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# Recoverable polystyrene-supported catalysts for Sharpless allylic alcohols epoxidations



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ARTICLE INFO	A B S T R A C T
Keywords:	In this work, new heterogeneous catalysts intended for enantioselective Sharpless epoxidation were prepared.
Sharpless epoxidation	The catalysts are based on Ti(IV) complexes of cross-linked swellable spherical copolymer beads of styrene with
Recyclable catalyst Spherical copolymer beads Enantiomeric excess Heterogeneous catalysis	ethyl-(4-vinylbenzyl)-L-tartrate, or with ethyl-(2 <i>R</i> ,3 <i>R</i> )-2,3-dihydroxy-4-oxo-5-(4-vinylphenyl)pentanoate. These catalysts were tested in epoxidation of cinnamyl alcohols. High conversion (up to 99%) and high enantios- electivity (up to 99% ee) were achieved in the case of catalysts based on copolymers of styrene with ethyl-(4-vinylbenzyl)-L-tartrate (5, 20, 50%). Unfortunately, the copolymers lost their enantioselectivity due to the leaching of L-tartrate, caused by alcoholysis of ester bond. This problem has been overcome by replacing the
	ester bond by a stable keto bond. The prepared catalyst based on the copolymer of styrene with ethyl-(2R,3R)-
	2.3-dihydroxy-4-oxo-5-(4-yinylphenyl)pentanoate (20%) achieved a similarly high conversion and enantios-

electivity as in the previous case (up to 99%, up to 99% ee) and was successfully recycled.

#### 1. Introduction

Sharpless epoxidation (SE) of substituted allylic alcohols by organic peroxides catalysed by Ti(IV) complexes of esters of tartaric acid belongs to the earliest known and very often used asymmetric reactions (Scheme 1) [1,2].

Optically pure 2-hydroxymethyloxiranes (glycidols) prepared by SE represent an important class of organic intermediates, which are applicable for the synthesis of many other multifunctional target molecules with defined chiral centres, such as natural compounds or drugs and their intermediates [3]. Nevertheless, experimental performance of SE is in some cases complicated by difficult separation of a homogeneous catalyst from the product [4-21]. This problem can be solved by application of esters of L-(+)-tartaric acid with poly(ethylene glycols), because such a polymeric catalyst can be separated and reused by means of precipitation with diethyl ether [18-20,22]. However, this method of isolation of the catalyst may not be acceptable for several reasons in industrial scale. From this point of view, easily separable heterogeneous catalysts are much more favourable. Heterogeneous catalysts based on Ti(IV) complexes of tartaric acid derivatives, which were immobilized on inorganic materials, represent recyclable forms of catalysts for SE [7-12]. Unfortunately, their maximal achieved enantioselectivity ranged only below 86% ee. Beside this, several studies examining the application of heterogeneous catalysts based on titanium (IV) complexes with different polyesters of L-(+)-tartaric acid in SE were published. However, only low enantioselectivity was found [5,14–16]. In more recent work [17], a post-modification strategy for preparation of a polymeric catalyst of SE was utilized. Herein, L-(+)-tartaric acid was attached in an ester form to chloromethylated polystyrenes (PS), cross-linked by divinylbenzene (DVB) (1% or 2%), tetra(ethylene glycol)-diacrylate (TEGDA) (1% or 2%) or diallyl-L-tartrate [17] (Scheme 2). These catalysts were recycled three times without any loss in yield and/or enantioselectivity in SE (Scheme 2) [17].

The aim of this work was the preparation of highly efficient heterogeneous recyclable catalysts for SE based on copolymers of styrene with an appropriate monomer of L-(+)-tartaric acid ester or with another analogical monomer (Scheme 3). The swellable funcionalized copolymers of styrene (*e.g.* Merrifield resin<sup>TM</sup> [23], JandaJel resin<sup>TM</sup> [24]) belong among the most useful carriers of catalysts [25–29], because they can be easily chemically modified due to their high reactivity. The remarkable advantage of such PS-supported catalysts lies in their simple separation and reusability, their low price and also in the possibility of their usage in non-hazardous continuous-flow procedures.

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Scheme 1. General scheme of Sharpless asymmetric epoxidation of allylic alcohols [1].

#### 2. Experimental

#### 2.1. Materials and instrumentation

The FT-IR spectra were recorded on FT-IR Nicolet iS50 using the ATR technique. The region of diamond crystal absorption  $(1900-2400 \text{ cm}^{-1})$  was removed from the spectra – in the case of absence of characteristic bands in this region.

NMR spectra were measured at room temperature using Bruker AVANCE III 400 or Bruker Ascend<sup>™</sup> 500. <sup>1</sup>H NMR spectra were calibrated to tetramethylsilane. <sup>13</sup>C NMR spectra were calibrated to the middle signal of the multiplet of used solvent. <sup>13</sup>C NMR spectra were measured with APT technique and with proton decoupling. <sup>13</sup>C NMR spectra of solid phase were measured by CP/MAS without a standard.

Mass spectra with high resolution were measured by "dried droplet" method on the MALDI mass spectrometer LTQ Orbitrap XL (Thermo Fisher Scientific, Bremen, Germany) equipped with a nitrogen UV laser (337 nm, 60 Hz). The spectra were taken in the positive ion mode with the resolution 100,000 at m/z = 400. The resulting spectrum represents an average of all measurements. The used matrix was 2,5-dihydrox-ybenzoic acid (DHB).

HPLC analysis were performed using the HPLC instrument with the UV–Vis diode array (200–800 nm) SYKAM 3240 and with chiral columns Daicel Chiralcel OD-H, OB-H, OJ-H. Optical rotation was measured on the Perkin Elmer Polarimeter Model 341 with a sodium-vapour lamp at the wavelength  $\lambda$  = 589 nm and the temperature 20 °C.

The samples were analysed using the scanning electron microscope TESCAN VEGA3 SBU with the EDX probe Bruker XFlash Detector 410-M. Accelerating voltage of the primary electron beam was 15 kV in the low vacuum mode ( $\sim$ 11 Pa). EDX spectra were performed using the point analysis and the mass concentration (in %) is an average of three measurements.

Measurement of swelling capacity of the prepared resin was done according to the method described in literature [30].

The starting chemicals were purchased from commercial resources and used without further purification. Column chromatography was performed on silica gel (SiO<sub>2</sub> 60, particle size 0.040–0.063 mm, Merck) with the use of commercially available solvents. Thin layer chromatography was performed on aluminium plates coated with silica gel SiO<sub>2</sub> with visualization by UV light (254 or 366 nm). Flash chromatography was performed on Reveleris<sup>®</sup> X2 on silica gel packed columns. Melting points were determined in open capillaries on Buchi B-540 and were not corrected.

#### 2.2. Preparation of monomers

#### 2.2.1. Ethyl-(4-vinylbenzyl)-L-tartrate (3)

The mixture of sodium ethyl-L-tartrate (12 g; 60 mmol), diMeOPEG (5 g), NaI (0.5 g) and hydroquinone (0.5 g) in DMF (600 ml) was heated to 85 °C under argon atmosphere, while 4-vinylbenzyl chloride (8 ml; 56.8 mmol) was added. After 17 days of stirring at 85 °C, the mixture was filtered through Celite<sup>®</sup> (5 g). The filtrate was evaporated to dryness and extracted several times in the system water – diethyl ether. Combined organic layers were dried over MgSO<sub>4</sub> and evaporated. The crude product was purified by column chromatography (AcOEt/hexane 1/1,  $R_{\rm F} = 0.55$ ) giving a white waxy solid **3** (10.8 g; 61%); mp: 43–44 °C.

[*a*]<sub>D</sub><sup>20</sup> -2.7 (CHCl<sub>3</sub>, *c* 1 g/100 ml); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ ppm: 7.42 (d, *J* = 8.2 Hz, 2H, C<u>H</u><sub>Ar</sub>), 7.34 (d, *J* = 8.2 Hz, 2H, C<u>H</u><sub>Ar</sub>), 6.72 (dd, *J* = 17.6, 10.9 Hz, 1H, Ar-C<u>H</u>=), 5.78 (d, *J* = 17.6 Hz, 1H, = C<u>H</u><sub>2</sub>), 5.29 (d, *J* = 10.8 Hz, 1H, =C<u>H</u><sub>2</sub>), 5.27 (dd, *J* = 19.6, 12.0 Hz, 2H, C<u>H</u><sub>2</sub>-Ar), 4.59 (dd, *J* = 7.3, 1.6 Hz, 1H, C<u>H</u>), 4.56 (dd, *J* = 6.9, 1.7 Hz, 1H, C<u>H</u>), 4.31 (dq, *J* = 7.1, 2.0 Hz, 2H, C<u>H</u><sub>2</sub>(Et)), 3.18 (d, *J* = 6.8 Hz, 1H, O<u>H</u>), 3.16 (d, *J* = 7.3 Hz, 1H, O<u>H</u>), 1.32 (t, *J* = 7.1 Hz, 3H, C<u>H</u><sub>3</sub>). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ ppm: 2 × 171.4, 138.0, 136.1, 134.1, 128.7, 126.4, 114.7, 72.1, 71.9, 67.8, 62.5, 14.1; FT-IR (ATR) cm<sup>-1</sup>: 3473; 3087; 3054–3006; 2982–2939; 1735; 1370; 1220; 1123; 1085; 913; 827. HRMS *m/z*: Calculated: [M + Na]<sup>+</sup> 317.10011; Found: [M + Na]<sup>+</sup> 317.10022; Δ = 0.35 ppm.

# 2.2.2. Ethyl-(2R,3R)-2,3-dihydroxy-4-oxo-5-(4-vinylphenyl)pentanoate (4)

To the suspension of magnesium (1 g; 41.1 mmol) in dry diethyl ether (50 ml; dried over 4 Å MS) containing 3 drops of CH<sub>3</sub>I, 4-vinylbenzyl chloride (3.2 ml; 22.7 mmol) was added portion-wise under ultrasonication (400 W) during 1 h. The mixture was stirred for an additional one hour at room temperature. The prepared solution of 4-vinylbenzylmagnesium chloride was cannulated within 15 min to the solution of diethyl-2,3-O-benzylidene-L-tartrate (6 g; 20.4 mmol) in dry DCM (40 ml) at -78 °C. In the course of 16 h, the reaction mixture was gradually heated to r.t. and the reaction was quenched by the addition of a saturated solution of NH<sub>4</sub>Cl (50 ml). The mixture was extracted with diethyl ether (3  $\times$  50 ml). The combined organic layers were washed with brine (50 ml), water (50 ml), dried over MgSO4 and evaporated. While cooling (0 °C), TFA (10 ml) containing 5 drops of water was added to the residue. The reaction progress was monitored by TLC  $(\sim 5 \text{ min})$ . After the disappearance of the starting compound, the mixture was diluted with AcOEt (50 ml) and neutralized by the step-wise addition of solid NaHCO<sub>3</sub>. After adding water (50 ml), the organic layer was removed and the water layer was extracted with AcOEt  $(3 \times 50 \text{ ml})$ . The combined organic layers were dried over MgSO<sub>4</sub> and evaporated. The residue was subjected to column chromatography (AcOEt/hexane 1:2,  $R_{\rm F}$  = 0.16), giving a white crystalline product 4 (1.12 g; 4.64 mmol); 23%; mp: 85-86 °C.

[*a*]<sub>D</sub><sup>20</sup> -0.68 (CHCl<sub>3</sub>, *c* 1 g/100 ml); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ ppm: 7.43–7.35 (m, 2H, CH<sub>Ar</sub>), 7.22–7.15 (m, 2H, CH<sub>Ar</sub>), 6.70 (dd, J = 17.6, 10.9 Hz, 1H, Ar-C<u>H</u>=), 5.75 (d, J = 17.6 Hz, 1H, =C<u>H</u><sub>2</sub>), 5.26 (d, J = 11.0 Hz, 1H, =C<u>H</u><sub>2</sub>), 4.67 (dd, J = 7.1, 1.8 Hz, 1H, C<u>H</u>), 4.60 (dd, J = 6.0, 1.8 Hz, 1H, C<u>H</u>), 4.32 (q, J = 7.1 Hz, 2H, C<u>H</u><sub>2</sub>(Et)), 3.96 (d, J = 16.3 Hz, 1H, CO-C<u>H</u><sub>2</sub>-Ar), 3.88 (d, J = 16.3 Hz, 1H, CO-C<u>H</u><sub>2</sub>-Ar), 3.67 (d, J = 6.1 Hz, 1H, O<u>H</u>), 3.15 (d, J = 7.1 Hz, 1H, O<u>H</u>), 1.33 (t, J = 7.1 Hz, 3H, C<u>H</u><sub>3</sub>). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ ppm: 205.6, 171.5, 137.0, 136.4, 132.2, 129.9, 126.8, 114.2, 77.4, 71.4, 62.7, 44.8, 14.3; FT-IR (ATR) cm<sup>-1</sup>: 3500; 3423; 3084; 3043–3001; 2978–2873; 1717; 1691; 1370; 1220; 1123; 1085; 913; 827. HRMS *m/z*: Calculated: [M + H] + 279.12270; Found: [M + H] + 279.12314; Δ = 1.58 ppm.

#### 2.3. Preparation of copolymers 1a-d and 2

Under the inflow of N<sub>2</sub> a solution of styrene (1a: 10 g; 1b: 4 g; 1c: 4 g; 1d: 0 g; 2: 5.14 g), ethyl-(4-vinylbenzyl)-L-tartrate (1a: 0.5 g; 1b: 1 g; 1c: 4 g; 1d: 5 g) or ethyl-(2*R*, 3*R*)-2,3-dihydroxy-4-oxo-5-(4-vinylphenyl)pentanoate (2: 1.17 g), tetra(ethylene glycol)-bis(4-vinylbenzyl) ether [31] (1a-d: 1.75% w/w; 2: 4.7% w/w) and dibenzoylperoxide (0.2 g) in chlorobenzene (1a-d;  $0.5 \text{ ml}\cdot\text{g}^{-1}$  monomers) or bromobenzene (2; 0.5 ml·g<sup>-1</sup> monomers) was suspended to the solution of PVA (1.365 g) and NaCl (15.3 g) in water (400 ml) in a sulphonation flask (500 ml) with oval magnetic stirrer (2 × 6.5 cm). Stirring was adjusted to 250 rpm and the mixture was heated to 85 °C within 30 min and stirred for 4 days. After cooling, the suspension was poured into water (11) and the sedimented copolymer was decanted repeatedly from the water (3 × 500 ml). The crude copolymer was gradually washed with water (3 × 200 ml), methanol (100 ml), THF (50 ml), DCM



Scheme 2. Preparation and use of L-(+)-tartaric acid esters immobilized on swellable copolymers of styrene [30].



Scheme 3. Newly suggested swellable copolymers of L-(+)-tartaric acid derivatives with styrene.

(50 ml) and THF (50 ml). Finally, the copolymer was extracted with the mixture of THF–water (2: 1) in the Soxhlet extractor for 24 h. The final spherical copolymer beads were obtained after drying in vacuum (1a: 1.5 g; 1b: 2 g; 1c: 4 g; 1d: 2.9 g; 2: 2 g).

Swelling in DCM (ml·g<sup>-1</sup>): 1a: 8.7 1b: 7 1c: 3.7 1d: 0.6 2: 3.

**1c:**<sup>13</sup>C NMR (126 MHz) CP/MAS, 20 kHz δ ppm: 172 (<u>C</u>OOR), 147 (<u>C</u><sub>q,Ar</sub>), 129 (<u>C</u>H<sub>Ar</sub>), 73 (<u>C</u>H–OH), 68 (Ar-<u>C</u>H<sub>2</sub>), 63 (<u>C</u>H<sub>2</sub>(Et)), 46 (<u>C</u>H), 41 (<u>C</u>H<sub>2</sub>), 15 (<u>C</u>H<sub>3</sub>).

**1a-c** (Identical frequencies of different band intensities): FT-IR (ATR) cm<sup>-1</sup>: 3488; 3103–3024; 2980–2850; 1738; 1493; 1451; 1370; 1222; 1123; 1085; 821; 760; 697.

**1d:** FT-IR (ATR) cm<sup>-1</sup>: 3475; 3053–2981; 2925; 2852; 1736; 1514; 1446; 1421; 1369; 1261; 1219; 1194; 1124; 1082; 1020; 937; 820; 733; 700; 598.

**2:**<sup>13</sup>C NMR (126 MHz) CP/MAS, 20 kHz  $\delta$  ppm: 147 ( $\underline{C}_{q,Ar}$ ), 129 ( $\underline{C}H_{Ar}$ ), 79 (CO- $\underline{C}H$ -), 72 ( $\underline{C}H$ -OH), 62 ( $\underline{C}H_2(Et)$ ), 45 ( $\underline{C}H$ ), 41 ( $\underline{C}H_2$ ), 14 ( $\underline{C}H_3$ ).

**2:** FT-IR (ATR) cm<sup>-1</sup>: 3487; 3082–3003; 2920; 2850; 1739; 1720; 1601; 1493; 1452; 1367; 1267; 1095; 1028; 756; 696; 538

#### 2.4. Catalytic tests

#### 2.4.1. Sharpless epoxidation with copolymers

Ti(O<sup>i</sup>Pr)<sub>4</sub> (7.5 mol%) and the solution of TBHP (200 mol%; 5.5 mol·1<sup>-1</sup> in decane) were added to the stirred mixture of copolymer (15.75 mol%, calculated to tartrate), molecular sieves 4 Å (1 g) and dry DCM (30 ml) in a Schlenk tube at -25 °C under dry argon atmosphere. After 1 h (-25 °C), the solution of substrate (0.9 mmol) in dry DCM (0.2 ml) was added. After 24 h, the reaction mixture was filtered and extracted first with a saturated solution of Na<sub>2</sub>SO<sub>3</sub> (ca 15 ml) and

second with brine (15 ml), then it was dried over MgSO<sub>4</sub> and evaporated. The conversion was determined by <sup>1</sup>H NMR. Consequently, flash-chromatography in AcOEt/hexane ( $0 \rightarrow 30\%$ ) was performed and the crude product was crystallized from the mixture of AcOEt/hexane.

In the cases involving recycling of the catalyst, the copolymer was filtered, washed with DCM, THF, water, THF, DCM, dried *in vacuo* and used in the next catalytic cycle.

#### 2.4.2. (3-Phenyl-2-oxiranyl)methanol

White solid (mp 51–52 °C); NMR in agreement with literature [32]: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  ppm: 7.38–7.26 (m, 5H), 4.05 (ddd, *J* = 12.8, 5.2, 2.4 Hz, 1H), 3.93 (d, *J* = 2.1 Hz, 1H), 3.80 (ddd, *J* = 12.7, 7.7, 3.8 Hz, 1H), 3.23 (dt, *J* = 4.0, 2.3 Hz, 1H), 1.94 (dd, *J* = 7.7, 5.3 Hz, 1H). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  ppm: 136.6, 128.5, 128.3, 125.7, 62.4, 61.2, 55.5.

The ee was determined by chiral HPLC [32]: Chiralcel OD-H column, 90/10 hexanes/IPA, flow rate: 0.8 ml/min,  $\lambda = 230$  nm; (2*S*,3*S*)-enantiomer  $t_r = 15.7$  min.; (2*R*,3*R*)-enantiomer  $t_r = 17.2$  min; 99% ee.

#### 2.4.3. (2-Methyl-3-phenyloxiran-2-yl)methanol

White solid (mp 57–58 °C); NMR in agreement with literature [32]: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  ppm: 7.39–7.24 (m, 5H), 4.21 (s, 1H), 3.86 (d, *J* = 12.4 Hz, 1H), 3.75 (dd, *J* = 12.0, 6.7 Hz, 1H), 2.34 (br s, 1H), 1.09 (s, 3H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  ppm: 135.7, 128.2, 127.7, 126.5, 65.12, 63.9, 60.3, 13.6.

The ee was determined by chiral HPLC [32]: Chiralcel OD-H column, 95/5 hexanes/IPA, flow rate: 0.8 ml/min,  $\lambda = 230$  nm; (2*S*,3*S*)-enantiomer  $t_r = 12.0$  min.; (2*R*,3*R*)-enantiomer  $t_r = 16.0$  min; 99% ee.



Scheme 4. Synthesis of monomer 3.

#### 2.4.4. (3-(4-Nitrophenyl)oxiran-2-yl)methanol

White solid (mp 97–98 °C); NMR in agreement with literature [33]: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  ppm: 8.27–8.16 (m, 2H), 7.49–7.40 (m, 2H), 4.15–4.01 (m, 2H), 3.94–3.80 (m, 1H), 3.21 (dd, *J* = 5.3, 2.2 Hz, 1H), 2.01 (dd, *J* = 7.8, 5.1 Hz, 1H). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  ppm: 147.9, 144.4, 126.4, 123.8, 63.1, 60.7, 54.4.

The ee was determined by chiral HPLC [34]: Chiralcel OJ-H column, 90/10 hexanes/IPA, flow rate: 1.0 ml/min,  $\lambda = 230$  nm; (2*R*,3*R*)-enantiomer  $t_r = 32.4$  min.; (2*S*,3*S*)-enantiomer  $t_r = 35.3$  min; 98% ee.

#### 2.4.5. (3-Methyl-3-(4-methylpent-3-en-1-yl)oxiran-2-yl)methyl-benzoate

After the epoxidation of geraniol, the crude reaction mixture was extracted with a saturated solution of Na<sub>2</sub>SO<sub>3</sub> and brine and conversion was determined by <sup>1</sup>H NMR. Consequently, 1.8 eq. TEA, 1.5 eq. benzoyl chloride and 3 drops of pyridine were added to the extract. After 10 min, the epoxy-geraniol could already not be detected (TLC) and the reaction mixture was evaporated and extracted with acetone (2 × 10 ml). After purification (flash chromatography with AcOEt/ hexane as eluent), a colourless oil was obtained; NMR in agreement with literature [35]; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  ppm: 8.11–8.05 (m, 2H), 7.61–7.54 (m, 1H), 7.49–7.41 (m, 2H), 5.14–5.04 (m, 1H), 4.57 (dd, *J* = 12.1, 4.3 Hz, 1H), 4.30 (dd, *J* = 12.1, 6.8 Hz, 1H), 3.14 (dd, *J* = 6.7, 4.4 Hz, 1H), 2.19–2.03 (m, 2H), 1.77–1.46 (m, 8H), 1.38 (s, 3H). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  ppm: 166.5, 133.3, 132.4, 129.9, 129.8, 128.5, 123.3, 64.0, 60.7, 59.9, 38.4, 25.8, 23.8, 17.8, 17.0.

The ee was determined by chiral HPLC [35]: Chiralcel OB-H column, 99.5/0.5 hexanes/IPA, flow rate: 1.0 ml/min,  $\lambda = 230$  nm; (2*S*,3*S*)-enantiomer  $t_r = 9.8$  min.; (2*R*,3*R*)-enantiomer  $t_r = 18.7$  min; 52% ee.

#### 2.4.6. (3,3-Diphenyloxiran-2-yl)methanol

Colourless oil; NMR in agreement with literature [36]. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  ppm: 7.44–7.21 (m, 10H), 3.63 (dd, *J* = 14.9, 9.5 Hz, 2H), 3.45–3.34 (m, 1H), 2.12 (br s, 1H). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  ppm: 140.2, 136.8, 128.4, 128.4, 2 × 128.0, 126.8, 66.2, 65.8, 62.1.

The ee was determined by chiral HPLC [36]: Chiralcel OD-H column, 95/5 hexanes/IPA, flow rate: 0.5 ml/min,  $\lambda = 230$  nm; (*S*)-enantiomer  $t_r = 12.0$  min.; (*R*)-enantiomer  $t_r = 13.6$  min; 40% ee.

#### 2.4.7. (3-(4-Chlorophenyl)oxiran-2-yl)methanol

White solid (mp 63–64 °C); NMR in agreement with literature [37]: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  ppm: 7.35–7.29 (m, 2H), 7.25–7.18 (m, 2H), 4.11–3.99 (m, 1H), 3.92 (d, J = 1.8 Hz, 1H), 3.85–3.75 (m, 1H), 3.23–3.14 (m, 1H), 2.11 (br s, 1H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  ppm: 135.2, 134.1, 128.8, 127.1, 62.6, 61.0, 54.9.

The ee was determined by chiral HPLC [37]: Chiralcel OD-H column, 85/15 hexanes/IPA, flow rate: 0.8 ml/min,  $\lambda = 230$  nm; (2*S*,3*S*)-enantiomer  $t_r = 12.3$  min.; (2*R*,3*R*)-enantiomer - not detected; >99% ee.

#### 2.5. List of symbols

AcOEt – ethyl-acetate; APT – attached proton test; ATR – attenuated total reflectance; CP/MAS – cross-polarization magic angle spinning; DCM – dichloromethane; DHB – 2,5-dihydroxybenzoic acid; diMeOPEG –  $\alpha$ , $\omega$ -dimethoxypoly(ethylene glycol); DMF – *N*,*N*-dimethylformamide; DVB – divinylbenzene; EDX – energy dispersive X-ray; ee – enantiomeric excess; FT-IR – fourier transform infrared; HPLC – high-performance liquid chromatography; HRMS – high resolution mass spectrometry; IPA – isopropyl alcohol; NMR – nuclear magnetic resonance; PS – polystyrene; PVA – poly(vinyl alcohol); *R*<sub>f</sub> – retardation factor; SE – Sharpless epoxidation; TBHP – *tert*-butyl hydroperoxide; TEA – triefhylamine; TEGDA – tetra(ethylene glycol) diacrylate; TFA – trifluoroacetic acid; THF – tetrahydrofuran; TLC – thin-layer chromatography; 4-VBC – 4-vinylbenzyl chloride; *p*-VBnMgCl - 4-vinylbenzylmagnesium chloride.

#### 3. 3. Results and discussion

#### 3.1. Synthesis and characterizations of copolymers 1a-d

The key monomer – ethyl-(4-vinylbenzyl)-L-tartrate (**3**) – was prepared from diethyl-L-tartrate [**3**8]. The sodium salt of monoethyl-L-tartrate obtained by its partial hydrolysis in 45% yield was subsequently alkylated with 4-vinylbenzyl chloride (4-VBC) in the presence of the catalytic amount of NaI and diMeOPEG in DMF (61%) (Scheme 4).

The copolymers **1a-d** were synthesized by suspension copolymerization of styrene and ethyl-(4-vinylbenzyl)-L-tartrate (**3**) under presence of 0.45% x/x tetra(ethylene glycol)-bis(4-vinylbenzyl)ether as a cross-linker (Scheme 5). The type and amount of cross-linker in polymer were chosen with respect to the stability of the ether bond and high swellability of the prepared copolymer (up to 8.7 ml·g<sup>-1</sup> of DCM), which is fundamental for easy diffusion of reactants to the catalytic centre [27,30]. The mass ratio of styrene/ligand **3** was defined for the individual copolymers as follows: **1a**: 95/5; **1b**: 80/20; **1c**: 50/50; **1d**: 0/100. The crude copolymers were purified from the residual monomers by a multiple extraction in the Soxhlet extractor.

The prepared copolymers **1a-d** were characterized by optical microscopy and FT-IR spectroscopy. Fig. 1 confirms the spherical character of the prepared copolymers **1a-d** and particle size below ca  $300 \,\mu\text{m}$ .

In all FT-IR spectra of copolymers **1a-d** (Fig. 2), intensive bands of valence C=O vibration of ester groups at  $1738 \text{ cm}^{-1}$  are observed together with bands at  $697 \text{ cm}^{-1}$  pertaining to phenyl out-of-plane bending vibrations.

Moreover, the copolymer **1c** was characterized by <sup>13</sup>C CP/MAS NMR spectroscopy (Fig. 3). The spectrum was measured at rotation frequency 20 kHz without a standard and was mathematically filtered by Gauss function. The signal at 172 ppm corresponds to carbonyl carbons, at 147 ppm to quaternary aromatic carbons, at 129 ppm to aromatic CH carbons, at 73 ppm to CH carbons in tartrate fragment, at 68 ppm to benzyl CH<sub>2</sub> carbons and at 63 ppm to CH<sub>2</sub> from ethoxy group. The signal at 46 ppm can be assigned to CH carbons bound to benzene rings and a more intensive signal at 41 ppm to the neighbouring CH<sub>2</sub> carbons. The signal at 26 ppm is probably a spinning sideband or a signal of residual THF, whereas the signal at 15 ppm is a signal of CH<sub>3</sub> carbons of ethoxy group.

#### 3.2. Study of catalytic activities of the catalysts based on the copolymers 1a-d

The catalytic activities and enantioselectivities of the catalysts based on the copolymers **1a-d** were studied in SE of (*E*)-cinnamyl alcohol with TBHP. The obtained results are summarized in Table 1.

The reaction catalysed by a homogeneous catalyst (Table 1, Entry 1) was performed for mutual comparison with heterogeneous forms of catalysts based on the copolymers **1a-d**. From Table 1 (Entries 2–4), it is



Scheme 5. Synthesis of copolymers 1a-d.



**Fig. 1.** Figures from optical microscope of copolymers 1a (A), 1b (B), 1c (C), 1d (D).

obvious that the epoxidation catalysed by the catalysts based on the copolymers 1a-c proceeded with excellent enantioselectivity (up to 99% ee). The configuration of the obtained product was determined to be (2S,3S)-. Generally, the configuration of the major product depends on the stoichiometry of the Ti(IV) complex with tartrate. While monomeric 2:1 Ti-tartrate complex gives the product with (2R,3R)configuration, dimeric 2:2 Ti-tartrate complex leads to the opposite enantiomer (2S,3S)- [20]. It means that the active species involved in reactions catalysed by the copolymers **1a-c** are dimeric 2:2 Ti-tartrate complexes. The conversions obtained by the copolymers 1a and 1b were almost quantitative (99%), even higher than in case of the homogeneous catalyst (81%). The application of the catalyst based on the copolymer 1c (50% of tartrate) (Entry 4) led to lower conversion (80%), however enantioselectivity remained unchanged (99% ee). Increased loading of the catalyst 1c (Entry 6) accelerated the rate of epoxidation (99% conversion). On the other hand, lowering of enantioselectivity was observed (86% ee). Usage of the catalyst based on the copolymer 1d (99% content of tartrate) (Entry 8) caused a dramatic decrease of conversion (32%, 72 h), as well as enantioselectivity (9% ee). From this result follows that the copolymer 1d forms a very dense network of catalytically inactive Ti(IV) complexes [39]. In summary, lower content of tartrate bound in polymeric matrix (5-20%) leads to



Fig. 2. Comparison of FT-IR spectra of copolymers: 1a (a), 1b (B), 1c (C), 1d (D).





#### Table 1

An	overview	of	performed	catalytic	experiments	with	the	use (	of co	opoly	mers	1a-	d
				-									

$\begin{array}{c} OH \\ \hline \\ \hline \\ copolymer, Ti(O'Pr)_4 \\ [Ar], 4 \text{ A MS,} \\ DCM, -25^{\circ}\text{C}, 24 \text{ h} \end{array} \xrightarrow{H} OH + \begin{array}{c} H_{A,} O \\ \hline \\ H \\ (2S,3S) \end{array} OH + \begin{array}{c} H_{A,} O \\ H \\ (2R,3R) \end{array} OH$						
Entry	Copolymer	Content tartrate in copolymer $(mmol \cdot g^{-1})^d$	Ratio substrate/Ti(IV)/tartrate	Cycle	Conv. <sup>a</sup> %	% <b>ee</b> <sup>b</sup> (2 <i>S</i> ,3 <i>S</i> )
1	Homog. system <sup>c</sup>	3.73	100:5:10	1st	81	97
2	1a	0.16	100:7.5:15	1st	99	99
3	1b	0.67	100:7.5:15	1st	99	95
4	1c	1.67	100:9:23	1st	80	99
5	1c	1.67	100:9:23	2nd	36	76
6	1c	1.67	100:23:50	1st	99	86
7	1c	1.67	100:23:50	2nd	70	34
8	1d	3.34	100:7.5:15	1st	32 (72 h)	9

<sup>a</sup> The conversion was determined after 24 h by <sup>1</sup>H NMR spectroscopy

<sup>b</sup> The enantiomeric excess determined by HPLC using Daicel Chiralcel OD-H column.

<sup>c</sup> Benzyl(ethyl)-L-tartrate.

<sup>d</sup> Estimated from ratio of monomers in starting mixture.

higher conversion and higher enantioselectivity. This effect is in agreement with the previously described so-called dilution effect of polymeric matrix [40].

Furthermore, the possibility of recycling of the polymer **1c** (Table 1, Entry 5, 7) was studied. Unfortunately, a dramatic decrease of both parameters was observed after the second catalytic cycle ( $80 \rightarrow 36\%$ ;  $99 \rightarrow 76\%$  ee and  $99 \rightarrow 70\%$ ;  $86 \rightarrow 34\%$  ee). This can be explained by comparison of FT-IR spectra of freshly prepared copolymer **1c** and the used copolymer **1c** after the first and second catalytic cycle (Fig. 4). The spectra show significant lowering of intensity of bands at  $1738 \text{ cm}^{-1}$ corresponding to the valence C=O vibration of ester groups, and bands in the range from  $1086 \text{ cm}^{-1}$  to  $1260 \text{ cm}^{-1}$  corresponding to the valence C-O vibrations of ester groups as well as to the valence C=O vibrations of alcohol groups in tartrate. This observation can be explained by leaching of tartrate from the polymeric matrix, caused by alcoholysis of ester bond by the present alcohols catalysed by Ti(IV) (Lewis acid). Leaching of L-tartrate leads to the formation of benzyl



**Fig. 4.** Illustration of leaching of L-tartrate from copolymer **1c.** FT-IR spectra of freshly prepared copolymer **1c** (a), used copolymer **1c** after first (b) and second (c) cycle and reference sample of **1c** after alcoholysis with MeONa  $1 \cdot \text{mol} \cdot l^{-1}$  (d).



Scheme 6. Alcoholysis of copolymer 1b.

alcohol moiety bonded to the polymeric matrix (Scheme 6), which can then coordinate Ti(IV) ions originating non-selectively catalysing complexes. These undesirable processes decrease both yield and enantioselectivity (Table 1).

#### 3.3. Synthesis and characterizations of the copolymer 2

To avoid leaching and to obtain a stable recyclable catalyst, the copolymer **2** based on ethyl-(2R,3R)-2,3-dihydroxy-4-oxo-5-(4-vinyl-phenyl)pentanoate (4) was prepared afterwards (Scheme 3). In the case of the copolymer **2**, the tartrate moiety is bound in the polymeric matrix *via* keto group, which cannot undergo alcoholysis.

The key monomer **4** for the preparation of the copolymer **2** (Scheme **3**) was synthesized by the reaction of diethyl-2,3-O-benzylidene-L-tartrate with one equivalent of 4-vinylbenzylmagnesium chloride followed by removing of an acetal group in 23% yield (Scheme 7).

The copolymer **2** was prepared by suspension copolymerization of ketone **4** with styrene (Scheme 8). According to findings from previously performed experiments, the concentration of ligand in monomer mixture was adjusted to  $0.67 \text{ mmol}\cdot\text{g}^{-1}$ . Moreover, the content of the cross-linker was enhanced to 1.35% x/x. Hence, the mass



Scheme 7. Synthesis of monomer 4.



Scheme 8. Synthesis of copolymer 2.

ratio of styrene/ligand **4** in the copolymer **2** was 80/20 (analogically to the polymer **1b**). The crude copolymer **2** was purified by a multiple extraction in the Soxhlet extractor similarly as in previous cases of copolymers **1a-d**.

The copolymer **2** was characterized by optical microscopy, FT-IR spectroscopy and CP MAS spectroscopy. The Fig. 5 confirms the spherical character of the prepared copolymer **2** with particle size below ca  $200 \,\mu\text{m}$ .

In the FT-IR spectra of the copolymer **2** (Fig. 6), characteristic bands of carbonyl valence C=O vibrations at 1739 cm<sup>-1</sup> (ester) and 1720 cm<sup>-1</sup> (ketone) can be observed. The most intensive band at 696 cm<sup>-1</sup> belongs to phenyl out-of-plane bending vibrations.

The Fig. 7 displays the <sup>13</sup>C CP/MAS NMR spectrum of the copolymer **2** at rotation frequency 20 kHz without a standard. The measured spectrum was mathematically filtered by the Gauss function. The signal at 147 ppm corresponds to quaternary aromatic carbons, at 129 ppm to aromatic CH carbons, at 79 ppm to CH carbons in tartrate fragment neighbouring to keto group, at 72 ppm to CH carbons neighbouring to ester group, at 62 ppm to CH<sub>2</sub> from ethoxy group. The signal at 45 ppm can be assigned to CH carbons bound to benzene rings and more intensive signal at 41 ppm to the neighbouring CH<sub>2</sub> carbons. The signal at 14 ppm belongs to CH<sub>3</sub> carbons of ethoxy group. The signals corresponding to quaternary carbons in <u>C</u>OOEt and <u>C</u>OCH<sub>2</sub> were not detected due to the low content of tartrate moiety in polymeric matrix. On the other hand, their presence was proved in FT-IR spectrum (Fig. 6).

#### 3.4. Study of catalytic activities of the catalyst based on the copolymer 2

The catalytic activity, enantioselectivity and recyclability of the catalyst based on the copolymer 2 was first tested in SE of (*E*)-cinnamyl alcohol and (*E*)-2-methylcinnamyl alcohol with TBHP. Both epoxidations were performed under the same reaction conditions used in the case of previously studied copolymer **1b**. From the results shown in



Fig. 5. Figures from optical microscope of copolymer 2.



**Fig. 6.** FT-IR spectrum of copolymer **2** (a) in the comparison with copolymer **1c** (b).



Fig. 7. <sup>13</sup>C CP/MAS NMR spectrum of copolymer 2.

#### Table 2

An overview of performed recycling experiments for epoxidation of (*E*)-cinnamyl alcohol and (*E*)-2-methylcinnamyl alcohol with the use of copolymer **2** (Ratio substrate/Ti(IV)/tartrate: 100:7.5:15; DCM, -25 °C, 24 h).

Product	Cycle	Conversion <sup>a</sup> %	% ee <sup>b</sup> (2 <i>S</i> ,3 <i>S</i> )
Q	1st	80	97
⇒ ∠ _OH	2nd	90	99
	3rd	80	96
	4th	67	97
Q OH	1st	99	99
$\sim$	2nd	99	89
	3rd	99	82
	4th	99	87

 $^{\rm a}\,$  The conversion was determined after 24 h by  $^1{\rm H}$  NMR spectroscopy  $\,$ 

<sup>b</sup> The enantiomeric excess determined by HPLC.

Table 2 follows that asymmetric SE catalysed by the Ti(IV) complex of the polymer **2** proceeds with high conversion and enantioselectivity. Contrary to the catalysts based on the copolymers **1a-b**, the catalyst formed from the copolymer **2** can be successfully recycled at least four times. During the recycling of the copolymer **2** applied in the SE of (*E*)-cinnamyl alcohol, good conversions  $(80 \rightarrow 90 \rightarrow 80 \rightarrow 67\%)$  with excellent values of enantioselectivity (97–99% ee) were observed. In the case of the SE of sterically more demanding (*E*)-2-methylcinnamyl alcohol, almost quantitative conversions (99%) were achieved, even in the fourth catalytic cycle. On the other hand, after the first and second catalytic cycle, a slight decrease of enantioselectivity was observed, while in the next cycle its minor increase occurred (99  $\rightarrow$  89  $\rightarrow$  82  $\rightarrow$  87% ee) (Table 2).

These experiments indirectly confirmed the assumption that anchoring of L-tartaric acid moiety *via* keto group utilized in the polymer **2** is significantly more stable. Therefore, no leaching of tartrate occurred in the case of the catalyst **2**, in contrast with the copolymers **1ab**. This conclusion was also supported by the comparison of FT-IR spectra of the freshly prepared copolymer **2** and copolymer **2** after the first and fourth cycle (Fig. 8).

Fig. 8 shows that the intensity of bands at 1739 and  $1720 \text{ cm}^{-1}$  corresponding to valence C=O vibrations remains unchanged during the recycling. On the other hand, an increase of overall background and



Fig. 8. Effect of recyclation on the quality of copolymer 2. FT-IR spectra of copolymer 2: freshly prepared (a), after first (b) and fourth (c) cycle and  $TiO_2$  (d).

#### Table 3

An overview of the performed catalytic experiments for different types of allylic alcohols with the use of copolymer **2** (Ratio substrate/Ti(IV)/tartrate: 100:7.5:15; DCM, -25 °C, 24 h).



<sup>a</sup> The conversion was determined after 24 h by <sup>1</sup>H NMR spectroscopy.

<sup>b</sup> The enantiomeric excess determined by HPLC.

<sup>c</sup> Product of epoxidation of geraniol was isolated in the form of benzoyl derivative.

bands in the range around  $1630 \text{ cm}^{-1}$  and  $1200-1000 \text{ cm}^{-1}$  was observed. These bands most probably belong to vibrations of TiO<sub>2</sub>, which is in agreement with literature [41]. The content of titanium in the copolymer **2** was independently determined by EDX. 1.5% w/w Ti was found in the recycled polymer **2** after the first catalytic cycle and 2.3% w/w Ti after the fourth catalytic cycle. Based on the presented findings, it is obvious that during the recycling the hydrolysis of Ti(O<sup>i</sup>Pr)<sub>4</sub> occurs and TiO<sub>2</sub> formed by this way partially inhibits the catalytic centres in the polymeric matrix. This leads to the observed slight decrease of catalytic activity.

The catalyst based on the copolymer **2** was further tested under the same experimental conditions for the SE of other allylic alcohols: (E)-4-nitrocinnamyl alcohol, (E)-4-chlorocinnamyl alcohol, 3,3-dipheny-lallylalcohol and geraniol (Table 3).

From the results presented in Table 3, it is obvious that with the application of the copolymer **2** high conversion and enantioselectivity for both (*E*)-4-nitrocinnamyl alcohol (98%, 98% ee) as well as for (*E*)-4-chlorocinnamyl alcohol (99%, 99% ee) were reached. On the other hand, the SE of 3,3-diphenylallyl alcohol and geraniol proceeded with satisfactory conversions (84% resp. 97%), but with only low enantioselectivity (40% resp. 52% ee). This variability of enantioselectivity can be affected by the character of the polymer network of the copolymer **2**, which possesses high substrate selectivity to (*E*)-cinnamyl alcohols due to its specific microenvironment [27].

#### 4. Conclusions

New swellable spherical copolymer beads **1a-d** and **2** of styrene with ethyl-(4-vinylbenzyl)-L-tartrate (**3**) or with ethyl-(2R,3R)-2,3-di-hydroxy-4-oxo-5-(4-vinylphenyl)pentanoate (**4**) with the addition of ca 1–2% x/x tetra(ethylene glycol)-bis(4-vinylbenzyl)ether as a cross-linker were prepared by suspension polymerization. These copolymers **1a-d** and **2** were used in the combination with Ti( $O^{i}Pr$ )<sub>4</sub> as hetero-geneous catalysts for enantioselective Sharpless epoxidation of sub-stituted allylic alcohols. The copolymers **1a-d** containing L-tartraic acid immobilized in polymeric matrix *via* ester bonds provided corresponding substituted hydroxymethyloxiranes with high conversion and high enantioselectivity (up to 99% and 99% ee). Unfortunately, recycling of these heterogeneous catalysts **1a-d** is not possible due to

gradual alcoholysis of ester bond, which leads to leaching of the chiral ligand from polymeric matrix. A dramatic loss of enantioselectivity of the catalysts 1a-d was caused by this way. Analogical swellable copolymer 2, in which L-tartaric acid was immobilized in polymeric matrix via keto bond, also provided corresponding substituted hydroxymethyloxiranes with high conversion and high enantioselectivity (up to 99% and 99% ee). Importantly, with regards to the stability of keto bond, the leaching of chiral ligand does not proceed. This fact leads to only minimal loss of enantioselectivity and opens the possibility of recycling of the copolymer **2**. This presumption was proved in four cycles for two substrates ((E)-cinnamyl alcohol and (E)-2-methylcinnamyl alcohol). The observed slight decrease of conversion resp. enantioselectivity during recycling was explained by gradual minor precipitation of TiO<sub>2</sub> in polymeric matrix. From the presented results follows that the copolymer 2 has a high application potential for practical performance of SE of substituted allylic alcohols in flow reactors, where a complete elimination of moisture action and thus formation of TiO<sub>2</sub> will be possible.

#### Data availability

The raw data required to reproduce these findings are included in the article and in the Supplementary data file.

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#### Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.reactfunctpolym.2019.01.009.

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