Phase Transfer Catalysed Asymmetric Epoxidation of Chalcones Using Chiral Crown Ethers Derived from D-Glucose and D-Mannose

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Abstract: New chiral monoaza-15-crown-5 lariat ethers synthesized from D-mannose and the glucose-based crown ethers of similar type generated significant asymmetric induction as phase transfer catalysts in the epoxidation of chalcones with *tert*-butyl-hydroperoxide (80–92% ee).

Key words: chiral crown ethers, asymmetric phase transfer catalysis, lariate ether, asymmetric epoxidation

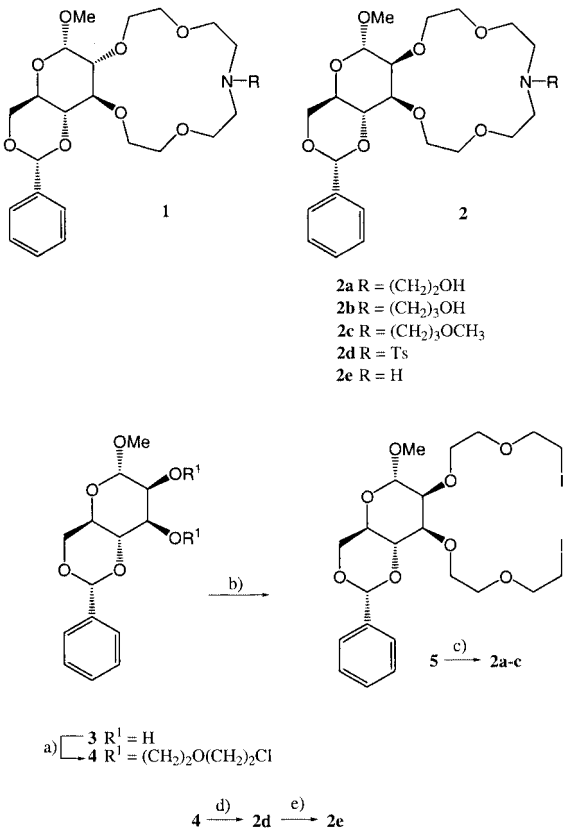
One of the most attractive approaches in catalytic asymmetric syntheses is the phase transfer catalytic technique in which the enantioselectivity is generated by a chiral crown ether catalyst.[1] A prominent group of optically active crown ethers contains carbohydrate moiety as the source of chirality. Although a number of chiral crown ethers have been prepared from monosaccharides,[2] only a few of them have been successfully used as catalysts in asymmetric reactions.[3] Recently, we have reported an asymmetric Michael addition and a Darzens condensation, in which the glucose-based chiral lariat ethers of type **1** generated high enantioselectivity (95% and 72%, respectively).[3,4] Now, we describe a new model reaction, in which the macrocycle **1** proved to be an effective catalyst, namely the epoxidation of chalcones under phase transfer conditions. New crown ethers of similar type incorporating a mannopyranoside unit (**2**) have been synthesized that could also be used in the above reaction.

Recently, efficient methods have been developed for the enantioselective epoxidation of α,β-enones applying poliamino acid catalysts,[5a,b] chiral phase transfer catalysts,[5c–e] chiral ligand-metal peroxide systems,[5f,g] and lanthanide-BINOL systems.[5h,i]

In this communication, the asymmetric epoxidation of chalcone is investigated in the presence of glucose- and mannose-based lariat ether catalysts **1** and **2** respectively.

The glucose-based crown ethers (**1**) were available by earlier methods,[6] while the mannose-based compounds **2** have been synthesized in analogous manner, via intermediates **3**–**5** (Scheme 1).

The vicinal hydroxy groups of the 4,6-*O*-benzylidene-α-D-mannopyranoside **3** were alkylated with bis(2-chloroethyl) ether in liquid-liquid two-phase system, in the presence of tetrabutylammonium hydrogen sulfate and 50% aqueous NaOH to give intermediate **4** after chromatography.[7]



Scheme 1 Reagents and conditions: a) $O(CH_2CH_2Cl)_2$, 50% aq NaOH, NBu_4HSO_4, 89%; b) NaI, acetone, reflux; c) RNH_2, Na_2CO_3, CH_3CN, reflux, 44–53%; d) $TsNH_2$, K_2CO_3, DMF, reflux, 55%; e) 4% Na/Hg_x, Na_2HPO_4, MeOH, reflux, 92%.

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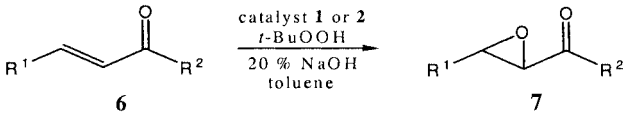
The exchange of chlorine for iodine in **4** was accomplished by NaI in acetone resulting in bis-iodo derivative **5**. Compound **5** was cyclized with various primary amines such as: ethanolamine, propanolamine and 3-methoxypropanolamine, in MeCN, in the presence of dry Na_2CO_3 to give **2a**, **2b** and **2c**, respectively by the extension of the method described.[6] After chromatography, the 15-membered macrocycles **2a**–**c** were obtained in 44–53%.

The *N*-tosyl macrocycle **2d** needed for the preparation of the unsubstituted derivative **2e** was obtained from dichloro intermediate **4** by treatment with one equivalent of *para*-toluene-sulfonamide in diluted DMF solution in the presence of dry K_2CO_3 in a yield of 55%. The tosyl group of **2d** was removed by 4% sodium amalgam in MeOH to give **2e** in a yield of 92% (Scheme 1). All new products and intermediates were characterised by ^{1}H NMR and mass spectroscopy. The elemental composition was supported by elemental analysis.

The epoxidation of chalcones **6** with *tert*-butyl hydroperoxide (TBHP, 2 equiv) was carried out in a liquid-liquid two-phase system in toluene, employing 20% aq NaOH (3.5 equiv) as the base and 7 mol% of chiral crown catalyst at a temperature of 5–6 °C (Scheme 2).

After the usual work-up procedure the product was isolated by preparative TLC. The asymmetric induction, expressed in terms of the enantiomeric excess (ee), was monitored by measuring the optical rotation of the product



Scheme 2

(**7a**, $R^1 = R^2$ = Ph) and comparing it with literature values and by ^{1}H NMR analysis using (+)-Eu(hfc)$_3$ as a chiral shift reagent (**7a**–**m**). The *trans*-epoxyketone **7** was obtained in all experiments.

Table 1 summarizes the results obtained in the presence of glucose- and mannose-based lariat ethers **1a**–**i** and **2a**–**e**, respectively, as catalyst. It can be seen that the yields and the enantioselectivities are significantly affected by the N-substituents. With respect to the activity of the glucose-based lariat ethers (**1a**–**i**, entries 1–9), one observes that the lowest enantiomeric excess values (ca 8–11%) were recorded in the case of catalysts **1b**, **1c** and **1i** containing a *n*-butyl, a benzyl and a diphenylphosphinobutyl N-substituent, respectively. The best results (92% and 81% ee) were obtained applying catalysts with γ-hydroxypropyl and β-hydroxyethyl substituents (**1f** and **1d**, respectively), but the 41% of ee detected using the δ-hydroxybutyl derivative (**1h**) is also considerable. It can be concluded that the length of the chain connecting the hydroxy group to the nitrogen atom plays an important role in the asymmetric induction and the optimum length is of three

Table 1 Effect of Chiral Crown Catalysts **1** and **2** on the Asymmetric Epoxidation of Chalcone (**6a**, $R^1 = R^2$ = Ph) by *t*-BuOOH, at 5 °C

Entry	Catalyst Compound	R	Time (h)	Yield[a] of **7a** (%)	$[\alpha]_D$[b]	ee[c] (%)
1	**1a**	H	4	47	+59	28
2	**1b**	Butyl	10	59	–24.3	11
3	**1c**	Benzyl	10	33	–16	8
4	**1d**	$(CH_2)_2OH$	1	65	–173	81 (82)[d]
5	**1e**	$(CH_2)_2OCH_3$	3	58	–43	20
6	**1f**	$(CH_2)_3OH$	1	82	–196	92 (94)[d]
7	**1g**	$(CH_2)_3OCH_3$	2	61	–49	23
8	**1h**	$(CH_2)_4OH$	1	65	–88	41
9	**1i**	$(CH_2)_4P(O)Ph_2$	2	64	–23	11
10	**2e**	H	9	25	+20	9
11	**2a**	$(CH_2)_2OH$	3	70	+154	72 (71)[d]
12	**2b**	$(CH_2)_3OH$	2	72	+171	80 (82)[d]
13	**2c**	$(CH_2)_3OCH_3$	6	67	+66	31

[a] Based on isolation by preparative TLC.
[b] In CH_2Cl_2 at 22 °C.
[c] Determined by optical rotation.
[d] Determined by ^{1}H NMR spectroscopy in the presence of Eu(hfc)$_3$ as chiral shift reagent.

carbon atoms as in **1f**. It is also important to see that methylation of the hydrophilic functions in **1d** and **1f** resulted in a dramatic decrease in the enantioselectivity as demonstrated by the ee of 20% and 23% obtained with **1e** and **1g**, respectively. It is clear that the hydrophilic substituents ensure a better transport of the catalyst between the toluene–water two-phase system, while the lipophilic $(CH_2)_nOMe$ substituents prevent the transport between the phases. The discrimination between the prochiral plane of the chalcone is the most efficient when catalyst **1f** assists the formation of the transient complex.

Remarkably, the use of catalysts **1b–i** promoted the formation of an excess of epoxyketone **7a** with negative optical rotation that is of 2*R*,3*S* configuration.[8] At the same time, in the unsubstituted case **1a**, the formation of the antipode with positive rotation was formed in excess (entry 1).

In the experiments using lariat ethers bearing a mannose unit (**2a–c**, **2e**) as catalyst, the epoxyketone **7a** with a positive optical rotation (*2S*,*3R*) was formed in excess. With regard to the impact of the length of chain and the nature of the substituent in lariat ethers **2a–c** on the ee values, a similar tendency can be observed as with glucose-based catalysts **1d**,**f**,**g**.

The catalyst with hydrophilic hydroxyethyl substituent, and especially that with a hydroxypropyl arm **2a** and **2b** were efficient chiral inductors providing **7g** with an ee of 72% and 80%, respectively.

The epoxidation of a series of chalcones (**6a–m**, Table 2) was examined in the presence catalyst **1f** that seemed to be the most efficient in the enantioselective epoxidation of chalcone **6a**.

Due to solubility problems, the experiments were carried out at room temperature. The *trans* epoxy-ketones **7a–m** were formed in all cases and as the enantiomer with negative optical rotation. The oxidation of monosubstituted derivatives (**7b–d** and **7g**,**h**) took place with a higher enantioselectivity (77–82%, entries 2–4, 7 and 8), as compared with that of the unsubstituted chalcone (**7a**, 73% ee). Among the disubstituted chalcones, the epoxidation of the derivatives containing 4-chloro or 4-methyl group in both phenyl rings (**7j** and **7l**) led to an ee of ca 77% (entries 10 and 12). Presumably, the significant differences observed in the enantioselectivities are the consequences of steric and electronic effects. The substitution pattern influences the solubility and lipophilicity of the substrates.

To explain the efficiency of the chiral crown ether in this oxidation, one should assume the formation of the *t*-$BuOO^-$ anion,[9] which is accompanied by the crown-sodium cation and this *tert*-butylhydroperoxide anion attacks the electron-deficient alkene. With respect to the efficiency of the crown ether in asymmetric induction, it is assumed that the substituent on the nitrogen atom assists the complexation of the cation of the salt in the third dimension. The complexing interaction is optimum with the hydroxypropyl substituent. Hence, we could achieve a fine tuning regarding the structure of the catalyst and the highest enantioselectivity.

Table 2 Epoxidation of Substituted Chalcones by *t*-BuOOH in the Presence of Catalyst **1f** at Room Temperature

Entry	R^1	R^2	Time [h]	Yield[a] [%]	$[\alpha]_D$[b]	ee[c] [%]
1	Ph	Ph	1	**7a**, 78	–155.1	73
2	Ph	*p*-Me-Ph	3	**7b**, 62	–169.7	81
3	Ph	*p*-OMe-Ph	3	**7c**, 53	–167.9	82
4	Ph	*p*-Cl-Ph	1	**7d**, 57	–156.1	80
5	Ph	*o*,*p*-di-Cl-Ph	1	**7e**, 82	–91.1	47
6	Ph	*m*,*p*-di-Cl-Ph	0.5	**7f**, 61	–129.3	66
7	*p*-Me-Ph	Ph	3	**7g**, 57	–183.4	77
8	*p*-NO_2-Ph	Ph	2	**7h**, 38	–195.9	79
9	*p*-OMe-Ph	*p*-NO_2-Ph	4	**7i**, 29	–45.2	27
10	*p*-Cl-Ph	*p*-Cl-Ph	1	**7j**, 66	–154.7	77
11	*p*-F-Ph	*o*-Cl-Ph	1	**7k**, 77	–6.6	3
12	*p*-Me-Ph	*p*-Me-Ph	3	**7l**, 64	–171.9	76
13	*p*-Me-Ph	*o*,*p*-di-Cl-Ph	0.5	**7m**, 82	–87.8	42

[a] Based on isolation by preparative TLC.
[b] In CH_2Cl_2 at 22 °C.
[c] Determined by ^1H NMR spectroscopy in the presence of $Eu(hfc)_3$ as chiral shift reagent.

Acknowledgement

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(11) Selected data for **5**: $[\alpha]_D^{20}$ +18.0 (*c* = 1, $CHCl_3$). ^1H NMR: δ = 7.47 (d, 2 H, ArH), 7.36 (t, 3 H, ArH), 5.59 (s, 1 H, benzylidene-CH), 4.78 (s, 1 H, anomer-H), 4.24 (q, *J* = 10.1 Hz, 1 H, H-6), 4.06 (t, *J* = 9.6 Hz, 1 H, H-6), 3.66–4.00 (m, 16 H, OCH_2, H-2, H-3, H-4, H-5), 3.38 (s, 3 H, OCH_3), 3.26 (t, 2 H, CH_2I), 3.18 (t, 2 H, CH_2I). For **2a**: $[\alpha]_D^{20}$ +16.0 (*c* = 1, $CHCl_3$). ^1H NMR: δ = 7.48 (d, 2 H, ArH), 7.35 (t, 3 H, ArH), 5.30 (s, 1 H, benzylidene-CH), 4.75 (s, 1 H, anomer-H), 4.24 (q, *J* = 10.1 Hz, 1 H, H-6), 4.11 (t, *J* = 9.6 Hz, 1 H, H-6), 3.55–3.98 (m, 18 H, OCH_2, H-2, H-3, H-4, H-5), 3.37 (s, 3 H, OCH_3), 2.78 (t, 6 H, CH_2N). FAB–MS: 484 [M^+ + H], 506 [M^+ + Na]. For **2b**: $[\alpha]_D^{20}$ +15.0 (*c* = 1, $CHCl_3$). FAB–MS: 498 [M^+ + H], 520 [M^+ + Na]. For **2c**: $[\alpha]_D^{20}$ +19.6 (*c* = 1, $CHCl_3$). ^1H NMR: δ = 7.39 (d, 2 H, ArH), 7.27 (t, 3 H, ArH), 5.52 (s, 1 H, benzylidene-CH), 4.67 (s, 1 H, anomer-H), 4.16 (q, *J* = 10.1 Hz, 1 H, H-6), 4.02 (t, *J* = 9.6 Hz, 1 H, H-6), 3.45–3.95 (m, 18 H, OCH_2, H-2, H-3, H-4, H-5), 3.31 (s, 3 H, OCH_3), 3.24 (t, 3 H, OCH_3), 2.72 (t, 4 H, CH_2N), 2.56 (t, 2 H, CH_2N), 1.69 (m, 2 H, CH_2). FAB–MS: 512 [M^+ + H], 534 [M^+ + Na]. For **2d**: $[\alpha]_D^{20}$ +18.8 (*c* = 1, $CHCl_3$). ^1H NMR: δ = 7.71 (d, 2 H, tosyl-ArH), 7.49 (d, 2 H, tosyl-ArH), 7.38 (d, 2 H, ArH), 7.32 (t, 3 H, ArH), 5.62 (s, 1 H, benzylidene-CH), 4.74 (s, 1 H, anomer-H), 4.26 (q, *J* = 10.1 Hz, 1 H, H-6), 4.12 (t, *J* = 9.6 Hz, 1 H, H-6), 3.51–4.00 (m, 16 H, OCH_2, H-2, H-3, H-4, H-5), 3.40 (s, 3 H, OCH_3), 3.20–3.26 (m, 4 H, CH_2N), 2.44 (s, 3 H, CH_3). FAB–MS: 594 [M^+ + H], 616 [M^+ + Na]. For **2e**: $[\alpha]_D^{20}$ +26.3 (*c* = 1, $CHCl_3$). ^1H NMR: δ = 7.47 (d, 2 H, ArH), 7.35 (t, 3 H, ArH), 5.60 (s, 1 H, benzylidene-CH), 4.78 (s, 1 H, anomer-H), 4.25 (q, *J* = 10.1 Hz, 1 H, H-6), 4.14 (t, *J* = 9.6 Hz, 1 H, H-6), 3.55–4.08 (m, 16 H, OCH_2, H-2, H-3, H-4, H-5), 3.39 (s, 3 H, OCH_3), 2.85 (t, 2 H, CH_2N), 2.76 (t, 2 H, CH_2N), 2.55 (m, 1 H, NH). FAB–MS: 440 [M^+ + H], 462 [M^+ + Na].

(12) General Procedure for the Epoxidation of Chalcones: Chalcone (1.44 mmol) and the crown ether (0.1 mmol) were dissolved in 3 mL of toluene and 1 mL of 20% aq NaOH was added maintaining the temperature at 5 °C with ice water. Then 0.5 mL of *tert*-butylhydroperoxide (5.5 M decane solution, 2.88 mmol) was added and the mixture stirred at 5 °C. After completing the reaction (1–48 h), a mixture of 7 mL of toluene and 10 mL of water was added. The organic phase was dried (Na_2SO_4) and concentrated in vacuo. The crude product was purified on silica gel by preparative TLC with hexane–EtOAc (10:1) as eluent, for **7a** $[\alpha]_D$ = –196 (*c* = 1, CH_2Cl_2, 20 °C) with 92% ee (lit., $[\alpha]_D$ –214 for the pure enantiomer);[10] mp 64–66 °C (EtOH). ^1H NMR ($CDCl_3$): δ = 8.02 (d, 2 H, *o*-COPh-H), 7.63 (t, 1 H, *p*-COPh-H), 7.50 (t, 2 H, *m*-COPh-H), 7.38–7.44 (m, 5 H, CHPh-H), 4.30 (d, *J* = 1.9 Hz, 1 H, COCH), 4.09 (d, *J* = 1.9 Hz, 1 H, PhCH). For **7c**: $[\alpha]_D$ = –167.9 (*c* = 1, CH_2Cl_2, 20 °C) with 82% ee; mp 81 °C (EtOH). ^1H NMR: δ = 8.01 (d, 2 H, *o*-COPh-H), 7.39 (m, 5 H, CHPh-H), 6.95 (d, 2 H, *m*-COPh-H), 4.25 (d, *J* = 1.7 Hz, 1 H, COCH), 4.07 (d, *J* = 1.3 Hz, 1 H, PhCH), 3.87 (s, 3 H, OCH_3). For **7d**: $[\alpha]_D$ = –156.1 (*c* = 1, CH_2Cl_2, 20 °C) with 80% ee; mp 121 °C (EtOH). ^1H NMR: δ = 7.96 (d, 2 H, *o*-COPh-H), 7.46 (d, 2 H, *m*-COPh-H), 7.40 (t, 3 H, *m*,*p*-CHPh-H), 7.36 (d, 2 H, *o*-CHPh-H), 4.23 (d, *J* = 1.6 Hz, 1 H, CO*CH*), 4.07 (d, *J* = 1.3 Hz, 1 H, PhCH).