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Asymmetric cyclopropanation reactions catalyzed by carbohydrate-based crown ethers

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ABSTRACT

Optically active cyclopropane derivatives were prepared by a novel, simple and green approach in high enantioselectivities using monosaccharide-based chiral crown ethers as phase transfer catalysts. The crown ethers having D-glucopyranoside, D-mannopyranoside and D-altropyranoside units proved to be efficient catalyst in a few asymmetric phase transfer cyclopropanation reactions. The Michael-initiated ring closure (MIRC) reactions of diethyl bromomalonate with chalcones took place with complete diastereoselectivity and up to 99% ee. Using benzylidenemalononitrile, 2-arylidenemalononitriles, 2-benzylidene-1,3-indandione, substituted 2-benzylidene-1,3-indandiones, 2-arylidene-1,3-indandiones and 2-benzylidene-1,3-diphenyl-1,3-propanediones enantioselectivities up to 92%, 99%, 54% 93%, 89% and 72%, respectively, were achieved, in the presence of chiral lariat ethers derived from different monosaccharides. The absolute configuration of a cyclopropane diester product was determined by a combined CD spectroscopic and theoretical study.

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1. Introduction

The cyclopropane ring is a scaffold in many natural products and in numerous biologically active compounds.[1] This saturated three-membered ring can be found in terpenes, pheromones, fatty acid metabolites and non-proteinogenic amino acids[2] possessing antiviral, antibacterial and antitumor activity.[3] Notably, pyrethroids, one of the most widespread and highly potent classes of insecticides, contain the cyclopropane unit as the pharmacophor.[4]

As a result of intensive research work, cyclopropane derivatives have been successfully utilized in many reactions with high atom-efficiency and stereoselectivity to construct a number of useful compounds.[5] The synthesis of such type building blocks has received much interest among organic chemists, and numerous methods have been reported.[6]

The Michael-initiated ring closure (MIRC) strategy is one of the most convenient ways, as it requires cheap and readily available reagents along with mild reaction conditions. In this case, conjugate addition to an electron poor alkene affords an enolate that undergoes an intramolecular ring closure. The final cyclopropane derivatives may be obtained directly in a domino process.[7] The stereoselective implement of the MIRC reaction has been intensively investigated, and enantioselective procedures using different catalysts have been developed.[5–8]

The asymmetric phase transfer catalysis is popular in academic and industrial setup as it uses low cost and safe reagents, and is easy to scale up. The use of chiral phase transfer catalysts to achieve stereoselective cyclopropanations has so far been limited to a few examples only.[9] Earlier, Waser and Herchl investigated the reaction of bromomalonates with *trans* chalcones to furnish cyclopropane-1,1-dicarboxylates in the presence of cinchona alkaloid ammonium salt catalysts.[10] These compounds known as a type of the activated donor-acceptor cyclopropanes are useful building blocks in organic syntheses.[11]

Crown ethers with carbohydrate moieties form a special group of optically active macrocycles which can be used as phase transfer

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catalyst. Building these carbohydrates scaffold into the macrocycles is advantageous for several reasons. The starting carbohydrates occur in nature, they are inexpensive, easily available as a commercial product, non-toxic, used also by the food industry and pharmaceutical industry. Crown ethers derived from monosaccharides probably are biodegradable.

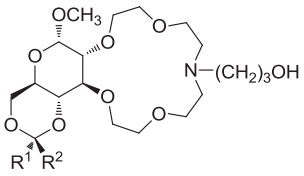
Earlier, we successfully used carbohydrate-based chiral crown ethers (lariat ethers) as phase transfer catalysts in asymmetric Michael additions,[12] and in a few cyclopropanation reactions.[13] The structure-activity relationship study of the crown ethers revealed that the molecules with a monoaza-15-crown-5 moiety are optimal as enantioselective catalysts, when the N atom of the ring bears a hydroxypropyl or a methoxypropyl side arm. (These species are also called „lasso" or lariat ethers). Beside this, the asymmetric induction generated by the catalysts strongly depends on the nature of carbohydrate annulated to the crown ring.

Herein, we report asymmetric cyclopropanation reactions catalyzed by monoaza-15-crown-5 type lariat ethers built up from different sugars. The protected α-D-hexopyranoside components of the macrocycles were derived from D-glucose (**1**–**3**), D-mannose (**4**) and D-altrose (**5**). The glucopyranoside moiety comprised 4,6-*O*-benzylidene (as in **1**), 4,6-*O*-(1-naphthyl)methylene (as in **2**) and 4,6-*O*-isopropylidene (as in **3**) protecting groups. The side arm of the macrocycles was in all cases a hydroxypropyl substituent (Fig. 1). These macrocycles were synthesized in our laboratory previously.[14]

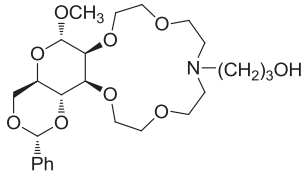
2. Results and discussion

In all of our experiments, the reaction of the different Michael acceptors (1.0 eq) with diethyl bromomalonate (**7**) (1.5 eq) resulted in chiral cyclopropane derivatives using a 4:1 mixture of ether-THF as the solvent and dry Na_2CO_3 (2.0 eq) as the base employing 15 mol% of the sugar-based crown ether catalyst at room temperature (previously the optimization of the conditions was performed).[12a] The corresponding cyclopropanes were isolated by preparative TLC, and the enantiomeric purity was determined by chiral HPLC.

First, we wished to study the reaction of diethyl bromomalonate with *trans* chalcones in the presence of glucose-based crown ether catalyst **1**. The asymmetric cyclopropanation of chalcones with malonates has been less studied and therefore it seemed to be interesting to explore its scope. Interestingly, catalyst **1** gave the



1 R^1 = Ph, R^2 = H
2 R^1 = 1-naphthyl, R^2 = H
3 $R^1 = R^2 = CH_3$



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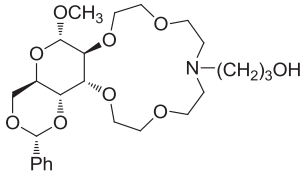

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Fig. 1. Monosaccharide-based lariat ethers used as asymmetric phase transfer catalysts.

trans isomer of the corresponding cyclopropane derivatives exclusively in all experiments.

It can be seen from Table 1 that the reaction of unsubstituted chalcone (**6a**) with bromomalonate **7** resulted in the *trans*-cyclopropane diester **8a** in a low yield, and in enantioselectivity of 88% (Table 1, entry 1). Next, the effect of the substituents of the chalcone on the yield, and on the enantioselectivity was examined (Table 1, entries 2–4 and 7–9).

First, the effect of the *para*-substituents on the phenyl group (α side) of chalcone (**6b-d**) was investigated (Table 1, entries 1–4). The substituents had a great impact on the enantioselectivity. The chloro-, nitro- and methyl-substituted products (**8b-d**) were obtained in ee values of 73%, 99% and 47%, respectively (Table 1, entries 2–4). The cyclopropanation of the chalcone with heteroaromatic substituents (**6e** and **6f**) gave the products (**8e** and **8f**) in medium ee values (55% and 44%) comparable with that obtained for the 4-Me-phenyl model (**6d** → **8d**, 47%) (Table 1, entries 5 and 6 versus entry 4). The reaction of bromomalonate with 4-nitro-chalcone (**6c**) was repeated in a 5 g scale, after column chromatography the product **8c** was obtained in 75% yield and with 98% ee.

Then, the effect of the substituents in the other aromatic ring (β side) of chalcone **(6g-i)** was evaluated (Table 1, entries 7–9). It can be seen from Table 1 that depending on the substituents, the cyclopropane diesters (**8g-i**) were formed in low to moderate yields, and in variable enantioselectivities of 42–55%. Independently of the electronic properties, the *para* substituents decreased the extent of asymmetric induction as compared to the unsubstituted case: the 4-nitro, 4-chloro and 4-methyl derivatives (**8g, 8h** and **8i**) were formed in ee values of 42%, 55% and 48%, respectively, while the unsubstituted product **8a** was obtained in an ee of 88% (Table 1, entries 7–9). The lower yields are probably the consequence of the dimerization side reaction of the bromomalonate during the long reaction time.[10] To our surprise, the cyclopropane derivative with 2-thienyl group (**8j**) was isolated in an ee of 94% (Table 1, entry 10). The experiment with the 2-furyl chalcone was unsuccessful.

It can be concluded that the properties of the substituents in the phenyl ring on the α side of chalcone influence strongly the enantioselectivity (46–99% ee), while the substituents on the β side caused only a little change in the enantioselectivity (42–55% ee).

As a new model reaction, the asymmetric cyclopropanation of benzylidenemalononitriles (**9a-t**) with diethyl bromomalonate (**7**) has also been developed in this study, in which the sugar-based lariat ethers **1**–**5** added as phase transfer catalysts generated the asymmetric induction. The optically active cyclopropane derivatives (**10a-t**) were prepared under similar conditions shown above. Table 2 shows the results of the reaction of benzylidenemalononitrile (**9a**) with diethyl bromomalonate (**7**) using different chiral macrocyclic catalysts (**1**–**5**).

It can be seen that in the case of glucose-based crown ethers (**1**–**3**), the change in the nature of the 4,6-*O*-protecting group (benzylidene, 1-naphthylidene, isopropylidene) did not have a significant impact on the asymmetric induction. The use of catalysts **1**–**3** afforded product **10a** in ee values of 32%, 30% and 29%, respectively (Table 3, entries 1–3). Applying mannose-based crown **4** and altrose-based species **5** as the catalyst, **10a** cyclopropane derivative was formed with lower optical purities of 21% and 12%, respectively (Table 2, entries 4 and 5). If the effects of the members (**1**, **4**, **5**) of the catalyst family are compared, one can see the important role of the annulated sugar moieties in the asymmetric induction. Depending on the configuration of the sugar moiety, the ee values fell in the range of 12–32% ee. For example the structure of the α-D-glucopyranoside-based **1** and the analogous α-D-altropyranoside-based **5** crown ethers are very similar, the only

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