Received: 21 October 2016 | Revised: 5 December 2016 | Accepted: 15 December 2016

DOI: 10.1002/chir.22678

REGULAR ARTICLE

WILEY

Synthesis of L-threitol-based crown ethers and their application as enantioselective phase transfer catalyst in Michael additions

Zsolt Rapi | Tamás Nemcsok | Ádám Pálvölgyi | György Keglevich | Alajos Grün | Péter Bakó

Department of Organic Chemistry and Technology, Budapest University of Technology and Economics, Budapest, Hungary

Correspondence
Péter Bakó, Department of Organic Chemistry and Technology, Budapest University of Technology and Economics, 1111 Budapest, Műegyetem rkp. 3, Hungary.
Email: pbako@mail.bme.hu

Funding Information
New Széchenyi Development Plan, Grant/Award Number: TÁMOP-4.2.1/B-09/1/KMR-2010-0002; Országos Tudományos Kutatási Alapprogramok, Grant/Award Number: PD 112166

Abstract

A few new L-threitol-based lariat ethers incorporating a monoaza-15-crown-5 unit were synthesized starting from diethyl L-tartrate. These macrocycles were used as phase transfer catalysts in asymmetric Michael addition reactions under mild conditions to afford the adducts in a few cases in good to excellent enantioselectivities. The addition of 2-nitropropane to *trans*-chalcone, and the reaction of diethyl acetamidomalonate with β-nitrostyrene resulted in the chiral Michael adducts in good enantioselectivities (90% and 95%, respectively). The substituents of chalcone had a significant impact on the yield and enantioselectivity in the reaction of diethyl acetoxymalonate. The highest enantiomeric excess (*ee*) values (99% *ee*) were measured in the case of 4-chloro- and 4-methoxychalcone. The phase transfer catalyzed cyclopropanation reaction of chalcone and benzylidene-malononitriles using diethyl bromomalonate as the nucleophile (MIRC reaction) was also developed. The corresponding chiral cyclopropane diesters were obtained in moderate to good (up to 99%) enantioselectivities in the presence of the threitol-based crown ethers.

KEYWORDS

asymmetric Michael reactions, cyclopropanation, enantioselectivity, phase transfer catalysis, sugar-based crown ethers

1 | INTRODUCTION

The development of new methodologies for efficient asymmetric Michael additions is of tremendous importance due to the increasing demand for optically active compounds. It is particularly important to develop new and efficient catalysts for the asymmetric reactions, and this task constitutes an attractive yet challenging area in current organic chemistry.[1-10] One of the catalytic methods is asymmetric phase transfer catalysis utilizing structurally well-defined chiral catalysts. This topic became of great scientific interest, and recent efforts have resulted in notable synthetic achievements. A variety of C-C bond-formation reactions were elaborated under mild phase transfer catalytic conditions. Chiral phase transfer catalysis has become an attractive area in the "green" chemical discipline, and many types of chiral catalysts have been developed and applied over the past few decades.[11-13]

Cram and Sogah published first the asymmetric phase transfer technique, in which the enantioselectivity was generated by a chiral crown ether catalyst.[14] Crown ethers with carbohydrate moieties form a special group of the chiral phase transfer catalysts. Over the past three decades, a lot of macrocycles containing one or more monosaccharide units (D-glucose, D-galactose, D-mannose, D- or L-xylose, etc.) were synthesized.[15-17] A few of them proved to be efficient phase transfer catalysts in certain asymmetric reactions.[18-25] Tartaric acid is also a useful source for chirality in the

synthesis of crown compounds. It has several advantages, being an inexpensive and easily available natural compound; moreover, the L-threitol can be derived from it in an enantiomerically pure form.[26,27]

Stoddart performed pioneering work in preparing and investigating macrocycles built up from sugar alcohols such as L-iditol, L-threitol, and D-mannitol.[15-17,26,27] At that time, they had not yet studied the catalytic effects of these compounds in phase transfer reactions. Later on, a few articles were published on the synthesis of chiral crown ethers derived from diethyl L-tartrate,[28-37] but from among the macrocycles prepared, only a few were investigated as chiral phase transfer catalysts, which were not too efficient.[38] The attachment of a side arm (linear or branched heteroatom-containing podand arms) with potential cation coordination sites to the rings leads to complexing agents, called "lasso" or lariat ethers that have unique binding properties towards a variety of guest cations.

Previously, chiral monoaza-15-crown-5 type lariat ethers incorporating an α-D-glucopyranoside unit were synthesized in our laboratory. The new lariat ethers showed catalytic effects in a few asymmetric reactions.[18-25,39,40] In the structure–activity relationships study of the crown ethers it was found 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. In order to benefit from the preferential catalytic property, this structural motif was kept in the synthesis of the new L-threitol-based macrocycles.

Herein we report the synthesis of a new monoaza-15-crown-5 type macrocycle family annelated to L-threitol (**6–8**), and the results of the catalytic activity of the new species in a few Michael addition reactions. The nucleophilic addition of malonates to electron-deficient alkenes, such as α,β-unsaturated carbonyl compounds is an important class of asymmetric C-C bond forming Michael addition reactions.[1-10] The products of the Michael reactions tested by us may be useful intermediates for a variety of biologically active materials. There are new model reactions among the asymmetric Michael additions investigated.

2 | MATERIALS AND METHODS

2.1 | General

Melting points were determined using a Büchi 510 apparatus and are uncorrected. The specific rotation was measured on a Perkin-Elmer (Boston, MA) 241 polarimeter at 22 °C. NMR 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 using Q-TOF Premier mass spectrometer (Waters, Milford, MA) in positive electrospray ionization mode. Analytical and preparative thin-layer chromatography was performed on silica gel plates (60 GF-254, Merck, Darmstadt, Germany), while column chromatography was carried out using 70–230 mesh silica gel (Merck). Chemicals were purchased from Aldrich Chemical (Milwaukee, WI).

2.1.1 | 1,4-Di-*O*-methyl-2,3-*O*-isopropylidene-L-threitol (2a).[41]

A suspension of NaH (60%, 20.7 g, 517 mmol) in dry THF (100 ml) was cooled to 5 °C with an ice bath, and 2,3-*O*-isopropylidene-L-threitol (**1**) (15.0 g, 92.6 mmol) and CH_3I (31.7 ml, 510 mmol) in anhydrous THF (75 ml) was added dropwise. The mixture was stirred at room temperature (RT) for 30 min, then refluxed for 1.5 h. After cooling, the mixture was concentrated in vacuum. The residue was suspended in $CHCl_3$ and the mixture was filtered. The residue was washed three times with $CHCl_3$. The combined organic phases were dried (Na_2SO_4) and concentrated. The crude product was distilled in vacuum (15 Hgmm, 90 °C) to give the pure product.

Yield: 93% (3.77 g); $[\alpha]_D^{22} = -1$ (c = 1, $CHCl_3$);^{1}H NMR ($CDCl_3$, 500 MHz), δ (ppm): 3.98–3.96 (m, 2H, 2 x C*H*), 3.54–3.51 (m, 4H, 2 x CH_2), 3.41 (s, 6H, 2x OCH_3), 1.43 (s, 6H, 2 x CCH_3); HRMS calcd for $C_9H_{18}O_4$ 190.1205, found 190.1201; Elem. Anal. calcd for $C_9H_{18}O_4$ C 56.82, H 9.54, found C 56.80, H 9.57.

2.1.2 | 1,4-Di-*O*-butyl-2,3-*O*-isopropylidene-L-threitol (2b).

To a solution of 2,3-*O*-isopropylidene-L-threitol (**1**) (5.21 g, 32 mmol) in dry THF (110 ml) was added NaH (60%, 5.15 g, 129 mmol) in small portions under Ar. After 30 min stirring at RT, butyl bromide (13.8 ml, 129 mmol)) was added to the mixture dropwise. Then the reaction mixture was refluxed for 10 h. After cooling, the mixture was filtered and then all volatiles were evaporated in vacuum. The residue was dissolved in $CHCl_3$ (100 ml), then washed with water (3 x 50 ml). The organic layer was dried, filtered, and evaporated to give the pure product.

Yield: 86% (7.60 g); $[\alpha]_D^{22} = -13.2$ (c = 1, $CHCl_3$);^{1}H NMR ($CDCl_3$, 500 MHz), δ (ppm): 4.00–3.94 (m, 2H, 2 x C*H*), 3.59–3.54 (m, 4H, 2 x OCH_2CH), 3.52–3.44 (m, 4H, 2x OCH_2CH$_2$), 1.57 (qui, J = 7 Hz, 4H, 2 x CH_2CH$_2$CH$_3$), 1.42 (s, 6H, 2 x CCH_3), 1.37 (sex, J = 7 Hz, 4H, 2 x CH_2CH$_3$), 0.92 (t, J = 7 Hz, 6H, 2 x CH$_2$CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz), δ (ppm): 109.22, 78.67, 71.64, 70.81, 31.84, 26.43, 19.29, 14.05; HRMS calcd for $C_{15}H_{30}O_4$ 274.2144, found 274.2150; Elem. Anal. calcd for $C_{15}H_{30}O_4$ C 65.66, H 11.02, found C 65.69, H 11.00.

2.1.3 | 1,4-Di-*O*-benzyl-2,3-*O*-isopropylidene-L-threitol (2c).[42,43]

A solution of 2,3-*O*-isopropylidene-L-threitol (**1**) (7.61 g, 47 mmol) in dry THF (35 ml) was added dropwise to a suspension of NaH (60%, 5.8 g, 0.15 mol) in dry THF (35 ml) under Ar. The mixture was stirred at RT for 9 h, then benzyl chloride (13 ml, 0.11 mol) was added dropwise. The reaction mixture was stirred at RT for 16 h, then refluxed for 3 h. After cooling, water (20 ml) was added, the organic layer was separated, and the aqueous layer was extracted with toluene. The combined organic solutions were dried then evaporated to give the pure product.

Yield: 96% (15.40 g); $[\alpha]_D^{22} = -7.6$ (c = 1, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz), δ (ppm): 7.40–7.24 (m, 10H, Ar*H*), 4.60–4.54 (m, 4H, 2 x PhCH_2), 4.05–4.02 (m, 2H, 2 x C*H*), 3.62–3.59 (m, 4H, 2 x CHCH_2), 1.43 (s, 6H, 2 x CCH_3); HRMS calcd for $C_{21}H_{26}O_4$ 342.1831, found 342.1841; Elem. Anal. calcd for $C_{21}H_{26}O_4$ C 73.66, H 7.65, found C 73.70, H 7.74.

2.2 | General procedure for preparation of di-*O*-alkyl-L-threitols

To a solution of 1,4-di-*O*-alkyl-2,3-*O*-isopropylidene-L-threitol in methanol 0.5 M *aq.* HCl was added and after the mixture was stirred at RT for 2 h, then the methanol was distilled off. To the residue 0.5 M *aq.* HCl and methanol were added, then the solvents were removed by distillation. The last step was repeated twice after adding methanol. The work-up procedure is described for each compound.

2.2.1 | 1,4-Di-*O*-methyl-L-threitol (3a).[44]

1,4-Di-*O*-methyl-2,3-*O*-isopropylidene-L-threitol (**2a**) (10.8 g, 56.7 mmol), methanol (50 ml, 15 ml, and 2 x 20 ml), 0.5 M *aq.* HCl (5 ml, then 3 ml). After the distillation, the residue was diluted with brine (20 ml), then the solution was extracted with $CHCl_3$ (6 x 15 ml). The organic phase was dried and evaporated to give the pure product.

Yield: 99% (8.50 g); $[\alpha]_D^{22} = -3.3$ (c = 0.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz), δ (ppm): 4.07 (br s, 2H, 2 x OH), 3.84–3.78 (m, 2H, 2 x C*H*), 3.54–3.49 (m, 4H, 2 x CH_2), 3.39 (s, 6H, 2x OCH_3); HRMS calcd for $C_6H_{14}O_4$ 150.0892, found 150.0895; Elem. Anal. calcd for $C_6H_{14}O_4$ C 47.99, H, 9.40, found C 48.01, H 9.37.

2.2.2 | 1,4-Di-*O*-butyl-L-threitol (3b).

1,4-Di-*O*-butyl-2,3-*O*-isopropylidene-L-threitol (**2b**) (7.60 g, 27.7 mmol), methanol (40 ml, then 10 ml, and 2 x 15 ml), 0.5 M *aq.* HCl (4 ml, then 2.5 ml). After the distillation, the residue was dissolved in $CHCl_3$ (30 ml) and the solution was washed with water (2 x 15 ml). The organic phase was dried and evaporated to give the pure product.

Yield: 94% (6.06 g); $[\alpha]_D^{22} = -3.8$ (c = 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz), δ (ppm): 3.87–3.79 (m, 2H, 2 x C*H*), 3.61–3.54 (m, 4H, 2 x OCH_2CH), 3.48 (t, J = 7.2 Hz, 4H, 2x OCH_2CH$_2$), 2.90 (br s, 2H, 2 x OH), 1.57 (qui, J = 7.2 Hz, 4H, 2 x CH_2CH$_2$CH$_3$), 1.36 (sex, J = 7.2 Hz, 4H, 2 x CH_2CH$_3$), 0.92 (t, J = 7.2 Hz, 6H, 2 x CH$_2$CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz), δ (ppm): 73.59, 70.75, 68.97, 31.83, 19.37, 13.92; HRMS calcd for $C_{12}H_{26}O_4$ 234.1831, found 234.1835; Elem. Anal. calcd for $C_{12}H_{26}O_4$ C 61.54 H 11.18, found C 61.55, H 11.19.

2.2.3 | 1,4-Di-*O*-benzyl-L-threitol (3c).[38]

1,4-Di-*O*-benzyl-2,3-*O*-isopropylidene-L-threitol (**2c**) (38.14 g, 0.11 mol), methanol (100 ml, then 15 ml and 2 x 50 ml), 0.5 M *aq.* HCl (10 ml, then 5 ml). After the distillation, the residue was diluted with water (20 ml), then the solution was extracted with toluene (3 x 30 ml). The organic phase was dried, evaporated, and the crude product was purified by crystallization (diethyl-ether-petrol ether 2:1).

Yield: 56% (18.7 g); $[\alpha]_D^{22} = -7.2$ (c = 1, CH_2Cl_2);^{1}H NMR ($CDCl_3$, 300 MHz), δ (ppm): 7.39–7.27 (m, 10H, Ar*H*), 4.56 (d, J = 12 Hz, 2H, PhCH_2), 4.54 (d, J = 12 Hz, 2H, PhCH_2), 3.91–3.85 (m, 2H, 2 x C*H*), 3.66–3.55 (m, 4H, 2 x CHCH_2), 2.78 (br s, 2H, 2 x OH). HRMS calcd for $C_{18}H_{22}O_4$ 302.1518, found 302.1522; Elem. Anal. calcd for $C_{181}H_{22}O_4$ C 71.50, H 7.33, found C 71.51; H 7.35.

2.3 | General procedure for preparation of bischloro compounds

A solution of 1,4-di-*O*-alkyl-L-threitol and tetrabutylammonium hydrogensulphate in bis(2-chloroethyl) ether was vigorously stirred with 50% *aq*. NaOH solution at RT for 10 h. Then the mixture was poured into a mixture of CH_2Cl_2 and water 1:1 (three times the volume of the reaction mixture) and the phases were separated. The water layer was extracted with CH_2Cl_2 twice, the combined organic layer was washed with water, dried, and the solvent was evaporated. The remaining bis(2-chloroethyl)ether was removed by vacuum distillation. The crude product was purified by column chromatography on silica gel to give the pure product.

2.3.1 | (7*S*,8*S*)-1,14-dichloro-7,8-bis (methoxymethyl)-3,6,9,12-tetraoxatetradecane (4a).

1,4-Di-*O*-methyl-L-threitol (**3a**) (8.5 g, 62 mmol); Bu_4NHSO_4 (16.27 g, 48 mmol); bis(2-chloroethyl)ether (120 ml, 1 mol); 50% *aq*. NaOH (120 ml). Eluent: $CHCl_3$-CH_3OH 100:0 → 100:5). Yield: 37% (7.55 g);

$[\alpha]_D^{22} = -1.9$ (c = 1, $CHCl_3$);^{1}H NMR ($CDCl_3$, 300 MHz), δ (ppm): 3.83–3.39 (m, 22H, 2 x CHCH_2, 2 x CH, 6 x OCH_2, 2 x CH_2Cl), 3.36 (s, 6H, 2 x OCH_3); ^{13}C NMR ($CDCl_3$, 75 MHz), δ (ppm): 79.31, 72.18, 71.83, 70.72, 70.43, 59.20, 42.64; HRMS calcd for $C_{14}H_{28}Cl_2O_6$ 362.1263, found 362.1267; Elem. Anal. calcd for $C_{14}H_{28}Cl_2O_6$ C 46.29, H 7.77, Cl 19.52, found C 46.32, H 7.80, Cl 19.51.

2.3.2 | (7*S*,8*S*)-7,8-bis(butoxymethyl)-1,14-dichloro-3,6,9,12-tetraoxatetradecane (4b).

1,4-Di-*O*-butyl-L-threitol (**3b**) (6.0 g, 25.6 mmol); Bu_4NHSO_4 (8.69 g, 25.6 mmol); bis(2-chloroethyl)ether (60 ml, 512 mmol); 50% *aq*. NaOH (60 ml). Eluent: $CHCl_3$-CH_3OH 100:0 → 100:2); Yield: 79% (9.05 g); $[\alpha]_D^{22} = +5.3$ (c = 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz), δ (ppm): 3.85–3.79 (m, 2H, 2 x CH), 3.72–3.70 (m, 6H, 2 x OCH_2CH$_2$O, OCH_2CH), 3.67–3.59 (m, 12H, 4 x OCH_2CH$_2$O, 2 x CH$_2$Cl), 3.54–3.48 (m, 2H, OCH_2CH), 3.46–3.40 (m, 4H, 2x OCH_2CH$_2$CH$_2$), 1.55 (qui, J = 7 Hz, 4H, 2 x CH_2CH$_2$CH$_3$), 1.36 (sex, J = 7 Hz, 4H, 2 x CH_2CH$_3$), 0.92 (t, J = 7 Hz, 6H, 2 x CH$_2$CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz), δ (ppm): 79.80, 72.09, 71.87, 70.59, 70.46, 70.39, 42.68, 31.75, 19.37, 13.92; HRMS calcd for $C_{20}H_{40}Cl_2O_6$ 446.2202, found 446.2210; Elem. Anal. calcd for $C_{20}H_{40}Cl_2O_6$ C 53.69, H 9.01, Cl 15.85, found C 53.72, H 9.05, Cl 15.87.

2.3.3 | (7*S*,8*S*)-7,8-bis((benzyloxy)methyl)-1,14-dichloro-3,6,9,12-tetraoxatetradecane (4c).

1,4-Di-*O*-benzyl-L-threitol (**3c**) (18.74 g, 62 mmol); Bu_4NHSO_4 (16.27 g, 48 mmol); bis(2-chloroethyl)ether (117 ml, 1 mol); 50% *aq*. NaOH (117 ml). Eluent: $CHCl_3$-CH_3OH 100:0 → 100:5. Yield: 25% (8.10 g); $[\alpha]_D^{22} = +15.2$ (c = 1, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz), δ (ppm): 7.36–7.26 (m, 10H, ArH), 4.52 (d, J = 12 Hz, PhCH_2O, 2H), 4.50 (d, J = 12 Hz, PhCH_2O, 2H), 3.84–3.53 (m, 22H, 2 x OCH, 2 x OCH_2CH, 4 x OCH_2CH_2); 138.33, 128.30, 127.66, 127.49, 79.85, 77.18, 72.06, 71.90, 70.51, 70.43, 42.34; HRMS calcd for $C_{26}H_{36}Cl_2O_6$ 514.1889, found 514.1896; Elem. Anal. calcd for $C_{26}H_{36}Cl_2O_6$ C 60.58, H, 7.04, Cl 13.76, found C 60.60, H 7.02, Cl, 13.78.

2.4 | General procedure for preparation of bisiodo compounds

A mixture of bischloro compound **4** and NaI in dry acetone was stirred under reflux for 40 h. After cooling, the precipitate was filtered and washed with acetone. The combined acetone solutions were evaporated in vacuum. The residue was dissolved in a mixture of $CHCl_3$ and water (1:1), the layers were separated and the organic phase was washed with water and dried ($NaSO_4$). Evaporation of the solvent afforded the products.

2.4.1 | (7*S*,8*S*)-1,14-diiodo-7,8-bis(methoxymethyl)-3,6,9,12-tetraoxatetradecane (5a).

Bischloro compound **4a** (7.55 g, 20.8 mmol); NaI (12.5 g, 83.2 mmol); dry acetone (160 ml). Yield: 76% (8.55 g); $[\alpha]_D^{22} = -3.5$ (c = 1, $CHCl_3$);^{1}H NMR ($CDCl_3$, 300 MHz), δ (ppm): 3.85–3.39 (m, 18H, 2 x CHCH_2, 2 x CH, 6 x OCH_2), 3.36 (s, 6H, 2 x OCH_3), 3.26 (t, J = 6.9 Hz, 4H, 2 x CH_2I); ^{13}C NMR ($CDCl_3$, 75 MHz), δ (ppm): 79.23, 72.19, 71.87, 70.69, 70.45, 59.18, 3.05; HRMS calcd for $C_{14}H_{28}I_2O_6$ 545.9975, found 545.9980; Elem. Anal. calcd for $C_{14}H_{28}I_2O_{66}$ C 30.79, H 5.17, I 46.47, found C 30.82, H 5.21, I 46.46.

2.4.2 | (7*S*,8*S*)-7,8-bis(butoxymethyl)-1,14-diiodo-3,6,9,12-tetraoxatetradecane (5b).

Bischloro compound **4b** (7.63 g, 17.1 mmol); NaI (10.24 g, 68.4 mmol); dry acetone (150 ml). Yield: 91% (9.75 g); $[\alpha]_D^{22} = +5.9$ (c = 1, $CHCl_3$);^{1}H NMR ($CDCl_3$, 300 MHz), δ (ppm): 3.86–3.78 (m, 2H, 2 x CH), 3.78–3.71 (m, 6H, 2 x OCH_2CH$_2$O, OCH_2CH), 3.68–3.57 (m, 8H, 4 x OCH_2CH$_2$O,), 3.55–3.48 (m, 2H, OCH_2CH), 3.44 (td, J = 7.2 Hz, 1.8 Hz, 4H, 2x OCH_2CH$_2$CH$_2$), 3.26 (t, J = 7.2 Hz, 4H, 2 x CH$_2$I), 1.55 (qui, J = 7.2 Hz, 4H, 2 x CH_2CH$_2$CH$_3$), 1.36 (sex, J = 7.2 Hz, 4H, 2 x CH_2CH$_3$), 0.92 (t, J = 7.2 Hz, 6H, 2 x CH$_2$CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz), δ (ppm): 79.72, 72.05, 71.93, 70.61, 70.49, 70.43, 31.81, 19.38, 13.90, 3.01; HRMS calcd for $C_{20}H_{40}I_2O_6$ 630.0914, found 630.0917; Elem. Anal. calcd for $C_{20}H_{40}I_2O_6$ C 38.11, H 6.40, I 40.27, found C 38.10, H 6.38, I 40.27.

2.4.3 | (7*S*,8*S*)-7,8-bis((benzyloxy)methyl)-1,14-diiodo-3,6,9,12-tetraoxatetradecane (5c).

Bischloro compound **4c** (7.29 g, 14.1 mmol); NaI (8.51 g, 56.7 mmol); dry acetone (150 ml). Yield: 90% (8.90 g); $[\alpha]_D^{22} = +13.2$ (c = 1, CH_2Cl_2);^{1}H NMR ($CDCl_3$, 300 MHz), δ (ppm): 7.37–7.24 (m, 10H, ArH), 4.53–4.50 (m, 4H, 2 x PhCH_2), 3.87–3.52 (m, 18H, 2 x CHCH_2, 2 x CH, 6 x OCH_2), 3.19 (t, J = 6.9 Hz, 4H, 2 x CH_2I); ^{13}C NMR ($CDCl_3$, 75 MHz), δ (ppm): 138.27, 128.32, 127.74, 127.48, 79.81, 77.20, 72.11, 71.88, 70.55, 70.38, 3.11; HRMS calcd for $C_{26}H_{36}I_2O_6$ 698.0601, found 698.0610; Elem. Anal. calcd for $C_{26}H_{36}I_2O_6$ C 44.72, H 5.20, I 36.34, found C 44.69, H 5.17, I 36.36.

2.5 | General procedure for preparation of threitol-based crown ethers

Bisiodo compound **5** was dissolved in dry CH_3CN, anhydrous Na_2CO_3 and the appropriate amine was added under Ar. The mixture was refluxed for 50 h. Then the solvent was removed, the residue was dissolved in a mixture of $CHCl_3$ and water, the layers were separated, and the organic phase was washed with water, dried, then concentrated. The crude product was purified by column chromatography.

2.5.1 | 3-[(5*S*,6*S*)-5,6-Bis(methoxymethyl)-1,4,7,10-tetraoxa-13-azacyclopentadecan-13-yl] propan-1-ol (6a).

Bisiodo compound **5a** (8.55 g, 15.7 mmol); dry CH_3CN (115 ml), anhydrous Na_2CO_3 (11.3 g, 106.6 mmol); 3-hydroxypropylamine (1.31 ml, 17.2 mmol). Eluent: $CHCl_3$-CH_3OH 100:0 → 100:10 silica gel). Yield: 41% (1.50 g); $[\alpha]_D^{22} = -5.9$ (c = 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz), δ (ppm): 3.84–3.54 (m, 18H, 2 x CHCH_2, 2 x CH, 6 x OCH_2), 3.46–3.39 (m, 2H, CH_2OH), 3.36 (s, 6H, 2 x OCH_3), 2.79–2.61 (m, 6H, 3 x NCH_2), 1.74–1.63 (m, 2H, CH_2CH$_2$OH); ^{13}C NMR ($CDCl_3$, 75 MHz), δ (ppm): 79.62, 77.24, 72.21, 72.09, 71.44, 71.03, 70.62, 70.29, 68.95, 66.96, 63.91, 59.21, 59.15, 56.15, 54.37, 53.83, 28.33; MS m/z: $[M + H]^+$ 366.1, $[M + Na]^+$ 388.3; HRMS calcd for $C_{17}H_{35}NO_7$ 365.2414, found 365.2416; Elem. Anal. calcd for $C_{17}H_{35}NO_7$ C 55.87, H 9.65, N 3.83, found C 55.90, H 9.66, N 3.79.

2.5.2 | (5*S*,6*S*)-5,6-Bis(methoxymethyl)-13-(3-methoxypropyl)-1,4,7,10-tetraoxa-13-azacyclopentadecane (6b).

Bisiodo compound **5a** (4.50 g, 8.3 mmol); dry CH_3CN (100 ml), anhydrous Na_2CO_3 (11.3 g, 106.6 mmol); 3-methoxypropylamine (0.85 ml, 8.3 mmol). Eluent: $CHCl_3$-CH_3OH 100:1 → 100:7 (silica gel). Yield: 73% (2.29 g); $[\alpha]_D^{22} = +4.8$ (c = 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz), δ (ppm): 3.79–3.30 (m, 29H, 2 x CHCH_2, 2 x CH, 6 x OCH_2CH_2, CH_3OCH$_2$, CH$_3$OCH_2, 2 x OCH_3), 2.79–2.61 (m, 6H, 3 x NCH_2), 1.72–1.70 (m, 2H, CH_2CH$_2$OH); ^{13}C NMR ($CDCl_3$, 75 MHz), δ (ppm): 79.66, 77.23, 72.26, 72.04, 71.48, 71.06, 70.94, 70.60, 70.33, 68.99, 66.93, 59.20, 59.17, 58.30, 56.11, 54.33, 53.86, 28.32; MS m/z: $[M + H]^+$ 380.5, $[M + Na]^+$ 402.5; HRMS calcd for $C_{18}H_{37}NO_7$ 379.2570, found 379.2575; Elem. Anal. calcd for $C_{18}H_{37}NO_7$ C 56.97, H 9.83, N 3.69, found C 57.00, H 9.85, N 3.70.

2.5.3 | 3-[(5*S*,6*S*)-5,6-Bis((benzyloxy)methyl)-1,4,7,10-tetraoxa-13-azacyclopentadecan-13-yl] propan-1-ol (7a).

Bisiodo compound **5b** (5.5 g, 7.9 mmol); dry CH_3CN (115 ml), anhydrous Na_2CO_3 (5.69 g, 53.7 mmol); 3-hydroxypropylamine (0.66 ml, 8.7 mmol). Eluent: $CHCl_3$ (Al_2O_3). Yield: 62% (2.50 g); $[\alpha]_D^{22} = +4.2$ (c = 1, toluene); ^{1}H NMR ($CDCl_3$, 500 MHz), δ (ppm): 7.35–7.24 (m, 10H, ArH), 4.49 (d, J = 12.5 Hz, 2H, PhCH_2), 4.46 (d, J = 12.5 Hz, 2H, PhCH_2), 3.87–3.42 (m, 20H, 2 x CHCH_2, 2 x CH, 6 x OCH_2, CH_2OH), 2.84–2.53 (m, 6H, 3 x NCH_2), 1.71–1.59 (m, 2H, CH_2CH$_2$OH); ^{13}C NMR ($CDCl_3$, 75 MHz), δ (ppm): 138.30, 128.30, 127.70, 127.52, 79.79, 77.14, 73.63, 73.53, 73.12, 72.95, 71.66, 70.96, 70.75, 70.38, 69.54, 69.05, 64.01, 56.30, 54.36, 53.86, 28.37; MS m/z: $[M + H]^+$ 518.1, $[M + Na]^+$ 540.0; HRMS calcd for $C_{29}H_{43}NO_7$ 517.3040, found 517.3045; Elem. Anal. calcd for $C_{29}H_{43}NO_7$ C 67.29, H 8.37, N 2.71, found C 67.31, H 8.40, N 2.69.

2.5.4 | (5*S*,6*S*)-5,6-Bis((benzyloxy)methyl)-13-(3-methoxypropyl)-1,4,7,10-tetraoxa-13-azacyclopentadecane (7b).

Bisiodo compound **5b** (3.3 g, 6.4 mmol); dry CH_3CN (115 ml), anhydrous Na_2CO_3 (4.61 g, 43.5 mmol); 3-methoxypropylamine (0.65 ml, 6.4 mmol). Eluent: $CHCl_3$-CH_3OH 100:0 → 100:10 (silica gel). Yield: 71% (2.40 g), $[\alpha]_D^{22} = +32.4$ (c = 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz), δ (ppm): 7.37–7.26 (m, 10H, ArH), 4.52–4.48 (m, 4H, 2 x PhCH_2), 3.93–3.45 (m, 20H, 2 x CHCH_2, 2 x CH, 6 x OCH_2, CH_2OCH$_3$), 3.36 (s, 3H, OCH_3), 2.83 (t, J = 6.5 Hz, 2H, NCH_2), 2.69–2.62 (m, 1H, NCH_2), 2.48–2.41 (m, 1H, NCH_2), 2.26 (d, J = 14 Hz, 2H, NCH_2), 1.63–1.55 (m, 2H, CH_2CH$_2$OH); ^{13}C NMR ($CDCl_3$, 75 MHz), δ (ppm): 138.32, 128.27, 127.73, 127.50, 79.75, 77.11, 73.64, 73.56, 73.11, 72.93, 71.69, 71.05, 70.95, 70.74, 70.40, 69.50, 69.07, 58.37, 56.31, 54.32, 53.87, 28.38; MS m/z: $[M + H]^+$ 532.2, $[M + Na]^+$ 554.1; HRMS calcd for $C_{30}H_{45}NO_7$ 531.3196, found 532.0001; Elem. Anal. calcd for $C_{30}H_{45}NO_7$ C 67.77, H 8.53, N 2.63, found C 67.80, H 8.57, N 2.60.

2.5.5 | 3-[(5*S*,6*S*)-5,6-Bis(butoxymethyl)-1,4,7,10-tetraoxa-13-azacyclopentadecan-13-yl] propan-1-ol (8a).

Bisiodo compound **5c** (3.15 g, 5 mmol); dry CH_3CN (50 ml), anhydrous Na_2CO_3 (3.18 g, 30 mmol); 3-hydroxypropylamine (0.38 ml, 5 mmol). Eluent: $CHCl_3$ (Al_2O_3). Yield: 64% (2.88 g); $[\alpha]_D^{22} = +4$ (c = 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz), δ (ppm): 3.84–3.74 (m, 6H, 2

x C*H*, 2 x OCH_2CH), 3.72–3.53 (m, 12H, 6 x OCH_2CH_2O,), 3.51–3.35 (m, 6H, 2x OCH_2CH_2CH_2, CH_2OH), 2.86–2.63 (m, 6H, 3 x NCH_2), 1.71–1.62 (m, 2H, CH_2CH_2OH), 1.54 (qui, J = 7.2 Hz, 4H, 2 x CH_2CH_2CH_3), 1.36 (sex, J = 7.2 Hz, 4H, 2 x CH_2CH_3), 0.91 (t, J = 7.2 Hz, 6H, 2 x CH_2CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz), δ (ppm): 79.85, 71.30, 71.29, 70.81, 70.32, 70.29, 63.90, 54.34, 54.07, 53.35, 31.85, 31.76, 19.37, 19.34, 13.92; MS m/z: $[M + H]^+$ 450.6, $[M + Na]^+$ 472.7; HRMS calcd for $C_{23}H_{47}NO_7$ 449.3305, found 449.3309; Elem. Anal. calcd for $C_{23}H_{47}NO_7$ C 61.44, H 10.54, N 3.12, found C 61.46, H 10.55, N 3.11.

2.5.6 | (5*S*,6*S*)-5,6-Bis(butoxymethyl)-13-(3-methoxypropyl)-1,4,7,10-tetraoxa-13-azacyclopentadecane (8b).

Bisiodo compound **5c** (3.15 g, 5 mmol); dry CH_3CN (50 ml), anhydrous Na_2CO_3 (3.18 g, 30 mmol); 3-methoxypropylamine (0.51 ml, 5 mmol). Eluent: $CHCl_3$-CH_3OH 100:0 → 100:4 (Al_2O_3). Yield: 86% (1.98 g); $[\alpha]_D^{22}$ = +5 (c = 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz), δ (ppm): 3.84–3.36 (m, 24H, 2 x C*H*, 2 x OCH_2CH, 6 x OCH_2CH_2O, 2x OCH_2CH_2CH_2, CH_2OCH_3), 3.32 (s, 3H, OCH_3), 2.85–2.52 (m, 6H, 3 x NCH_2), 1.71–1.62 (m, 2H, CH_2CH_2OH), 1.54 (qui, J = 7.2 Hz, 4H, 2 x CH_2CH_2CH_3), 1.36 (sex, J = 7.2 Hz, 4H, 2 x CH_2CH_3), 0.91 (t, J = 7.2 Hz, 6H, 2 x CH_2CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz), δ (ppm): 79.81, 71.33, 71.27, 71.00, 70.82, 70.34, 70.29, 58.65, 54.31, 54.10, 53.34, 31.86, 31.75, 19.38, 19.35, 13.93; MS m/z: $[M + H]^+$ 464.4, $[M + Na]^+$ 486.5; HRMS calcd for $C_{24}H_{49}NO_7$ 463.3509, found 463.3512; Elem. Anal. calcd for $C_{24}H_{49}NO_7$ C 62.17, H 10.65, N 3.02, found C 62.16, H 10.67, N 3.01.

2.5.7 | 4-Methy-4-nitro-1,3-diphenylpentan-1-one (11).[45]

Chalcone (0.29 g, 1.4 mmol), 2-nitropropane (0.31 ml, 3.4 mmol) and crown catalyst (0.1 mmol) were dissolved in dry toluene (3 ml), and sodium *tert*-butoxide (50 mg, 0.5 mmol) was added. After completion of the reaction, the mixture was diluted with water (10 ml) and toluene (7 ml). The phases were separated. The organic layer was washed with cold 10% HCl (3 x 10 ml) and then with water (10 ml), dried (Na_2CO_3 and Na_2SO_4), and concentrated. The crude product was purified by preparative TLC using silica gel and hexane-EtOAc (10:1) as the eluent. The enantioselectivity was determined by ^{1}H NMR spectroscopy in the presence of Eu(hfc)$_3$ as a chiral shift reagent.

Yield: 68% (0.28 g); white solid; mp. 146–148 °C; $[\alpha]_D^{22}$ = +71.4 (c = 1, $CHCl_3$); enantiomeric excess (*ee*) 89%; ^{1}H NMR ($CDCl_3$, 500 MHz), δ (ppm): 7.85 (d, J = 7.5 Hz, 2H, Ar*H*), 7.53 (t, J = 7.5 Hz, 1H, Ar*H*), 7.42 (t, J = 7.5 Hz, 2H, Ar*H*), 7.32–7.18 (m, 5H, Ar*H*), 4.15 (dd, J = 10.5 Hz, 3.5 Hz, 1H, C*H*), 3.67 (dd, J = 17.5 Hz, 10.5 Hz, 1H, CH_2), 3.27 (dd, J = 17.5 Hz, 3.5 Hz, 1H, CH_2), 1.63 (s, 3H, CH_3), 1.54 (s, 3H, CH_3).

2.6 | General procedure for asymmetric model reactions using malonates[46-48]

Unsaturated compound (1 mmol), substituted malonate (1.5 mmol) and the crown ether (0.15 mmol) were dissolved in a mixture of anhydrous THF (0.6 ml) and Et_2O (2.4 ml) and dry Na_2CO_3 (0.22 g, 2 mmol) was added. The reaction mixture was stirred at RT. After completion of the reaction the organic phase was concentrated in vacuum and the residue was dissolved in CH_2Cl_2 (10 ml), washed with cold 10% *aq*. HCl (3 x 10 ml) and water (10 ml), dried (Na_2CO_3 and Na_2SO_4), and concentrated. The crude product was purified on silica gel by preparative TLC with hexane-EtOAc (5:1) as eluent. Enantioselectivities were determined by chiral high-performance liquid chromatography (HPLC) analyzing using a Chiralpak column with hexane-*i*PrOH mixture as eluent, in comparison with authentic racemic materials.

2.6.1 | Diethyl 2-acetamido-2-(2-nitro-1-phenylethyl)malonate (14).

Yield: 65% (0.24 g); white solid; mp 135–136 °C; $[\alpha]_D^{22}$ = −40.7; (c = 1, $CHCl_3$); *ee* 95%; AD-H column, hexane:*i*PrOH 85:15, major t_r = 14.6 min, minor t_r = 20.5 min; ^{1}H NMR ($CDCl_3$, 500 MHz), δ (ppm): 7.31–7.28 (m, 3H, Ar*H*), 7.22–7.18 (m, 2H, Ar*H*), 6.89 (br s, 1H, NH), 5.54–5.48 (m, 1H, CH_2NO$_2$), 4.73–4.66 (m, 2H,CH_2NO$_2$, PhC*H*), 4.34–4.23 (m, 2H, CH_2CH$_3$), 4.20–4.13 (m, 1H, CH_2CH$_3$), 4.08–4.01 (m, 1H, CH_2CH$_3$), 2.12 (s, 3H, COCH_3), 1.27 (t, J = 7 Hz, 3H, CH$_2$CH_3), 1.25 (t, J = 7 Hz, 3H, CH$_2$CH_3).

2.6.2 | Diethyl 2-acetoxy-2-(3-oxo-1,3-diphenylpropyl)malonate (16a).

Yield: 68% (0.29 g); yellow oil; $[\alpha]_D^{22}$ = 9.3; (c = 1, $CHCl_3$); *ee* 96%; AS-H column, hexane:*i*PrOH 90:10, major enantiomer t_r = 9.9 min, minor enantiomer t_r = 13.2 min; ^{1}H NMR (500 MHz, $CDCl_3$), δ (ppm): 7.90 (d, J = 7.5 Hz, 2H, Ar*H*), 7.53 (t, J = 7.5 Hz, 1H, Ar*H*), 7.43 (t, J = 7.5 Hz, 2H, Ar*H*), 7.35 (d, J = 7.5 Hz, 2H, Ar*H*), 7.26–7.20 (m, 3H, Ar*H*), 4.37 (dd, J = 8.5 Hz, 4 Hz, 1H, PhC*H*), 4.24–4.16 (m, 2H, OCH_2), 4.02–3.89 (m, 2H, OCH_2), 3.67 (dd, J = 16 Hz, 4 Hz, 1H, COCH_2), 3.59 (dd,

J = 17.5 Hz, 8.5 Hz, 1H, COCH_2), 2.23 (s, 3H, COCH_3), 1.23 (t, J = 7 Hz, 3H, CH_2CH_3), 1.06 (t, J = 7 Hz, 3H, CH_2CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz), δ (ppm): 196.75, 169.50, 165.95, 165.34, 138.35, 136.76, 133.13, 129.47, 128.56, 128.10, 128.01, 127.65, 84.38, 62.45, 62.03, 45.49, 39.87, 20.76, 13.82, 13.68; HRMS calcd for $C_{24}H_{26}O_7$ 426.1679, found 426.1680.

2.6.3 | Diethyl 2-acetoxy-2-(1-(4-chlorophenyl)-3-oxo-3-phenylpropyl)malonate (16b).

Yield: 76% (0.35 g); yellow oil; $[\alpha]_D^{22}$ = +21.1; (c = 1, $CHCl_3$); *ee* 99%; AD-H column, hexane:*i*PrOH 90:10, major enantiomer t_r = 13.7 min, minor enantiomer t_r = 11.9 min; ^{1}H NMR (500 MHz, $CDCl_3$), δ (ppm): 7.89 (d, J = 7.5 Hz, 2H, ArH), 7.55 (t, J = 7.5 Hz, 1H, ArH), 7.44 (t, J = 7.5 Hz, 2H, ArH), 7.29 (d, J = 8.5 Hz, 2H, ArH), 7.22 (d, J = 8.5 Hz, 2H, ArH), 4.34 (dd, J = 9 Hz, J = 4 Hz, 1H, ArCH), 4.24–4.17 (m, 2H, OCH_2), 4.06–3.92 (m, 2H, OCH_2), 3.73 (dd, J = 17.7 Hz, 4.5 Hz, 1H, COCH_2), 3.56 (dd, J = 18 Hz, 9 Hz, 1H, COCH_2), 2.23 (s, 3H, COCH_3), 1.24 (t, J = 7 Hz, 3H, CH_2CH_3), 1.10 (t, J = 7 Hz, 3H, CH_2CH_3); HRMS calcd for $C_{24}H_{25}ClO_7$ 460.1289, found 460.1294.

2.6.4 | Diethyl 2-acetoxy-2-(1-(3-nitrophenyl)-3-oxo-3-phenylpropyl)malonate (16c).

Yield: 79% (0.37 g); orange oil; $[\alpha]_D^{22}$ = +14.5; (c = 1, $CHCl_3$); *ee* 48%; AD-H column, hexane:*i*PrOH 90:10, major enantiomer t_r = 25.0 min, minor enantiomer t_r = 21.1 min; ^{1}H NMR (500 MHz, $CDCl_3$), δ (ppm): 8.30 (s, 1H, ArH), 8.10 (d, J = 8 Hz, 1H, ArH), 7.91 (d, J = 7 Hz, 2H, ArH), 7.71 (d, J = 7.5 Hz, 1H, ArH), 7.57 (t, J = 7.5 Hz, 1H, ArH), 7.45 (td, J = 8 Hz, 2 Hz, 3H, ArH), 4.49 (dd, J = 9.2 Hz, 4 Hz, 1H, ArCH), 4.27–4.20 (m, 2H, OCH_2), 4.08–3.95 (m, 2H, OCH_2), 3.81 (dd, J = 18.2 Hz, 4 Hz, 1H, COCH_2), 3.64 (dd, J = 18.2 Hz, 9 Hz, 1H, COCH_2), 2.25 (s, 3H, COCH_3), 1.26 (t, J = 7 Hz, 3H, CH_2CH_3), 1.12 (t, J = 7 Hz, 3H CH_2CH_3); HRMS calcd for $C_{24}H_{25}NO_9$ 471.1529, found 471.1531.

2.6.5 | Diethyl 2-acetoxy-2-(1-(4-nitrophenyl)-3-oxo-3-phenylpropyl)malonate (16d).

Yield: 85% (0.40 g); yellowish-brown powder; mp 93–96 °C; $[\alpha]_D^{22}$ = +3.9; (c = 1, $CHCl_3$); *ee* 86%; AD-H column, hexane:*i*PrOH 90:10, major enantiomer t_r = 54.1 min, minor enantiomer t_r = 40.5 min; ^{1}H NMR (500 MHz, $CDCl_3$), δ (ppm): 8.27 (d, J = 9 Hz, 2H, ArH), 8.04 (d, J = 9 Hz, 2H, ArH), 7.35–7.21 (m, 5H, ArH), 4.36 (dd, J = 8.2 Hz, 5 Hz, 1H, ArCH), 4.25–4.18 (m, 2H, OCH_2), 4.02–3.87 (m, 3H, COCH_2, OCH_2), 3.55 (dd, J = 18 Hz, 8.5 Hz, 1H, COCH_2), 2.24 (s, 3H, COCH_3), 1.25 (t, J = 7 Hz, 3H, CH_2CH_3), 1.07 (t, J = 7 Hz, 3H, CH_2CH_3); HRMS calcd for $C_{24}H_{25}NO_9$ 471.1529, found 471.1527.

2.6.6 | Diethyl 2-acetoxy-2-(1-(3-methoxyphenyl)-3-oxo-3-phenylpropyl)malonate (16e).

Yield: 64% (0.29 g); yellow oil; $[\alpha]_D^{22}$ = +12.8; (c = 1, $CHCl_3$); *ee* 57%; AD-H column, hexane:*i*PrOH 90:10, major enantiomer t_r = 23.1 min, minor enantiomer t_r = 17.5 min; ^{1}H NMR (500 MHz, $CDCl_3$), δ (ppm): 7.90 (d, J = 7.5 Hz, 2H, ArH), 7.54 (t, J = 7.5 Hz, 1H, ArH), 7.43 (t, J = 7.5 Hz, 2H, ArH), 7.14 (t, J = 8 Hz, 1H, ArH), 6.96–6.90 (m, 2H, ArH), 6.75 (dd, J = 8 Hz, 2.5 Hz, 1H, ArH), 4.35 (dd, J = 9 Hz, 4 Hz, 1H, ArCH), 4.25–4.15 (m, 2H, OCH_2), 4.05–3.94 (m, 2H, OCH_2), 3.76 (s, 3H, ArOCH_3), 3.71 (dd, J = 18 Hz, 4 Hz, 1H, COCH_2), 3.56 (dd, J = 18 Hz, 9 Hz, 1H, COCH_2), 2.23 (s, 3H, COCH_3), 1.23 (t, J = 7 Hz, 3H, CH_2CH_3), 1.09 (t, J = 7 Hz, 3H, CH_2CH_3); HRMS calcd for $C_{25}H_{28}O_8$ 456.1784, found 456.1788.

2.6.7 | Diethyl 2-acetoxy-2-(1-(4-methoxyphenyl)-3-oxo-3-phenylpropyl)malonate (16f).

Yield: 33% (0.15 g); light yellow; $[\alpha]_D^{22}$ = +19.7 (c = 1, $CHCl_3$); *ee* 99%; AD-H column, hexane:*i*PrOH 90:10, major enantiomer t_r = 24.9 min, minor enantiomer t_r = 22.8 min; ^{1}H NMR (500 MHz, $CDCl_3$), δ (ppm): 7.89 (dd, J = 7.5 Hz, 1 Hz, 2H, ArH), 7.53 (t, J = 7.5 Hz, 1H, ArH), 7.43 (t, J = 7.5 Hz, 2H, ArH), 7.26 (d, J = 8.5 Hz, 2H, ArH), 6.77 (d, J = 8.5 Hz, 2H, ArH), 4.31 (dd, J = 8.5 Hz, J = 4 Hz, 1H, ArCH), 4.24–4.15 (m, 2H, OCH_2), 4.06–3.92 (m, 2H, OCH_2), 3.75 (s, 3H, ArOCH_3), 3.71 (dd, J = 18 Hz, 4 Hz, 1H, COCH_2), 3.56 (dd, J = 18 Hz, J = 9 Hz, 1H, COCH_2), 2.23 (s, 3H, COCH_3), 1.23 (t, J = 7 Hz, 3H, CH_2CH_3), 1.10 (t, J = 7 Hz, 3H, CH_2CH_3); HRMS calcd for $C_{25}H_{28}O_8$ 456.1784, found 456.1785.

2.6.8 | Diethyl 2-benzoyl-3-phenylcyclopropane-1,1-dicarboxylate (18).

Yield: 28% (0.10 g); yellow oil; $[\alpha]_D^{22}$ = +28.0; (c = 1, $CHCl_3$); *ee* 99%; AS-H column, hexane:*i*PrOH 90:10, major enantiomer t_r = 5.0 min, minor enantiomer t_r = 9.3 min;^{1}H NMR (500 MHz, $CDCl_3$), δ (ppm): 8.11 (d, J = 7.5 Hz, 2H, ArH), 7.62 (t, J = 7.5 Hz, 1H, ArH), 7.51 (t, J = 7.5 Hz, 2H, ArH), 7.33–7.26 (m, 5H, ArH), 4.14 (q, J = 7 Hz, 2H, OCH_2), 4.12 (d, J = 7.5 Hz, 1H, COCH), 4.00 (q, J = 7 Hz, 2H, OCH_2),

3.89 (d, J = 7.5 Hz, 1H, PhC*H*), 1.11 (t, J = 7 Hz, 3H, C*H*$_3$), 0.99 (t, J = 7 Hz, 3H, C*H*$_3$). ^{13}C NMR ($CDCl_3$, 75 MHz), δ (ppm): 193.58, 165.93, 165.69, 136.78, 133.62, 133.61, 133.47, 128.73, 128.61, 128.60, 128.58, 128.50, 128.31, 128.30, 127.66, 61.97, 61.89, 49.10, 35.87, 35.00, 13.85, 13.80; HRMS calcd for $C_{22}H_{22}O_5$ 366.1467, found 366.1470.

2.6.9 | Diethyl 2,2-dicyano-3-phenylcyclopropane-1,1-dicarboxylate (20a).

Yield: 81% (0.25 g); yellow oil; $[\alpha]_D^{22}$ = −14.1; (c = 1, $CHCl_3$); *ee* 85%; AS-H column, hexane:*i*PrOH 90:10, major enantiomer t_r = 13.5 min, minor enantiomer t_r = 12.2 min; ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 7.45–7.35 (m, 5H, Ar*H*), 4.43 (q, J = 7.2 Hz, 2H, OC*H*$_2$), 4.30–4.18 (m, 2H, OC*H*$_2$), 3.96 (s, 1H, ArC*H*), 1.39 (t, J = 7.2 Hz, 3H, CH$_2$C*H*$_3$), 1.19 (t, J = 7.2 Hz, 3H, CH$_2$C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 163.05, 161.06, 129.67, 129.10, 128.76, 127.31, 111.86, 109.71, 64.50, 63.62, 46.39, 40.08, 16.32, 13.97, 13.60; HRMS calcd for $C_{17}H_{16}N_2O_4$ 312.111, found 312.1104.

2.6.10 | Diethyl 2,2-dicyano-3-(2-methyphenyl) cyclopropane-1,1-dicarboxylate (20b).

Yield: 72% (0.23 g); yellow oil; $[\alpha]_D^{22}$ = +7.8; (c = 1, $CHCl_3$); *ee* 23%;Yellow oil; AD-H column, hexane:*i*PrOH 80:20, major enantiomer t_r = 3.7 min, minor enantiomer t_r = 3.3 min; ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 7.37 (d, J = 7.2 Hz, 1H, Ar*H*), 7.33–7.26 (m, 2H, Ar*H*), 7.20 (td, J = 7.2 Hz, 1.2 Hz, 1H, Ar*H*), 4.44 (q, J = 6.9 Hz, 2H, OC*H*$_2$), 4.23 (q, J = 6.9 Hz, 2H, OC*H*$_2$), 3.87 (s, 1H, ArC*H*), 2.43 (s, 3H, ArC*H*$_3$), 1.40 (t, J = 6.9 Hz, 3H), 1.17 (t, J = 6.9 Hz, 3H); HRMS calcd for $C_{18}H_{18}N_2O_4$ 326.1267, found 326.1265.

2.6.11 | Diethyl 2,2-dicyano-3-(3-methyphenyl) cyclopropane-1,1-dicarboxylate (20c).

Yield: 74% (0.24 g); orange oil; $[\alpha]_D^{22}$ = −22.2.; (c = 1, $CHCl_3$); *ee* 99%; AD-H column, hexane:*i*PrOH 80:20, major enantiomer t_r = 4.1 min, minor enantiomer t_r = 5.7 min; ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 7.29 (t, J = 7.2 Hz, 1H, Ar*H*), 7.22 (s, 1H, Ar*H*), 7.21–7.13 (m, 2H, Ar*H*), 4.42 (q, J = 6.9 Hz, 2H, OC*H*$_2$), 4.24 (q, J = 6.9 Hz, 2H, OC*H*$_2$), 3.93 (s, 1H, ArC*H*), 2.36 (s, 3H, ArC*H*$_3$), 1.39 (t, J = 6.9 Hz, 3H), 1.20 (t, J = 6.9 Hz, 3H); HRMS calcd for $C_{18}H_{18}N_2O_4$ 326.1267, found 326.1268.

2.6.12 | Diethyl 2,2-dicyano-3-(4-methyphenyl) cyclopropane-1,1-dicarboxylate (20d).

Yield: 86% (0.28 g); orange oil; $[\alpha]_D^{22}$ = −15.5; (c = 1, $CHCl_3$); *ee* 86%; AD-H column, hexane:*i*PrOH 80:20, major enantiomer t_r = 4.3 min, minor enantiomer t_r = 5.0 min; ^{1}H NMR (500 MHz, $CDCl_3$), δ (ppm): 7.25 (d, J = 8 Hz, 2H, Ar*H*), 7.20 (d, J = 8 Hz, 2H, Ar*H*), 4.42 (q, J = 7 Hz, 2H, OC*H*$_2$), 4.30–4.20 (m, 2H, OC*H*$_2$), 3.92 (s, 1H, ArC*H*), 2.35 (s, 3H, ArC*H*$_3$), 1.38 (t, J = 7 Hz, 3H), 1.21 (t, J = 7 Hz, 3H). HRMS calcd for $C_{18}H_{18}N_2O_4$ 326.1267, found 326.1270.

2.6.13 | Diethyl 2,2-dicyano-3-(4-nitrophenyl) cyclopropane-1,1-dicarboxylate (20e).

Yield: 67% (0.24 g); orange oil; $[\alpha]_D^{22}$ = −2.0; (c = 1, $CHCl_3$); *ee* 75%; AD-H column, hexane:*i*PrOH 90:10, major enantiomer t_r = 26.4 min, minor enantiomer t_r = 31.3 min; ^{1}H NMR (500 MHz, $CDCl_3$), δ (ppm): 8.29 (d, J = 8.5 Hz, 2H, Ar*H*), 7.62 (d, J = 8.5 Hz, 2H, Ar*H*), 4.46 (q, J = 7 Hz, 2H, OC*H*$_2$), 4.32–4.23 (m, 2H, OC*H*$_2$), 4.01 (s, 1H, ArC*H*), 1.41 (t, J = 7 Hz, 3H, CH$_2$C*H*$_3$), 1.24 (t, J = 7 Hz, 3H, CH$_2$C*H*$_3$); HRMS calcd for $C_{17}H_{15}N_3O_6$ 357.0961, found 357.0958.

2.6.14 | Diethyl 2,2-dicyano-3-(4-chlorophenyl) cyclopropane-1,1-dicarboxylate (20f).

Yield: 80% (0.25 g); yellow oil; $[\alpha]_D^{22}$ = −27.0; (c = 1, $CHCl_3$); *ee* 59%; AD-H column, hexane:*i*PrOH 90:10, major enantiomer t_r = 4.5 min, minor enantiomer t_r = 4.0 min; ^{1}H NMR (500 MHz, $CDCl_3$), δ (ppm): 7.39 (d, J = 8.5 Hz, 2H, Ar*H*), 7.33 (d, J = 8.5 Hz, 2H, Ar*H*), 4.43 (q, J = 6 Hz, 2H, OC*H*$_2$), 4.30–4.20 (m, 2H, OC*H*$_2$), 3.91 (s, 1H, ArC*H*), 1.39 (t, J = 6 Hz, 3H, C*H*$_3$), 1.39 (t, J = 6 Hz, 3H, C*H*$_3$); HRMS calcd for $C_{17}H_{15}ClN_2O_4$ 346.0720, found 346.0726.

2.6.15 | Diethyl 2,2-dibenzoyl-3-phenylcyclopropane-1,1-dicarboxylate (22).

Yield: 38% (0.18 g); yellow oil; $[\alpha]_D^{22}$ = +64.9 (c = 1, $CHCl_3$); *ee* 57%; AD-H column, hexane:*i*PrOH 90:10, major enantiomer t_r = 11.9 min, minor enantiomer t_r = 41.1 min; ^{1}H NMR (500 MHz, $CDCl_3$), δ (ppm) = 7.53 (d, J = 7.5 Hz, 2H, Ar*H*), 7.44 (d, J = 7.5 Hz, 2H, Ar*H*), 7.33 (d, J = 7 Hz, 2H, Ar*H*), 7.26–7.19 (m, 5H, Ar*H*), 7.14 (t, J = 7.5 Hz, 2H, Ar*H*), 7.10 (t, J = 7.5 Hz, 2H, Ar*H*), 5.64 (s, 1H, PhC*H*), 4.47–4.40 (m, 1H, OC*H*$_2$), 4.38–4.29 (m, 1H, OC*H*$_2$), 3.87–3.80 (m, 1H, OC*H*$_2$), 3.64–3.57 (m, 1H, OC*H*$_2$), 1.35 (t, J = 7 Hz, 3H, C*H*$_3$), 0.84 (t, J = 7 Hz, 3H, C*H*$_3$). ^{13}C NMR ($CDCl_3$, 75 MHz), δ (ppm): 191.77,

185.72, 166.92, 165.33, 138.20, 136.88, 131.80, 131.79, 130.58, 129.64, 129.11, 128.78, 128.33,128.32, 127.83, 127.82, 114.79, 91.73, 62.95, 62.07, 57.43, 14.05, 13.43; HRMS calcd for $C_{29}H_{26}O_6$ 470.1729, found 470.1733.

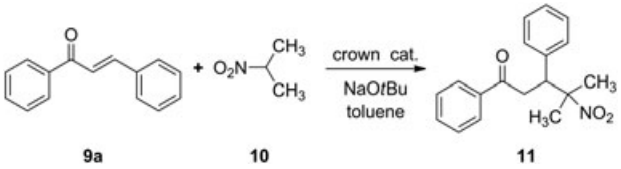
3 | RESULTS AND DISCUSSION

The 2,3-*O*-isopropylidene-L-threitol (**1**) was prepared from commercially available diethyl L-tartrate according to a known procedure.[49-52] The dialkylation of diol **1** by methyl iodide,[41] *n*-butyl bromide, and benzyl chloride[42] in THF using NaH afforded intermediates **2a**, **2b,** and **2c**, respectively. The isopropylidene protecting groups were then removed by HCl/MeOH,[38,44] to furnish optically active diols **3a–c** in good yields.

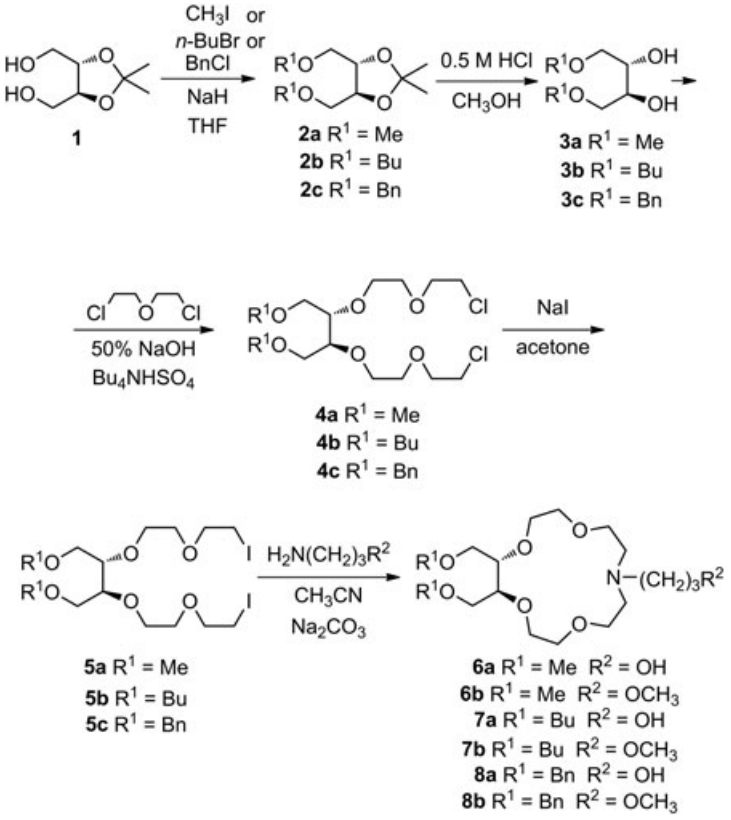
The vicinal hydroxyl groups of compounds **3a–c** were then alkylated with bis(2-chloroethyl) ether in the presence of 50% *aq.* NaOH as the base and tetrabutylammonium hydrogensulfate (Bu_4HSO_4) as the phase transfer catalyst in a liquid–liquid two-phase system to give key intermediates **4a–c** in 37%, 79%, and 25% yields, respectively, after chromatography. The exchange of chlorine to iodine in intermediates **4a–c** was accomplished by reaction with NaI in boiling acetone to provide bis-iodo derivatives **5a–c** in good yields (in average 90%). These species (**5a–c**) were then cyclized with 3-aminopropanol and 3-methoxypropylamine in boiling acetonitrile, in the presence of Na_2CO_3 to result in the formation of lariat ethers **6–8**. The ring closure reactions with 3-aminopropanol took place in yields of 41% (**6a**), 62% (**7a**), and 64% (**8a**), respectively, while with 3-methoxypropylamine the yields were 73% (**6b**), 71% (**7b**), and 86% (**8b**) (Scheme 1).

The macrocycles synthesized (**6–8**) were tested as chiral catalysts in Michael addition reactions under solid–liquid phase transfer conditions, at RT. The corresponding products were obtained by preparative TLC, and the enantiomeric purity was measured by ^{1}H NMR spectroscopy or chiral HPLC.

The addition of 2-nitropropane (**10**) to *trans*-chalcone (**9**) was carried out in toluene, in the presence of solid sodium *tert*-butoxide (35 mol%) using one of the chiral catalysts (7 mol%) prepared by us as reported previously[16,45] (Scheme 2).



SCHEME 2 Michael addition of 2-nitropropane to chalcone

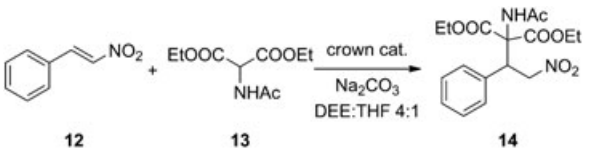


SCHEME 1 The synthesis of L-threitol-based crown ethers from diethyl L-tartrate

Another Michael reaction, the conjugate addition of diethyl acetamidomalonate **13** to β-nitrostyrene **12** was carried out in a mixture of THF-ether in the presence of dry Na_2CO_3 employing 15 mol% of the crown ether (Scheme 3).[39,40] Experimental data of the two asymmetric Michael addition reactions are shown in Table 1.

It can be seen from Table 1 that the outcome of the Michael additions depended on the substituent of the threitol-based crown ether. In the addition of 2-nitropropane to chalcone, from the point of view of yield and enantioselectivity, the most efficient catalyst was threitol-based lariat ether with hydroxypropyl side arm (**6a**) giving product (**11**) in a yield of 68% and in an *ee* of 89%. In the case, where there was MeO end-group instead of the OH function (**6b**), the product was obtained in a lower yield (56%) and in a lower *ee* (67%) (Table 1, entry 2).

Comparative results were obtained applying macrocycle **8a** with two benzyl groups (Table 1**,** entry 4), while the use of lariat ether with butyl groups (**7a**) gave the lowest yield (20%) and *ee* (31%). In the case of the reaction of nitrostyrene **12** with diethyl acetamidomalonate (**13**), surprisingly, the dibenzyl substituted crown ether (**8a**) induced an *ee* of 95%,



SCHEME 3 Michael addition of diethyl acetamidomalonate to β-nitrostyrene

TABLE 1 Asymmetric Michael addition of 2-nitropropane (**10**) and diethyl acetamidomalonate (**13**) to chalcone (**9a**) and nitrostyrene (**12**), respectively, in the presence of threitol-based lariat ethers

Entry	Catalysts	Time (h)	Yield (%) [a]	ee (%)
1	**6a**	28	**11**: 68	89 (*R*)[b]
2	**6b**	22	**11**: 56	67 (*R*)[b]
3	**7a**	24	**11**: 20	31 (*R*)[b]
4	**8a**	24	**11**: 62	75 (*R*)[b]
5	**6a**	8	**14**: 67	58 (*S*)[c]
6	**6b**	7	**14**: 56	38 (*S*)[c]
7	**8a**	9	**14**: 65	95 (*S*)[c]
8	**8b**	27	**14**: 22	51 (*S*)[c]

[a]Based on isolation by preparative TLC.

[b]Enantioselectivities were determined by ^{1}H NMR spectroscopy; The (+)-(*R*)-antipode of **11** was formed in excess.

[c]Determined by chiral HPLC analysis, the (−)-(*S*) enantiomer predominated. Absolute configurations were assigned by comparison of specific rotations with the literature value.

while dimethyl substituted catalyst **6a** led to a lower *ee* of 58% (Table 1**,** entries 7 and 5). Comparison of the effect of catalysts **6a** and **6b** as well as the effect of **8a** and **8b** referred to the advantage of the hydroxyl end-group (58% and 95% *ee*, respectively) in relation to a methoxy group (38% and 51% *ee*, respectively) (Table 1, entries 5 and 6). This observation may be in accord with the hydrogen bond forming ability of the OH moiety.

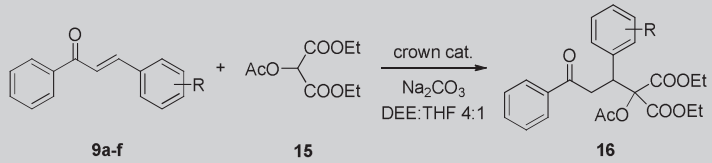
The asymmetric addition of dialkyl malonates to *trans*-chalcones have been studied in the presence of chiral catalysts in several reports. For example, the reaction was investigated in the presence of La-BINOL complexes,[53,54] L-proline derivatives,[55] chiral aminoalcohol-Al complexes,[56,57] pyrrolidylalkyl ammonium hydroxide, and chiral ammonium salts[58] as the catalysts. There are also a few examples in this field for chiral phase transfer catalysis.[59,60] Recently, successful applications of cinchona alkaloids-derived quaternary ammonium salts have been reported in catalytic asymmetric syntheses.[61]

Previously, we found that a glucopyranoside-based macrocycle generated asymmetric induction in the reaction of chalcone **9a** with diethyl acetoxymalonate (**15**).[46] It was a challenge for us to test the threitol-based lariat ethers in this reaction. In our experiments, the conjugate addition of diethylmalonate (**15)** to *trans*-chalcones **9a–f** was carried in a mixture of THF-ether as the solvent in the presence of Na_2CO_3 (used in 2-fold excess) employing 15 mol% of the crown ether at room temperature to afford the chiral Michael adducts **16a–f**. The experimental data obtained by the application of the threitol-based lariat ethers are shown in Table 2.

In the reaction of chalcone **9a**, the highest asymmetric induction (96% *ee*) was generated by threitol-based crown ether **6a** with two methyl groups. Species **16a** was isolated in a yield of 68% (Table 2, entry 1). Somewhat lower *ee* values (83–87% *ee*) were detected using the dibutyl and dibenzyl catalysts **7a** and **8a** (Table 2, entries 3 and 5). The catalysts with MeO end-group (**6b** and **7b**) led again to lower *ee* values than the species with OH groups (Table 2, entries 2 and 4).

In general, the reaction of 4-chlorochalcone (**9b**) gave the products (**16b**) in higher *ee* values of 82–99%, but the tendency was different as in the previous case. The higher *ee* value (99% *ee*) was obtained with the dibenzyl substituted macrocycle **8a** (Table 2, entry 9), followed by catalysts **7a** and **6a** resulting in *ee* values of 98% and 90%, respectively, (Table 2, entries 7 and 6). The lowest induction (82% *ee*) was shown by dibutyl macrocycle **7b** with a MeO end-group (Table 2, entry 8). It is noteworthy that in reaction of the 3-nitrochalcone, catalysts **6a**, **7a,** and **8a** with hydroxypropyl side arm gave the adducts (**16c**) in relative good yields, but in rather modest *ee* values of 38–48% *ee* (Table 2, entries 10–12). The use of catalyst **7a** in the reaction of

TABLE 2 The addition of diethyl acetoxymalonate (**15**) to *trans*-chalcones (**9a–f**) in the presence of threitol-based lariat ethers



9a-f 15 16

Entry	Catalyst	R	Time (h)	Yield (%) [a]	ee (%)[b]
1	**6a**	**9a:**H	170	**16a**: 68	96
2	**6b**	**9a:**H	120	**16a:** 49	61
3	**7a**	**9a:**H	72	**16a**: 65	87
4	**7b**	**9a:**H	120	**16a**: 62	77
5	**8a**	**9a:**H	130	**16a:** 65	83
6	**6a**	**9b**:4-Cl	72	**16b**: 67	90
7	**7a**	**9b**:4-Cl	48	**16b**: 72	98
8	**7b**	**9b**:4-Cl	48	**16b**: 57	82
9	**8a**	**9b**:4-Cl	48	**16b**: 76	99
10	**6a**	**9c**:3-NO_2	72	**16c:** 64	38
11	**7a**	**9c**:3-NO_2	72	**16c**: 79	48
12	**8a**	**9c**:3-NO_2	72	**16c**: 59	42
13	**7a**	**9d**:4-NO_2	72	**16d:** 85	86
14	**8a**	**9e**:3-OMe	140	**16e**: 64	57
15	**7a**	**9f**:4-OMe	168	**16f:** 33	99

[a]Based on isolation by preparative TLC.

[b]The enantioselectivities were determined by chiral HPLC analysis.

4-NO_2-chalcone was more successful, as the *ee* value was in this case 86% (Table 2, entry 13). The same can be said about the reaction of 4-MeO-chalcone in the presence of catalyst **7a**, as the *ee* was as high as 99%, although the yield was low (33%) (Table 2, entry 15). The 3-MeO substituted model led again to a lower *ee* value of 57% using catalyst **8a** in this case. It can be concluded that beside the steric factors, the electronic properties also have an impact on the outcome of the additions. However, in this series it is not possible to establish a general rule. The only thing that can be said is that the application of the dimethyl and the dibutyl substituted macrocycles with hydroxypropyl side arm (**6a** and **7a**) is advantageous.

The cyclopropane moiety is an important building block in a large number of biologically active compounds; therefore, the development of novel strategies to make these important compounds available is a challenge. The Michael Initiated Ring Closure (MIRC) reaction represents an elegant approach, which has been applied extensively for the construction of cyclopropane derivatives. The MIRC reaction strategy may also be utilized through a one-pot multicomponent reaction, which has been gaining interest by synthetic organic chemists in recent times.[62-71]

Surprisingly, the use of chiral phase transfer catalysts to established asymmetric cyclopropanation reactions has so far been limited to only a few examples.[72-74] Previously Waser and Herchl investigated the asymmetric reaction of bromomalonates with *trans*-chalcones in the presence of cinchona alkaloid ammonium salt catalysts to furnish cyclopropane derivatives.[75]

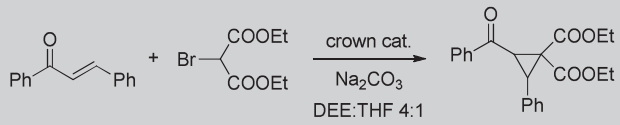
We performed the reaction of bromomalonate **17** with chalcone **9a** under solid–liquid phase transfer catalytic conditions discussed above (Table 3).

The cyclopropane diester (**18**) was obtained in modest yields (28–33%) from the reaction under discussion, but high *ee* values were detected. Lariat ethers **6a** and **7a** generated *ee* values of 98/99%, while macrocycle **8a** allowed an *ee* of 86%. The reason for the low yields may be the base-catalyzed dimerization side reaction of diethyl bromomalonate (**17**).

In the next stage, the model reaction of benzylidenemalononitriles (**19a–f**) with diethyl bromomalonate was investigated under solid–liquid phase transfer catalytic conditions discussed above in the presence of lariat ethers incorporating L-threitol (Table 4).

The corresponding chiral cyclopropane derivatives **20a–f**, with one exception, were formed in acceptable to

TABLE 3 Phase transfer catalysis-promoted MIRC-reaction of diethyl bromomalonate (**17**) with chalcone (**9a**)



9a **17** **18**

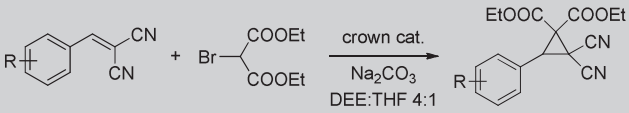
Entry	Catalyst	Time (day)	Yield (%) [a]	[α][b]	ee (%) [c]
1	**6a**	8	**18**: 31	27.8	98
2	**7a**	8	**18:** 28	28.0	99
3	**8a**	10	**18**: 33	20.4	86

[a]Based on isolation by preparative TLC.

[b]In $CHCl_3$, *c* 1.

[c]The enantioselectivities were determined by chiral HPLC analysis.

TABLE 4 Scope of the phase transfer catalyzed MIRC-reaction of bromomalonate (**17**) with benzylidenemalononitrile derivatives (**19a–f**)



19 **17** **20**

Entry	Catalyst	R	Time (h)	Yield (%) [a]	ee (%)[b]
1	**6a**	H	20	**20a**: 74	51
2	**6b**	H	20	**20a**: 69	45
3	**7a**	H	24	**20a**: 81	85
4	**7b**	H	24	**20a**: 32	38
5	**8a**	H	72	**20a**: 58	42
6	**6a**	2-Me	24	**20b**: 84	15
7	**6a**	3-Me	24	**20c**: 74	99
8	**6a**	4-Me	24	**20d**: 76	99
9	**8a**	2-Me	24	**20b**: 72	23
10	**8a**	3-Me	24	**20c**: 74	34
11	**8a**	4-Me	24	**20d**: 86	86
12	**6a**	4-NO_2	24	**20e**: 67	74
13	**8a**	4-NO_2	24	**20e**: 60	72
14	**6a**	4-Cl	20	**20f**: 72	20
15	**8a**	4-Cl	20	**20f**: 80	59

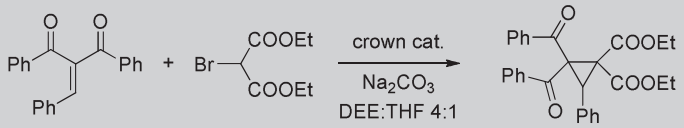
[a]Based on isolation by preparative TLC.

[b]The enantioselectivities were determined by chiral HPLC analysis.

good (58–86%) yields. Five macrocycles synthesized by us were tested as catalysts in the reaction of unsubstituted benzylidenemalononitrile (Table 4, entries 1–5). The highest *ee* value (85%) was generated by the dibutyl lariat ether **7a** bearing hydroxypropyl side arm to afford the product **20a** in a yield of 81% (Table 4, entry 3). The lowest *ee* value (38%) was produced by its methoxypropyl substituted version **7b** (Table 4, entry 4).

It was again a general experience that the catalysts with hydroxyl end-groups (**6a** and **7a**) induced a higher enantioselectivity than the species with methoxy end-groups (**6b** and **7b**). From the next experiments it can be seen that the enantioselectivity is strongly dependent on the substituent of the benzylidenemalononitrile (Table 4, entries 6–15). Performing the reaction of the 2-, 3-, and 4-Me substituted malononitriles in the presence of catalyst **6a**, the

TABLE 5 The MIRC reaction of diethyl bromomalonate (**17**) with 2-benzylidene-1,3-diphenylpropane-1,3-dione (**21**)



21 **17** **22**

Entry	Catalyst	Time (h)	Yield (%) [a]	[α][b]	ee (%) [c]
1	**7a**	240	51	61.7	50
2	**8a**	240	38	64.9	57

[a]Based on isolation by preparative TLC.

[b]In $CHCl_3$, *c* 1.

[c]The enantioselectivities were determined by chiral HPLC analysis.

corresponding cyclopropane derivatives (**20b–d**) were formed in *ee* values of 15%, 99%, and 99%, respectively (Table 4, entries 6–8).

Using dibenzyl lariat ether **8a** in the same reaction, products **20b–d** were formed with enantioselectivity of 23%, 34%, and 86%, respectively (Table 4, entries 9–11).

It seems that the farther the methyl group is located from the reaction center, the higher the optical purity of the products is. The highest enantioselectivities (99% and 86% *ee*) were detected with the 4-Me substituted acceptors. Then the 4-NO_2 and the 4-Cl substrates (**19e** and **19f**, respectively) were reacted in the presence of dimethyl and dibenzyl macrocycles **6a** and **8a**. The 4-NO_2 cyclopropane derivative **20e** was obtained in *ee* values of 74% and 72% (Table 4, entries 12 and 13), while the 4-chloro product **20f** was formed in lower *ee* values of 20% and 59% (Table 4, entries 14 and 15). In most cases, the relatively high yields of 60–86% suggested that following the 20–72-h reaction times the base-catalyzed dimerization of bromomalonate was not significant.

As a new model reaction, the cyclopropanation of 2-benzylidene-1,3-diphenylpropane-1,3-dione (**21**) with diethyl bromomalonate (**17**) was also investigated (Table 5).

Conditions of the solid–liquid phase transfer catalytic reaction were the same, as described above. Application of the dibutyl substituted **7a** and the dibenzyl substituted **8a** macrocycles led to rather similar *ee* values of 50% and 57%, respectively (Table 5, entries 1 and 2). This new model reaction is to be studied further.

4 | CONCLUSION

In summary, six members of a new chiral crown ether family with substituents of different lipophilicity were synthesized from diethyl L-tartrate. These macrocycles proved to be efficient enantioselective catalysts in a few Michael additions and cyclopropanation reactions carried out under solid–liquid phase transfer conditions at ambient temperature. We could not find a relationship between the structure of the unsaturated substrates/catalysts and the enantioselectivity. Different lariat ethers were found optimal in the different model reactions. In the addition of 2-nitropropane to chalcone, catalyst **6a** generated the best enantioselectivity; at the same time, in the reaction of diethyl acetamidomalonate with nitrostyrene, dibenzyl substituted **8a** proved to be the most efficient. Three new model reactions were studied, in which the L-threitol-based catalysts developed by us induced good enantioselectivities. In the reaction of diethyl acetoxymalonate with *trans*-chalcones, the stereochemical outcome was strongly dependent on the substituents of the chalcone. The highest *ee* values were obtained with the unsubstituted, 4-chloro and 4-methoxy chalcones. In these cases, catalysts **7a** and **8a** generated excellent *ee* values (98% and 99% *ee*).

The new catalysts were also tried out in cyclopropanation reactions using diethyl bromomalonate as the nucleophile. Excellent enantioselectivities were obtained in the reaction with chalcone, but the yields were low. In the reaction with benzylidenemalononitriles, it was found that the substituents in the aromatic ring had a strong impact on the outcome of the reaction. The highest *ee* values were observed in the reaction of the 3-Me and 4-Me substituted malononitriles. The MIRC reaction of 2-benzylidene-1,3-diphenylpropane-1,3-dione with diethyl bromomalonate afforded the corresponding cyclopropane derivatives in moderate optical purity. This novel reaction is to be explored further, and the evaluation of the absolute configuration is also a challenge.

ACKNOWLEDGEMENTS

Financial support by the Hungarian Scientific Research Found (OTKA No. PD 112166) is gratefully acknowledged. This work was financially supported by the New Széchenyi Development Plan (TÁMOP-4.2.1/B-09/1/KMR-2010-0002).

REFERENCES

1. Noyori R. *Asymmetric Catalysis in Organic Synthesis*. New York: John Wiley and Sons; 1994.
2. Krause N, Hoffman-Röder A. Recent advances in catalytic enantioselective Michael additions. *Synthesis*. 2001;171-196.
3. Berkessel A, Gröger H. *Asymmetric Organocatalysis*. Weinheim, Germany: Wiley-VCH; 2005:45-82.
4. Ooi T, Maruoka K. Recent advances in asymmetric phase-transfer catalysis. *Angew Chem Int Ed*. 2007;46:4222-4266.
5. Maruoka K. Practical aspects of recent asymmetric phase-transfer catalysis. *Org Process Res Dev*. 2008;12:679-697.
6. Maruoka K, Shirakawa S. Recent development of asymmetric phase-transfer reactions. *Angew Chem Int Ed*. 2013;52:4312-4348.
7. Ingemann S, Hiemstra H. Cinkonas and cupreidines. In: Dalko PI, ed. *Comprehensive Enantioselective Organocatalysis*. Vol.1 Weinheim, Germany: Wiley-VCH; 2013:119-160.
8. Kim DY, Huh SC, Kim SM. Enantioselective Michael reaction of malonates and chalcones by phase-transfer catalysis using chiral quaternary ammonium salt. *Tetrahedron Lett*. 2001;42:6299-6301.
9. Cao D, Fang G, Zhang J, Wang H, Zheng C, Zhao G. Enantioselective Michael addition of malonates to chalcone derivatives catalyzed by dipeptide-derived multifunctional phosphonium salts. *J Org Chem*. 2016;81:9973-9982.
10. Tiffner M, Novacek J, Busillo A, Gratzer K, Massa A, Waser M. Design of chiral urea-quaternary ammonium salt hybrid catalysts for asymmetric reactions of glycine Schiff bases. *RSC Adv*. 2015;5:78941-78949.
11. O'Donnell MI. Catalytic asymmetric synthesis. In: Ojima I, ed. *Asymmetric Phase-Transfer Reactions*. 2nd ed. New York: Wiley-VCH; 2000:231-280.
12. Hashimoto T, Maruoka K. Recent development and application of chiral phase-transfer catalysts. *Chem Rev*. 2007;107:5656-5682.
13. Marouka K. *Asymmetric Phase Transfer Catalysis*. Weinheim, Germany: Wiley-VCH; 2008.
14. Cram DJ, Sogah GDY. Chiral crown complexes catalyze Michael addition reactions to give adducts in high optical yield. *J Chem Soc Chem Commun*. 1981;625-628.
15. Stoddart JF. Molecules from natural products. In: Izatt RM, Christensen JJ, eds. *Progress in Macrocyclic Chemistry*. Vol.2 New York: John Wiley & Sons; 1981:173-250.
16. Bakó P, Czinege E, Bakó T, Czugler M, Tőke L. Asymmetric C-C bond forming reactions with chiral crown catalysts derived from D-glucose and D-galactose. *Tetrahedron:Asymmetry*. 1999;10:4539-4551.
17. Jarosz S, Listkowski A. Sugar derived crown ethers and their analogs: Synthesis and properties. *Curr Org Chem*. 2006;10:643-662.
18. Itoh T, Shirakami S. Synthesis of chiral azacrown ethers derived from alpha-D-glucose and their catalytic properties on the asymmetric Michael addition. *Heterocycles*. 2001;55:37-43.
19. Bakó P, Keglevich G, Rapi Z. Asymmetric phase transfer reactions catalyzed by chiral crown ethers derived from monosaccharides. *Lett Org Chem*. 2010;7:645-656.
20. Makó A, Rapi Z, Keglevich G, et al. Asymmetric epoxidation of substituted chalcones and chalcone analogues catalyzed by α-D-glucose- and α-D-mannose-based crown ethers. *Tetrahedron: Asymmetry*. 2010;21:919-925.
21. Bakó P, Rapi Z, Keglevich G, et al. Asymmetric C-C bond formation via Darzens condensation and Michael addition using monosaccharide-based chiral crown ethers. *Tetrahedron Lett*. 2011;52:1473-1476.
22. Rapi Z, Szabó T, Keglevich G, Szöllősy Á, Drahos L, Bakó P. Enantioselective synthesis of heteroaromatic epoxyketones under phase-transfer catalysis using D-glucose- and D-mannose-based crown ethers. *Tetrahedron:Asymmetry*. 2011;22:1189-1196.
23. Rapi Z, Bakó P, Keglevich G, et al. Asymmetric phase transfer Darzens reactions catalyzed by D-glucose and D-mannose-based chiral crown ethers. *Tetrahedron:Asymmetry*. 2012;23:489-496.
24. Rapi Z, Bakó P, Keglevich G, Szöllősy Á, Drahos L, Hegedűs L. Synthesis of *ribo*-hexopyranoside- and altrose-based azacrown ethers and their application in an asymmetric Michael addition. *Carbohydr Res*. 2013;365:61-68.
25. Bakó P, Rapi Z, Keglevich G. Catalytic asymmetric Darzens reactions. *Curr Org Synth*. 2014;11:361-376.
26. Gratzer K, Gururaja GN, Waser M. Towards tartaric-acid-derived asymmetric organocatalysts. *Eur J Org Chem*. 2013;4471-4482.
27. Soddart JF. Chiral crown ethers. *Top Stereochem*. 1987;17:207-288.
28. Girodeau JM, Lehn JM, Sauvage JP. Polyfunctional chiral macrocyclic polyether derived from L-(+)-tartaric acid. *Angew Chem Int Ed*. 1975;14:764-764.
29. Curtis WD, Laidler DA, Stoddart JF, Jones GH. Synthesis of configurationally chiral cryptands and cryptates from carbohydrate precursors. *J Chem Soc Chem Commun*. 1975;833-835.
30. Curtis WD, Laidler DA, Stoddart JF, Jones GH. Enzyme analogs by lock and key chemistry with crown compounds. 1. Enantiomeric differentiation by configurally chiral críptands synthesized from L-tartaric acid and D-mannitol. *J Chem Soc Perkin Trans 1*. 1977;1756-1770.
31. Matsui T, Koga K. Functionalized macrocycles. 1. Synthesis of thiol-bearing crown ethers as an approach to regioselective catalysts. *Chem Pharm Bull*. 1979;27:2295-2303.
32. Ando N, Yamamoto Y, Oda J, Inouye Y. Facile synthesis of chiral 18-crown-6 derivatives from L-tartaric acid. *Synthesis*. 1978; 688-690.
33. Behr JP, Girodeau JM, Hayward RC, Lehn JM, Sauvage JP. Molecular receptors — Functionalized and chiral macrocyclic polyethers derived from tartaric acid. *Helv Chim Acta*. 1980;63:2096-2111.
34. Chénevert R, Voyer N, Plante R. Synthesis of chiral 12-crown-4 and 15-crown-5 derivatives from L-tartaric acid. *Synthesis*. 1982; 782-785.
35. Bogatsky AV, Lukyanenko NG, Lobach AV, Nazarova NY, Kaprenko LP. Macroheterocycles; XVIII. Synthesis of binuclear chiral crown ethers on the base of L-tartaric acid. *Synthesis*. 1984;139-140.
36. Kataky R, Nicholson PE, Parker D. Comparative-study of monosubstituted and disubstituted 14-crown-4 derivatives as lithium ionophores. *J Chem Soc Perkin Trans*. 1990;2:321-327.
37. Lukyanenko NG, Lobach AV, Leus ON, Titova NY. Synthesis and enantiomeric selectivity of chiral crown ethers. *Russ J Org Chem*. 2002;38:895-899.

38. Dehmlow EV, Sauerbier C. Application of phase-transfer catalysis. 45. Enantioselective phase-transfer catalysis by optically active crown ethers. *Liebigs Ann Chem*. 1989;181-185.
39. Rapi Z, Démuth B, Keglevich G, et al. Enantioselective Michael addition of malonates to aromatic nitroalkenes catalyzed by monosaccharide-based chiral crown ethers. *Tetrahedron: Asymmetry*. 2014;25:141-147.
40. Rapi Z, Bakó P, Drahos L, Keglevich G. Side-arm effect of a methyl α-D-glucopyranoside-based lariat ether catalysts in asymmetric syntheses. *Heteroatom Chem*. 2015;26:63-71.
41. Shi M, Jiang JK, Feng YS. Chiral C-2-symmetric 2,3-disubstituted aziridine and 2,6-disubstituted piperidine as chiral ligands in the addition reaction of diethylzine with arylaldehydes. *Tetrahedron: Asymmetry*. 2000;11:4923-4933.
42. Feit PW. 1,4-Bismethanesulfonates of the stereoisomeric butanetetraols and related compounds. *J Med Chem*. 1964;7:14-17.
43. Colera M, Costero AM, Gaviña P, Gil S. Synthesis of chiral 18-crown-6 ethers containing lipophilic chains and their enantiomeric recognition of chiral ammonium picrates. *Tetrahedron: Asymmetry*. 2005;16:2673-2679.
44. Seebach D, Kalinowski HO, Bastani B, et al. Preparation of auxiliaries for asymmetric syntheses from tartaric acid. Addition of butyllithium to aldehydes in chiral media. *Helv Chim Acta*. 1977;60:301-325.
45. Makó A, Szöllősy Á, Keglevich G, Menyhárd DK, Bakó P, Tőke L. Synthesis of methyl-α-D-glucopyranoside-based azacrown ethers and their application in enantioselective reactions. *Monatsh Chem*. 2008;139:525-535.
46. Bakó P, Rapi Z, Grün A, Nemcsok T, Hegedűs L, Keglevich G. Asymmetric Michael addition of malonates to enones catalyzed by an α-D-glucopyranoside-based crown ether. *Synlett*. 2015;26:1847-1851.
47. Rapi Z, Grün A, Nemcsok T, et al. Crown ether derived from D-glucose as an efficient phase-transfer catalyst for the enantioselective Michael addition of malonates to enones. *Tetrahedron Asymmetry*. 2016;27:960-972.
48. Rapi Z, Grün A, Gy K, Stirling A, Bakó P. Synthesis of α-D-galactose-based azacrown ethers and their application as enantioselective catalysts in Michael reactions. *New J Chem*. 2016;40:7856-7865.
49. Fernandes RA. An efficient synthesis of (−)-posticlure: The sex pheromone of Orgyia Postica. *Eur J Org Chem*. 2007;5064-5070.
50. Dahlgren A, Branalt J, Kvarnstrom I, Nilsson I, Musil D, Samuelsson B. Synthesis of potential thrombin inhibitors. Incorporation of tartaric acid templates as P2 proline mimetics. *Bioorg Med Chem*. 2002;10:1567-1570.
51. Townsend JM, Blount JF, Sun RC, Zawoiski S, Valentine D. Novel copper-complexes of chiral diphosphines — Preparation, structure, and use to form rhodium complex catalysts for chiral hydrogenations. *J Org Chem*. 1980;45:2995-2999.
52. Tamoto K, Sugimori M, Terashima S. Novel resolution of the anthracyclinone intermediate by the use of (2*R*,3*R*)-(+)- and (2*S*,3*S*)-(−)-1,4-bis(4-chlorobenzyloxy)butane-2,3-diol — A simple and efficient synthesis of optically pure 4-demethoxydaunomycinone and 4-demethoxyadriamycidone. *Tetrahedron*. 1984;40:4617-4623.
53. Kim YS, Matsunaga S, Das J, Sekine A, Ohshima T, Shibasaki M. Stable, storable, and reusable asymmetric catalyst: A novel La-linked-BINOL complex for the catalytic asymmetric Michael reaction. *J Am Chem Soc*. 2000;122:6506-6507.
54. Matsunaga S, Ohshima T, Shibasaki M. Immobilization of asymmetric multifunctional catalysts on an insoluble polymer. *Tetrahedron Lett*. 2000;40:8473-8478.
55. Hanessian S, Pham V. Catalytic asymmetric conjugate addition of nitroalkanes to cycloalkenones. *Org Lett*. 2000;2:2975-2978.
56. Narasimhan S, Balakumar VR, Radhakrishnan V. Novel enantiomer-switching catalysts for asymmetric reductions and Michael reactions. *Tetrahedron Lett*. 2001;42:719-721.
57. Sundararajan G, Prabagaran N. A new polymer-anchored chiral catalyst for asymmetric Michael addition reactions. *Org Lett*. 2001;3:389-392.
58. Perrard T, Plaquevent LC, Desmurs JR, Hebrault D. Enantioselective synthesis of both enantiomers of methyl dihydrojasmonate using solid-liquid asymmetric phase-transfer catalysis. *Org Lett*. 2000;2:2959-2962.
59. Ooi T, Ohara D, Fukumoto K, Maruoka K. Importance of chiral phase-transfer catalysts with dual functions in obtaining high enantioselectivity in the Michael reaction of malonates and chalcone derivatives. *Org Lett*. 2005;7:3195-3197.
60. Dere RT, Pal RR, Patil PS, Salunkhe MM. Influence of ionic liquids on the phase transfer-catalysed enantioselective Michael reaction. *Tetrahedron Lett*. 2003;44:5351-5353.
61. Wang J, Li H, Zu L, et al. Organocatalytic enantioselective conjugate additions to enones. *J Am Chem Soc*. 2006;128:12652-12653.
62. Lebel H, Marcoux JF, Molinaro C, Charette AB. Stereoselective cyclopropanation reactions. *Chem Rev*. 2003;103:977-1050.
63. Reissig HU, Zimmer R. Donor-acceptor-substituted cyclopropane derivatives and their application in organic synthesis. *Chem Rev*. 2003;103:1151-1196.
64. Gaunt MJ, Johansson CCC. Recent developments in the use of catalytic asymmetric ammonium enolates in chemical synthesis. *Chem Rev*. 2007;107:5596-5605.
65. De Simone FD, Waser J. Cyclization and cycloaddition reactions of cyclopropyl carbonyls and imines. *Synthesis*. 2009;3353-3374.
66. Lindsay VNG, Nicolas C, Charette AB. Asymmetric Rh(II)-catalyzed cyclopropanation of alkenes with diacceptor diazo compounds: P-methoxyphenyl ketone as a general stereoselectivity controlling group. *J Am Chem Soc*. 2011;133:8972-8981.
67. Falkowski JM, Liu S, Wang C, Lin W. Chiral metal-organic frameworks with tunable open channels as single-site asymmetric cyclopropanation catalysts. *Chem Commun*. 2012;48:6508-6510.
68. Benfatti F, de Nanteuil F, Waser J. Catalytic enantiospecific [3+2] annulation of aminocyclopropanes with ketones. *Chem A Eur J*. 2012;18:4844-4849.
69. Benfatti F, de Nanteuil F, Waser J. Iron-catalyzed [3+2] annulation of aminocyclopropanes with aldehydes: Stereoselective synthesis of aminotetrahydrofurans. *Org Lett*. 2012;14:386-389.
70. Liu JWX, Dong S, Lin L, Feng X. Asymmetric organocatalytic cyclopropanation of cinnamone derivatives with stabilized sulfonium ylides. *J Org Chem*. 2013;78:6322-6327.

71. Bandar JS, Lambert TH. Enantioselective Brønsted base catalysis with chiral cyclopropenimines. *J Am Chem Soc*. 2012;134:5552-5555.

72. Arai S, Nakayama K, Ishida T, Shioiri T. Asymmetric cyclopropanation reaction under phase-transfer catalyzed conditions. *Tetrahedron Lett*. 1999;40:4215-4218.

73. Herchl R, Waser M. Stereoselective cyclization reactions under phase-transfer catalysis. *Tetrahedron*. 2014;70:1935-1960.

74. Donslund BS, Jessen NI, Jakobsen JB, Monleón A, Nielsen RP, Jørgensen KA. Enantioselective formation of cyclopropane spiroindenes from benzofulvenes by phase transfer catalysis. *Chem Commun*. 2016;52:12474-12477.

75. Herchl R, Waser M. Asymmetric cyclopropanation of chalcones using chiral phase-transfer catalysts. *Tetrahedron Lett*. 2013;54:2472-2475.

How to cite this article: Rapi Z, Nemcsok T, Pálvölgyi Á, Keglevich G, Grün A, Bakó P. Synthesis of L-threitol-based crown ethers and their application as enantioselective phase transfer catalyst in Michael additions. *Chirality*. 2017. https://doi.org/10.1002/chir.22678