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Asymmetric C–C bond formation via Darzens condensation and Michael addition using monosaccharide-based chiral crown ethers

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ABSTRACT

Liquid–liquid phase asymmetric Darzens condensations were promoted by D-glucose- and D-mannose-based crown ethers. The corresponding aromatic and heteroaromatic α,β-epoxyketones were obtained with moderate to high enantioselectivities (up to 96%) as well as diastereoselectivities (up to 98:2) under mild reaction conditions. The absolute configurations of several of the epoxyketones were determined by single crystal X-ray analysis. The Michael additions of diethyl acetylaminomalonate to *trans*-β-nitroalkenes were carried out in a solid–liquid two-phase system in the presence of a D-glucose-based crown catalyst with up to 99% ee.

An attractive approach in catalytic asymmetric synthesis is the phase-transfer catalytic technique in which the enantioselectivity is generated by a chiral crown catalyst.[1] Optically active crown ethers in this prominent group contain a carbohydrate moiety as the source of chirality. However, until now, only a limited number of asymmetric reactions have been reported, in which the application of a monosaccharide-based crown catalyst resulted in a good enantioselectivity.[2] Previously, chiral monoaza-15-crown-5 type macrocycles incorporating an α-D-glucopyranoside or an α-D-mannopyranoside unit (**1** and **2**) were synthesized in our laboratory, and proved to be efficient catalysts in a few asymmetric reactions.[3]

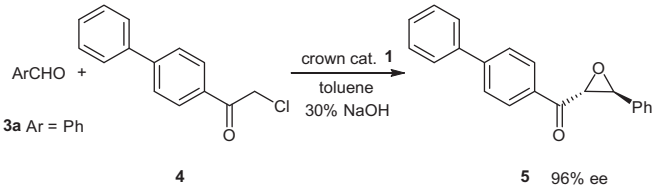
Herein we report two model reactions, a Darzens condensation and a Michael addition, in which the monosaccharide-based chiral macrocycles generated high enantioselectivities in the products.

Chiral epoxides are well-known building blocks in the preparation of optically pure bioactive compounds and this explains the current interest in the enantioselective synthesis of chiral epoxides. One of the simplest ways to prepare chiral epoxides involves a Darzens condensation carried out under phase-transfer catalytic conditions in the presence of optically active catalysts.[4]

We describe the asymmetric Darzens condensation of aromatic and heteroaromatic chloromethyl ketones with various aromatic aldehydes. The reactions were carried out in a liquid–liquid two-phase system in toluene, employing 30% aq NaOH as the base and 7 mol % of chiral crown catalyst **1** or **2** at a temperature of −5 °C. The products were isolated by preparative TLC and found to be *trans*-epoxyketones in all cases. The asymmetric induction expressed in terms of the enantiomeric excess (ee), was determined by ^{1}H NMR analysis in the presence of Eu(hfc)$_3$ as the chiral shift reagent.[5a] 4-Phenyl-phenacyl chloride (**4**) was found to be a promising reagent for the Darzens condensation with benzaldehyde (**3a** Ar = Ph) (Scheme 1).

After a 3-h reaction time at rt in the presence of catalyst **1**, *trans*-epoxyketone **5** was formed in a yield of 50% and de of >98% as a mixture containing the antipode with negative optical rotation in 96% ee (100% ee after recrystallization).[5b] The use of the mannose-based crown ether **2** promoted formation of the enantiomer with positive optical rotation in an ee of 65% (Fig. 1).

On the other hand, the Darzens condensation of heteroaromatic α-chloroacetyl derivatives **6** and **8** with aromatic aldehydes was



Scheme 1.

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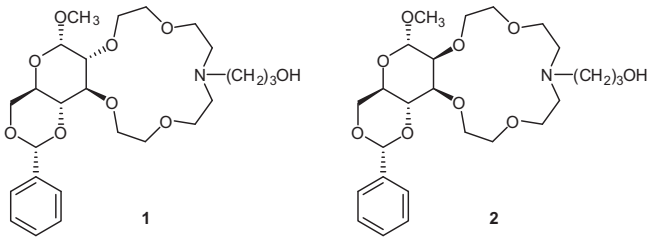
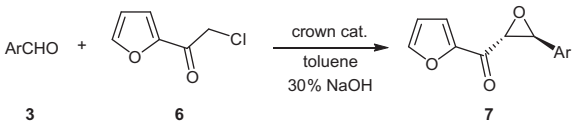
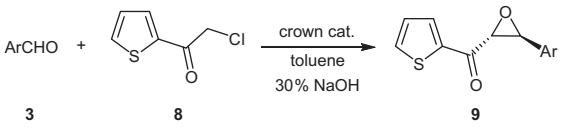


Figure 1. Crown ethers **1** and **2** incorporating an α-D-glucopyranoside and an α-D-mannopyranoside unit.



Scheme 2.



Scheme 3.

Table 1
Asymmetric Darzens condensation of 2-chloroacetylfuran (**6**) with aromatic aldehydes in the presence of catalyst **1** at −5 °C

Entry	Ar	Time (h)	Yield[a] (%)	$[\alpha]_D^{22}$[b]	ee[c] (%)
1	Ph	8	**7a**: 55	−117.7	54
2	2-H_3C–C_6H_4	12	**7b**: 64	−33.1	57 (72)
3	2-Cl–C_6H_4	5	**7c**: 77	−14.9	70 (91)
4	4-Cl–C_6H_4	3	**7d**: 67	−146.5	62
5	Piperonyl	3	**7e**: 45	−151.3	64
6	2-Naphthyl	1	**7f**: 30	−73.6	28

[a] Based on isolation by preparative TLC.
[b] In $CHCl_3$, $c = 1$.
[c] Determined by ^1H NMR spectroscopy, the ee given in parentheses was obtained after one recrystallization from EtOH.

Table 2
Asymmetric Darzens condensation of 2-chloroacetylthiophene (**8**) with aromatic aldehydes in the presence of catalyst **1**, at −5 °C

Entry	Ar	Time (h)	Yield[a] (%)	$[\alpha]_D^{22}$[b]	ee[c] (%)
1	Ph	5	**9a**: 63	−169.8	71 (84)
2	2-Cl–C_6H_4	4.5	**9b**: 53	−10.0	51
3	3-Cl–C_6H_4	6	**9c**: 56	−142.1	60 (75)
4	4-Cl–C_6H_4	20	**9d**: 54	−139.0	65 (79)
5	4-F–C_6H_4	22	**9e**: 55	−119.7	62 (73)
6	2-H_3C–C_6H_4	3	**9f**: 79	−45.7	68 (85)
7	1-Naphthyl	5	**9g**: 87	+54.0	64 (75)
8	2-Naphthyl	6	**9h**: 54	−163.0	62
9	Piperonyl	5	**9i**: 57	−131.5	86 (100)

[a] Based on isolation by preparative TLC.
[b] In $CHCl_3$, $c = 1$.
[c] Determined by ^1H NMR spectroscopy, the ee given in parentheses was obtained after one recrystallization from EtOH.

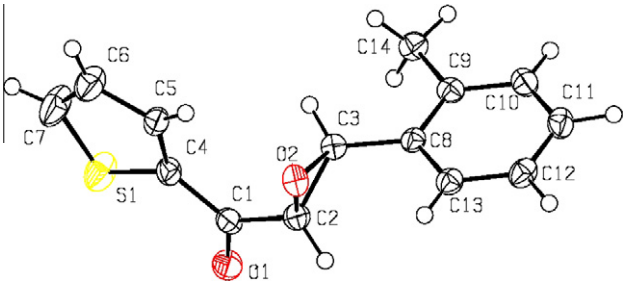


Figure 2. Compound **9f**: ORTEP representation at 50% probability level.

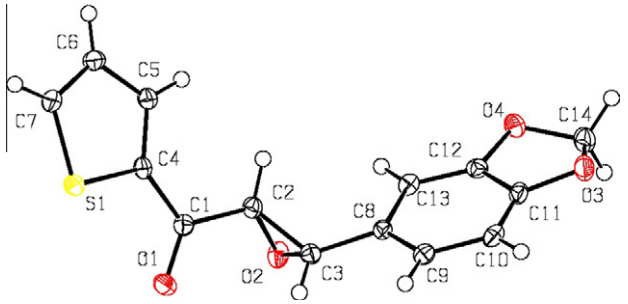


Figure 3. Compound **9i**: ORTEP representation at 50% probability level.

also studied using the same conditions, but at −5 °C (Schemes 2 and 3). (There was no asymmetric induction with aliphatic aldehydes.)

Experimental data for the reactions of 2-chloroacetylfuran (**6**) are listed in Table 1.

trans-Epoxyketones **7a–f** were formed with negative optical rotation values in yields ranging from 30% to 77%. Reaction of **6** with benzaldehyde gave the 2*R*,3*S*-epoxyketone (**7a**) in an enantiomeric excess of 54%.[6] The use of substituted benzaldehydes led to increased ee values (57–70%). The maximum selectivity was obtained in the reaction of 2-chlorobenzaldehyde, epoxide **7c** being formed in 70% ee.[5c] Recrystallization of epoxyketones **7b** and **7c** from ethanol resulted in higher ee values of 72% and 91%, respectively.

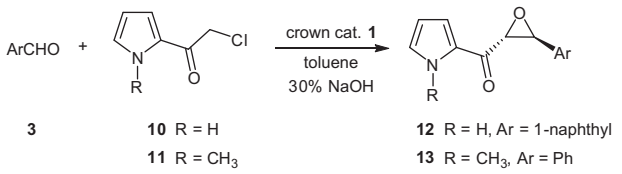
A reverse trend was experienced in the phase-transfer Darzens reaction of 2-chloroacetylthiophene (**8**), (Scheme 3, Table 2).

In the reaction of 2-chloroacetylthiophene (**8**) with benzaldehyde, product **9a** was formed in 71% ee.[7] The use of substituted benzaldehydes led to lower ee values of 51–68% (Table 2, entries 2–8). In the substituted series, 2-methylbenzaldehyde gave the best optical purity (68% ee). After recrystallization this value increased to 85%. It is noteworthy, that the more distant the chloro atom is situated from the reaction center, the greater the extent of asymmetric induction, the best ee (65%) being obtained with *p*-chlorobenzaldehyde. It is worth mentioning that the use of 1-naphthaldehyde and 2-naphthaldehyde led to products **9g** and **9h** with opposite optical rotation, but approximately the same ee value. The reaction of chloroacetylthiophene with piperonal gave the best enantioselectivity (86%). Moreover, after completion of the reaction, about half of epoxyketone **9i** precipitated from the mixture as the pure enantiomer (100% ee).[5d]

To the best of our knowledge, only Arai et al., have reported high enantioselectivities of up to 86% ee for the reaction of cyclic α-chloroketones and aldehydes in the presence of a cinchonine derivative after reaction times of 80–200 h.[8]

In the reactions shown in Schemes 2 and 3, the mannose-based crown ether **2** generated lower enantioselectivities using benzaldehyde, products **7a** and **9a** (both with positive optical rotation) being obtained in ee's of 42% and 59%, respectively.

Repeated recrystallization of products **9f** and **9i** led to pure enantiomers whose absolute configurations were determined by



3 10 R = H; 11 R = CH_3 12 R = H, Ar = 1-naphthyl; 13 R = CH_3, Ar = Ph

Scheme 4.

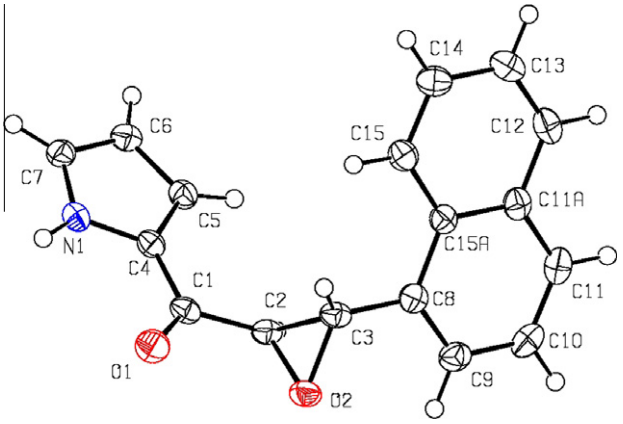
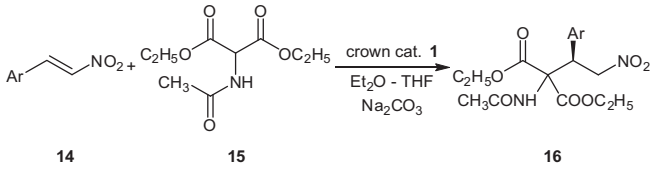


Figure 4. Compound **12**: ORTEP representation at 50% probability level.



14 15 16

Scheme 5.

single crystal X-ray analysis. In both cases the configuration of the chiral carbon atoms was found to be 2*R*,3*S* (Figs. 2 and 3).[5d,9]

Analogous reactions between aromatic aldehydes and 2-chloroacetylpyrrole (**10**) or *N*-methyl-2-chloroacetylpyrrole (**11**) under similar conditions took place (Scheme 4) but led to lower enantioselectivities (16–51% ee). The best result was achieved with 1-naphthaldehyde (51% ee). Compound **12** (Ar = 1-naphthyl) could be purified by repeated recrystallization and the absolute configuration was found to be 2*R*,3*S* after a single crystal X-ray study (Fig. 4).[5e]

The Michael reaction of nitroalkanes represents a convenient access to substituted nitroalkanes which are versatile intermediates in organic synthesis. The nitro functionality can be easily converted into other groups, giving access to a wide range of synthetically important compounds. Although catalytic asymmetric versions of this reaction have been developed, most required metal catalysts or forcing reaction conditions. The addition of diethyl acetamidomalonate to nitroalkenes has also been studied. These malonate reactions can be used to prepare pyrrolidinones. Furthermore, homogeneous catalytic methods have led generally to moderate to good enantioselctivities.[10]

We report the development of a highly selective conjugate addition of diethyl acetamidomalonate (**15**) to nitrostyrene derivatives **14** under phase-transfer conditions in the presence of monosaccharide-based crown ether **1** (Scheme 5, Table 3).[11a]

The Michael addition was carried out in a solid–liquid two-phase system employing 15 mol % of crown ether **1**. The organic phase comprised the starting materials and the catalyst in a mixture of THF–ether (4:1). Na_2CO_3, used in twofold excess, formed the solid phase. The products (**16a**–**g**) were obtained by preparative TLC, while the optical purity was measured by chiral HPLC. After reaction times of 2–7 h, ee values ranging from 34% to 99% were obtained in the presence of catalyst **1**. The best results were obtained with β-nitrostyrene **14a** and *p*-chloro-β-nitrostyrene **14d** leading to an ee of 99% in both cases.[11b] The absolute configuration of Michael adduct **16a** with negative optical rotation was (*S*).[10b] It is noteworthy that the mannose-based catalyst **2** was completely inefficient but the reason for this is unclear.

Table 3
Michael addition of diethyl acetamidomalonate (**15**) to *trans*-β-nitroalkenes in the presence of catalyst **1**

Entry	Ar	Time (h)	Yield[a] (%)	$[\alpha]_D^{22}$[b]	ee[c] (%)
1	Ph	3	**16a**: 60	−42.8	99
2	2-Cl–C_6H_4	3.5	**16b**: 76	−11.1	67
3	3-H_3CO–C_6H_4	2	**16c**: 51	−25.3	60
4	4-Cl–C_6H_4	4	**16d**: 45	−35.5	99
5	4-O_2N–C_6H_4	6	**16e**: 78	−11.1	97
6	4-H_3CO–C_6H_4	4	**16f**: 39	−6.4	34
7	Piperonyl	7	**16g**: 52	−32.5	72

[a] Based on isolation by preparative TLC.
[b] In $CHCl_3$, $c = 1$.
[c] Enantioselectivities were determined by chiral HPLC analysis in comparison with authentic racemic material.

In summary, the α-D-glucopyranoside-based chiral crown ether **1** afforded moderate to good enantioselectivities in the phase-transfer Darzens condensation of aromatic aldehydes with 2-chloroacetylfuran (up to 70% ee), 2-chloroacetylthiophene (up to 86% ee), 4-phenyl-phenacyl chloride (96% ee). The reactions of 2-chloroacetylpyrrole and *N*-methyl-2-chloroacetylpyrrole led to lower enantioselectivities (up to 51% ee) The addition of diethyl acetamidomalonate to *trans*-β-nitroalkenes resulted in 34–99% ee values in the presence of catalyst **1**.

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5. (a) *General procedure for the Darzens condensation*: A toluene solution (3 mL) of aromatic 2-chloroketone (1.87 mmol), aromatic aldehyde (2.8 mmol) and the crown ether (0.14 mmol) was cooled to −5 °C, and treated with 30% aqueous NaOH (1 mL). The mixture was stirred at this temperature for 1–22 h. A mixture of toluene (7 mL) and H_2O (3 mL) was added and the solution stirred for 10 min. The organic phase was washed with cold 10% HCl (3 × 10 mL) and H_2O (20 mL), dried (Na_2CO_3) and concentrated. The crude product was purified on silica gel by preparative TLC with hexane–EtOAc (10:1) as eluent. The enantioselectivities were determined by ^1H NMR spectroscopy in the presence

of Eu(hfc)$_3$ as the chiral shift reagent.; (b) *Compound* **5**: $[\alpha]_D^{22} = -155.2$ (*c* 1, CH_2Cl_2, 96% ee); after crystallization: $[\alpha]_D^{22} = -173.1$ (*c* 1, CH_2Cl_2, 100% ee). Mp 130–132 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 4.11 (d, *J* = 1.5 Hz, 1H), 4.34 (d, *J* = 1.5 Hz, 1H), 7.36–7.52 (m, 8H), 7.63 (d, *J* = 8.4 Hz, 2H), 7.71 (d, *J* = 8.4 Hz, 2H), 8.10 (d, *J* = 8.4 Hz, 2H).; (c) *Compound* **7c**: yield: 77%; $[\alpha]_D^{22} = -14.9$ (*c* 1, $CHCl_3$, 70% ee); after one crystallization: 91% ee. Mp 82–85 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 4.03 (s, 1H), 4.48 (s, 1H), 6.61 (d, *J* = 2 Hz, 1H), 7.28–7.42 (m, 4H), 7.47 (d, 1H), 7.69 (s, 1H).; (d) *Compound* **9i**: yield: 57%; $[\alpha]_D^{22} = -131.5$ (*c* 1, CH_2Cl_2, 86% ee); after crystallization: $[\alpha]_D^{22} = -268.8$ (*c* 1, CH_2Cl_2, 100% ee); Mp: 108–110 °C; ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ (ppm) = 4.06 (s, 1H), 4.09 (s, 1H), 5.99 (s, 2H), 6.75–6.89 (m, 3H), 7.18 (s, 1H), 7.74 (d, *J* = 4.5 Hz, 1H), 8.00 (s, 1H).*Crystal data for* **9i**: CCDC 794986 contains the supplementary crystallographic data for this structure. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.; (e) *Compound* **12**: yield: 32%; $[\alpha]_D^{22} = +24.9$ (*c* 1, $CHCl_3$, 51% ee); after repeated crystallization: $[\alpha]_D^{22} = +56.5$ (*c* 1, $CHCl_3$, 100% ee); Mp 168 °C (dec) ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 4.04 (s, 1H); 4.79 (s, 1H); 6.35 (t, *J* = 3.5 Hz,1H); 7.16–7.20 (m, 2H); 7.48–7.54 (m, 3H); 7.58 (d, *J* = 7 Hz, 1H); 7.86 (d, *J* = 8.5 Hz, 1H); 7.91 (t, *J* = 4.5 Hz, 1H); 8.01 (t, *J* = 4.5 Hz, 1H); 9.67 (br s, 1H, NH).*Crystal data for* **12**: CCDC 794984 contains the supplementary crystallographic data for this structure. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.*Absolute configuration crystal data*: Rigaku R-AXIS Rapid Diffractometer, CuKα radiation, λ = 1.54187 Å, *T* = 133(2) K, *R* = 3.08, R_w = 7.78, *N* = 2414, Friedel Pair Coverage = 95%, Flack parameter: 0.1(2), Hooft parameter: 0.09(10).

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9. *Crystal data for* **9f**: CCDC 794985 contains the supplementary crystallographic data for this structure. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
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11. (a) *General Procedure for the Michael addition*: The *trans*-β-nitroalkene (1.01 mmol), diethyl acetamidomalonate (**15**) (1.47 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 (2.08 mmol) was added. The reaction mixture was stirred at room temperature. After completion of the reaction (2–7 h), the organic phase was concentrated in vacuo and the residue was dissolved in toluene (10 mL) and washed with cold 10% HCl (3 × 10 mL) and water (20 mL), dried (Na_2CO_3) and concentrated. The crude product was purified on silica gel by preparative TLC with hexane–EtOAc (3:1) as eluent. Enantioselectivities were determined by chiral HPLC analysis using a Chiralpack AD column, (20 °C, 256 nm, 85:15 hexane/*i*-PrOH, 0.8 mL/min) in comparison with authentic racemic material; R_t = 17.8 min (major), R_t = 27.7 min (minor).; (b) *Data for* **16d**: $[\alpha]_D^{22} = -35.5$ (*c* 1, $CHCl_3$, 99% ee). Mp 126–128 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.23 (t, 3H, *J* = 7.1 Hz), 1.25 (t, 3H, *J* = 7.1 Hz), 2.12 (s, 3H), 4.03 (dq, 1H, *J* = 10.7, 7.2 Hz), 4.15 (dq, 1H, *J* = 10.7, 7.2 Hz), 4.24 (dq, 1H, *J* = 10.7, 7.2 Hz), 4.29 (dq, 1H, *J* = 10.7, 7.2 Hz), 4.59–4.71 (m, 2H), 5.50 (dd, 1H, *J* = 21.7, 12.2 Hz), 6.69 (br s, 1H), 7.14 (d, 2H, *J* = 8.4 Hz), 7.28 (d, 2H, *J* = 8.7 Hz).