unfavorable for enantioselectivity.

Experimental

General

Chemicals were purchased from Merck KGaA. Analytical and preparative thin layer chromatography was performed on silica gel (60 GF_{254}, Merck) or aluminium oxide (60 F_{254} neutral (Type E)) plates, while column chromatography was carried out using 70–230 mesh silica gel and Brockman II neutral aluminium oxide. Visualization of compounds on the TLC plates was performed using 254 nm UV light, iodine vapor or 5 V/V% sulfuric acid/methanol stain. NMR spectra were obtained on a Bruker DRX-500 or Bruker-300 instrument in $CDCl_3$. Determination of the enantiomeric excess values 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 set to 254 nm. LC-MS measurements were conducted on a Shimadzu LC-40D XR UPLC-MS system equipped with a SIL-40 C XR autosampler, SPD-M40 photodiode array detector, an RF-20 A XS fluorescent detector and an LCMS-2020 DUIS Mass Spectrometer operated in alternating negative and positive modes. An Ascentis Express C18, 2 μm UHPLC column (L × I.D. 5 cm × 2.1 mm) was used at 40 °C provided by a CTO-40s column oven. Gradient elution was applied with 0.1% v/v TFA in CH_3CN. The specific rotation was measured on a Perkin-Elmer 341LC polarimeter at 22 °C. HRMS measurements were performed on a Xevo G2-XS Q-Tof mass spectrometer, with the default ESI ionization method.

Synthesis of known compounds

Methyl 2,3:4,6-di-*O*-benzylidene-α-ᴅ-mannopyranoside (**3**) see Ref [17].

Methyl 4,6-*O*-benzylidene-α-ᴅ-mannopyranoside (**4**) see Ref [18].

Methyl 2,3-bis-*O*-(2-chloroethoxyethyl)-4,6-*O*-benzylidene-α-ᴅ-mannopyranoside (**5**).

see Ref [10].

Methyl 2,3-bis-*O*- (2-iodoethoxyethyl)-4,6-*O*-benzylidene-α-ᴅ-mannopyranoside (**6**).

see Ref [10].

General procedure for the synthesis of crown ethers

Diiodo podant **6** (4 mmol) was dissolved in dry acetonitrile (55 mL) under Ar atmosphere. Then, dry sodium carbonate (2.54 g, 24 mmol) and the appropriate primary amine or amine hydrochloride (4 mmol) were added, and the mixture was heated to reflux for 48–55 h. When an amine hydrochloride was used, then 3.5 mL (20 mmol) ethyl diisopropyl amine was also added to the reaction. After the appropriate time has passed, the mixture was allowed to cool down, then it was filtered, and evaporated. The oily residue was then partitioned between dichloromethane (30 mL) and water (20 mL), and the organic phase was washed with water (2 × 20 mL). Then the aqueous phase was extracted with dichloromethane (2 × 15 mL) and the combined organic phase was dried with Na_2SO_4 and evaporated. The crude product was purified by column chromatography.

Methyl-4,6-*O*-benzylidene-2,3-dideoxy-α-d-mannopyranosido[2,3-h]-*N*-[3-(1*H*-pyrrol-1-yl)-propyl]-1,4,7,10-tetraoxa-13-azacyclopentadecane (7a)

Synthesized according to the general procedure. Amine used: 0.392 g (4 mmol) 3-(1*H*-pyrrol-1-yl)-1-propanamine. Chromatography: 60 g of Al_2O_3, eluent: CH_2Cl_2. Yield: 70% (1.21 g), $[\alpha]_D^{22} = +20.1$ ($c = 1$, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51–7.46 (m, 2 H, Ar*H*), 7.41–7.34 (m, 3 H, Ar*H*), 6.72–6.67 (m, 2 H, Pyr*H*), 6.16–6.12 (m, 2 H, Pyr*H*), 5.57 (s, 1H, ArC*H*), 4.75 (d, *J* = 1.6 Hz, 1H, H-1), 4.26 (dd, *J* = 10.0, 4.6 Hz, 1H, H-6a), 4.17–4.08 (m, 1H, C*H*), 4.07–3.50 (m, 18 H, 6 x OC*H*$_2$, PyrNC*H*$_2$, 3 x C*H*, H-6b), 3.38 (s, 3 H, OC*H*$_3$), 2.82–2.63 (m, 4 H, 2 x NC*H*$_2$), 2.53–2.41 (m, 2 H, NC*H*$_2$), 1.92 (p, *J* = 6.9 Hz, 2 H, CH$_2$C*H*$_2$CH$_2$).

^{13}C NMR (126 MHz, $CDCl_3$) δ 137.77 (Ar*C*CH), 128.80 (Ar*C*), 128.19 (Ar*C*), 126.06 (Ar*C*), 120.64 (PyrN*C*), 120.47 (PyrN*C*), 108.68 (PyrC*C*), 107.81 (PyrC*C*), 101.41 (Ar*C*H), 99.97 (*C*-1-OMe), 79.29 (*C*H), 77.94 (*C*H), 76.61 (*C*H), 71.93 (O*C*H$_2$), 71.09 (O*C*H$_2$), 70.57 (O*C*H$_2$), 70.44 (O*C*H$_2$), 70.11 (O*C*H$_2$), 69.70 (O*C*H$_2$), 68.86 (O*C*H$_2$), 63.91 (*C*H), 54.95 (N*C*H$_2$), 54.87 (O*C*H$_3$), 54.69 (N*C*H$_2$), 53.39 (N*C*H$_2$), 47.08 (N*C*H$_2$), 29.53 (CH$_2$*C*H$_2$CH$_2$).

ESI-MS: 547 (M^++H), 569 (M^++Na); HRMS calculated for $C_{29}H_{43}N_2O_8^+$ 547.3014 $[M+H]^+$; Found 547.3018.

Methyl-4,6-*O*-benzylidene-2,3-dideoxy-α-d-mannopyranosido[2,3-h]-*N*-[2-(1*H*-imidazol-4-yl)-ethyl]-1,4,7,10-tetraoxa-13-azacyclopentadecane (7b)

Synthesized according to the general procedure. Amine used: 0.736 g (4 mmol) histamine dihydrochloride. Chromatography: 69 g of Al_2O_3, eluent: $CH_2Cl_2 \rightarrow CH_2Cl_2$:MeOH 100:1. Yield: 41% (878 mg), $[\alpha]_D^{22} = +1$ ($c = 1$, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 11.28 (br s, 1H, N*H*), 7.76 (s, 1H, Im*H*), 7.58–7.53 (m, 2 H, Ar*H*), 7.40–7.29 (m, 3 H, Ar*H*), 6.77 (s, 1H, Im*H*), 5.62 (s, 1H, ArC*H*), 4.76 (s, 1H, H-1), 4.24 (dd, *J* = 9.8, 4.3 Hz, 1H, H-6), 4.10 (t, *J* = 9.4 Hz, 1H, H-5), 3.91–3.74 (m, 8 H, 3xOC*H*$_2$, H-6, C*H*), 3.72–3.42 (m, 8 H, 3xOC*H*$_2$, 2xC*H*), 3.39 (s, 3 H, OC*H*$_3$), 2.85–2.58 (m, 8 H, 3xNC*H*$_2$, NCH$_2$C*H*$_2$).

^{13}C NMR (126 MHz, $CDCl_3$) δ 137.74 (Ar*C*CH), 135.40 (Im*C*H), 131.10 (Im*C*), 128.98 (Ar*C*), 128.34 (Ar*C*), 126.44 (Ar*C*), 126.19 (Im*C*H), 101.77 (Ar*C*H), 98.82 (*C*-1-OMe), 78.42 (*C*H), 77.49 (*C*H), 76.51 (*C*H), 70.68 (O*C*H$_2$), 70.36 (O*C*H$_2$), 70.17 (O*C*H$_2$), 70.12 (O*C*H$_2$), 69.29 (O*C*H$_2$), 68.86 (O*C*H$_2$), 68.81 (O*C*H$_2$), 64.16 (*C*H), 55.56 (N*C*H$_2$), 55.13 (N*C*H$_2$), 55.12 (O*C*H$_3$), 54.93 (N*C*H$_2$), 23.11 (NCH$_2$*C*H$_2$).

ESI-MS: 534 (M^++H), 556 (M^++Na); HRMS calculated for $C_{27}H_{40}N_3O_8^+$ 534.2810 $[M+H]^+$; Found 534.2820.

Methyl-4,6-*O*-benzylidene-2,3-dideoxy-α-d-mannopyranosido[2,3-h]-*N*-[2-(1*H*-pyrrol-1-yl)-ethyl]-1,4,7,10-tetraoxa-13-azacyclopentadecane (7c)

Synthesized according to the general procedure. Amine used: 435 µL (4 mmol) 2-(1*H*-pyrrol-1-yl)-1-ethanamine. Chromatography: 71 g of Al_2O_3, eluent: CH_2Cl_2. Yield: 83% (1.77 g), $[\alpha]_D^{22} = +21.2$ ($c = 1$, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52–7.46 (m, 2 H, Ar*H*), 7.42–7.34 (m, 3 H, Ar*H*), 6.72–6.65 (m, 2 H, Pyr*H*), 6.16–6.10 (m, 2 H, Pyr*H*), 5.60 (s, 1H, ArC*H*), 4.76 (s, 1H, H-1), 4.27 (dd, *J* = 10.1, 4.7 Hz, 1H, H-6), 4.12 (t, *J* = 9.7 Hz, 1H, H-5), 4.09–3.47 (m, 18 H, 6 x OC*H*$_2$, PyrNC*H*$_2$, 3 x C*H*, H-6b), 3.40 (s, 3 H, OC*H*$_3$), 2.90 (t, *J* = 7.0 Hz, 2 H, NC*H*2), 2.88–2.72 (m, 4 H, 2xNC*H*2).

^{13}C NMR (126 MHz, CDCl$_3$) δ 137.76 (Ar*C*CH), 128.80 (ArC), 128.18 (ArC), 126.05 (ArC), 120.81 (PyrN*C*), 107.97 (PyrC*C*), 101.44 (ArCH), 99.99 (*C*-1-OMe), 79.38 (*C*H), 77.98 (*C*H), 76.70 (*C*H), 72.07 (O*C*H$_2$), 71.17 (O*C*H$_2$), 70.65 (O*C*H$_2$), 70.62 (O*C*H$_2$), 70.09 (O*C*H$_2$), 69.92 (O*C*H$_2$), 68.88 (O*C*H$_2$), 63.93 (*C*H), 58.19 (N*C*H$_2$), 55.23 (N*C*H$_2$), 55.17 (N*C*H$_2$), 54.89 (O*C*H$_3$), 48.25 (PyrN*C*H$_2$).

ESI-MS: 533 (M$^+$+H), 555 (M$^+$+Na); HRMS calculated for $C_{28}H_{41}N_2O_8^+$ 533.2857 [M + H]$^+$; Found 533.2854.

Methyl-4,6-*O*-benzylidene-2,3-dideoxy-α-d-mannopyranosido[2,3-h]-*N*-[2-(thiophen-2-yl)-ethyl]-1,4,7,10-tetraoxa-13-azacyclopentadecane (7d)

Synthesized according to the general procedure. Amine used: 470 µL (4 mmol) 2-Thiopheneethylamine. Chromatography: 75 g of Al_2O_3, eluent: CH_2Cl_2. Yield: 56% (1.23 g), $[\alpha]_D^{22} = +23.9$ (*c* = 1, CHCl$_3$).

^{1}H NMR (500 MHz, CDCl$_3$) δ 7.49–7.44 (m, 2 H, Ar*H*), 7.39–7.30 (m, 3 H, Ar*H*), 7.11 (dd, *J* = 5.2, 1.2 Hz, 1H, Ar*H*), 6.91 (dd, *J* = 5.1, 3.4 Hz, 1H, Ar*H*), 6.81 (d, *J* = 3.6 Hz, 1H, Ar*H*), 5.57 (s, 1H, ArC*H*), 4.74 (d, *J* = 1.6 Hz, 1H, *H*-1), 4.24 (dd, *J* = 10.1, 4.6 Hz, 1H, *H*-6a), 4.15–3.45 (m, 17 H, 6 x OC*H*$_2$, *H*-2, *H*-3, *H*-4, *H*-5, *H*-6b), 3.37 (s, 3 H, OC*H*$_3$), 2.96 (d, *J* = 74.7 Hz, 8 H, 3 x NC*H*$_2$, NCH$_2$C*H*$_2$).

^{13}C NMR (126 MHz, CDCl$_3$) δ 137.71 (Ar*C*), 128.83 (Ar*C*), 128.20 (Ar*C*), 126.74 (Ar*C*), 126.05 (Ar*C*), 124.81 (Ar*C*), 123.44 (Ar*C*), 101.45 (Ar*C*H), 99.83(*C*-1-OMe), 79.35 (*C*H), 78.00 (*C*H), 76.66 (*C*H), 71.96 (O*C*H$_2$), 71.15 (O*C*H$_2$), 70.72 (O*C*H$_2$), 70.12 (O*C*H$_2$), 68.86 (O*C*H$_2$), 63.90 (*C*H), 58.33 (N*C*H$_2$), 54.94 (O*C*H$_3$), 54.62 (N*C*H$_2$), 54.35 (N*C*H$_2$), 33.65 (NCH$_2$*C*H$_2$).

ESI-MS: 550 (M$^+$+H), 572 (M$^+$+Na); HRMS calculated for $C_{28}H_{40}NO_8S^+$ 550.2469 [M + H]$^+$; Found 550.2470.

Diethyl 2,2-dicyano-3-phenylcyclopropane-1,1-dicarboxylate (10)

Benzylidenemalononitrile (**8**) (0.077 g, 0.5 mmol), diethyl bromomalonate (**9**) (130 µL, 0.75 mmol) and the appropriate crown ether (10 mol%) were dissolved in 3 mL of dry DCM. Then, dry Na_2CO_3 (0.11 g, 1 mmol) was added. The reaction mixture was stirred at room temperature until TLC (hexane: EtOAc 4:1) showed no remaining starting material. After completion of the reaction, the mixture was diluted with DCM and filtered. The residue was washed with additional DCM and the filtrate was concentrated. The crude product was purified via preparative TLC using hexane–EtOAc (5:1) as the eluent to give an orange oil. The properties of the compound were identical to those reported in the literature [7].

^{1}H NMR (300 MHz, CDCl$_3$), δ 7.45–7.35 (m, 5 H, Ar*H*), 4.43 (q, *J* = 7.2 Hz, 2 H, OC*H*$_2$), 4.30–4.18 (m, 2 H, OC*H*$_2$), 3.96 (s, 1H, ArC*H*), 1.39 (t, *J* = 7.2 Hz, 3 H, CH$_2$C*H*$_3$), 1.19 (t, *J* = 7.2 Hz, 3 H, CH$_2$C*H*$_3$).

^{13}C NMR (75 MHz, CDCl$_3$), δ 163.05 (*C*OOC$_2$H$_5$), 161.06 (*C*OOC$_2$H$_5$), 129.67 (*ArC*), 129.10 (*ArC*), 128.76 (*ArC*), 127.31 (*ArC*), 111.86 (*C*N), 109.71 (*C*N), 64.50 (*C*H$_2$CH$_3$), 63.62 (*C*H$_2$CH$_3$), 46.39 (OC*C*CO), 40.08 (Ph*C*H), 16.32 (NC*C*CN), 13.97 (CH$_2$*C*H$_3$), 13.60 (CH$_2$*C*H$_3$).

Triethyl 2-cyano-3-phenylcyclopropane-1,1,2-tricarboxylate (12)

Ethyl benzylidenecyanoacetate (**11**) (0.101 g, 0.5 mmol), diethyl bromomalonate (**9**) (130 µL, 0.75 mmol), and the appropriate crown ether (10 mol%) were dissolved in dry dichloromethane (3 mL), and anhydrous Na_2CO_3 (0.11 g, 1 mmol) was added. The reaction mixture was stirred at room temperature. The reaction was monitored via TLC (hexane: EtOAc 4:1). After completion, the mixture was diluted with DCM and filtered. The residue was washed with additional DCM and the filtrate was concentrated. The crude product was purified by preparative TLC using hexane: EtOAc (5:1) as the eluent to give a pale yellow oil. The properties of the compound were identical to those reported in the literature [20].

^{1}H NMR (500 MHz, CDCl$_3$) δ 7.41–7.31 (m, 5 H, Ar*H)*, 4.42–4.21 (m, 4 H, OC*H*$_2$CH$_3$), 4.14 (qd, *J* = 7.1, 2.0 Hz, 2 H, OC*H*$_2$CH$_3$), 3.94 (s, 1H, ArC*H*), 1.39 (t, *J* = 7.1 Hz, 3 H, OCH$_2$C*H*$_3$), 1.31 (t, *J* = 7.1 Hz, 3 H, OCH$_2$C*H*$_3$), 1.10 (t, *J* = 7.1 11 Hz, 3 H, OCH$_2$C*H*$_3$).

^{13}C NMR (75 MHz, CDCl$_3$) δ 164.52 (*C*OOCH$_2$), 164.05 (*C*OOCH$_2$), 162.74 (*C*OOCH$_2$), 129.90 (Ar*C*), 128.93 (Ar*C*), 128.84 (Ar*C*), 128.77(Ar*C*), 112.94 (*C*N), 64.33 (O*C*H$_2$CH$_3$), 63.17 (O*C*H$_2$CH$_3$), 63.02 (O*C*H$_2$CH$_3$), 48.07 (OC*C*CO), 39.37 (Ar*C*H), 30.91 (NC*C*CO), 14.18 (OCH$_2$*C*H$_3$), 14.08 (OCH$_2$*C*H$_3$), 13.77 (OCH$_2$*C*H$_3$).

Diethyl 2-cyano-3-phenyl-2-(phenylsulfonyl) cyclopropane-1,1-dicarboxylate (14)

3-Phenyl-2-(phenylsulfonyl) acrylonitrile (**13**) (0.134 g, 0.5 mmol) was dissolved in dry dichloromethane (3 mL), and to this solution, 130 µL (0.75 mmol) of diethyl bromomalonate (**9**) along with the appropriate crown ether (10 mol%) were added. To start the reaction, 0.11 g (1 mmol) of sodium carbonate was added, and the mixture was stirred at room temperature. The progress of the reaction was monitored via TLC (hexane: EtOAc 4:1). After completion, the mixture was diluted with dichloromethane, filtered and concentrated. The crude product was purified via preparative TLC using hexane: EtOAc 5:1 as the eluent to obtain a pale yellow oil. The properties of the compound were identical to those reported in the literature [21].

^{1}H NMR (500 MHz, CDCl$_3$) δ 8.13 (dd, *J* = 8.5, 1.3 Hz, 2 H, Ar*H*), 7.81 (tt, *J* = 7.5, 1.2 Hz, 1H, Ar*H*), 7.68 (t, *J* = 7.9 Hz, 2 H, Ar*H*), 7.31 (dd, *J* = 4.9, 2.0 Hz, 3 H, Ar*H*), 7.17–7.11 (m, 2 H, Ar*H*), 4.50–4.37 (m, 2 H, OC*H*$_2$), 4.16 (s, 1H, PhC*H*), 4.13 (qd, *J* = 7.1, 2.6 Hz, 2 H, OC*H*$_2$), 1.42 (t, *J* = 7.1 Hz, 3 H, C*H*$_3$), 1.10 (t, *J* = 7.1 Hz, 3 H, C*H*$_3$).

^{13}C NMR (75 MHz, CDCl$_3$) δ 162.94 (Ar*C*O), 162.06 (Ar*C*O), 136.12 (Ar*C*), 135.59 (Ar*C*), 130.13 (Ar*C*), 129.59 (Ar*C*), 128.98 (Ar*C*), 128.94 (Ar*C*), 128.65 (Ar*C*), 128.27 (Ar*C*), 111.52 (*C*N), 63.55 (O*C*H$_2$CH$_3$), 63.46 (O*C*H$_2$CH$_3$), 48.24 (NC*C*S), 47.58 (OC*C*CO), 36.95 (Ph*C*H), 13.82 (OCH$_2$*C*H$_3$), 13.60 (OCH$_2$*C*H$_3$).

Diethyl 1′,3′-dioxo-3-phenyl-1′,3′-dihydrospiro[cyclopropane-1,2′-indene]-2,2-dicarboxylate (16)

Benzylidene-1,3-indanedione (**15**) (0.117 g, 0.5 mmol), diethyl bromomalonate (**9**) (130 µL, 0.75 mmol), and the appropriate crown ether (10 mol%) were dissolved in dry DCM (3 mL), and anhydrous Na$_2$CO$_3$ (0.11 g, 1 mmol) was added. The reaction mixture was stirred at room temperature and it was monitored via TLC (hexane: EtOAc 4:1). After completion of the reaction, the mixture was diluted with DCM, filtered, and the filtrate was concentrated. The crude product was purified by preparative TLC using hexane: EtOAc mixture (5:1) as the eluent, resulting in a yellow oil. The properties of the compound were identical to those reported in the literature [7].

^{1}H NMR (500 MHz, CDCl$_3$) δ 8.04–7.93 (m, 2 H, Ar*H*), 7.88–7.81 (m, 2 H, Ar*H*), 7.35–7.25 (m, 5 H, Ar*H*), 4.40–4.25 (m, 2 H, OC*H*$_2$), 4.25–4.15 (m, 2 H, OC*H*$_2$), 4.16 (s, 1H, PhC*H*), 1.31 (t, *J* = 7.2 Hz, 3 H, C*H*$_3$), 1.18 (t, *J* = 7.2 Hz, 3 H, C*H*$_3$).

^{13}C NMR (75 MHz, CDCl$_3$), δ 194.69 (Ar*C*O), 191.41 (Ar*C*O), 164.37 (*C*OOC$_2$H$_5$), 162.53 (*C*OOC$_2$H$_5$), 143.10 (Ar*C*), 141.24 (Ar*C*), 135.58 (Ar*C*), 135.25 (Ar*C*), 130.17 (Ar*C*), 127.86 (Ar*C*), 123.18 (Ar*C*), 62.89 (*C*H$_2$CH$_3$), 62.39 (*C*H$_2$CH$_3$), 51.74 (ArOC*C*COAr), 45.23(OOC*C*COO), 42.35 (Ph*C*H), 13.98 (CH$_2$*C*H$_3$), 13.71 (CH$_2$*C*H$_3$).

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Data availability No datasets were generated or analysed during the current study.

Declarations

Competing interests The authors declare no competing interests.

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