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Enantiopure poly(glycidyl methacrylate-*co*-ethylene glycol dimethacrylate): a new material for supported catalytic asymmetric hydrogen transfer reduction

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Abstract—A novel copolymer containing chiral epoxy residues was prepared. Free radical initiated suspension copolymerization of (*R*)- or (*S*)-glycidyl methacrylate with ethylene glycol dimethacrylate afforded crosslinked copolymer **1** in high yield. Optically active polymers containing amino alcohol functionalities were then formed from **1** through epoxide ring opening with a number of achiral and homochiral amines. It was shown that ruthenium complexes based on these new polymeric amino alcohol ligands were effective catalysts for the asymmetric hydrogen transfer reduction of acetophenone. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

Natural optically active polymers such as proteins and genes have played a major role in molecular recognition and catalytic investigations owing to their specific chiral structure. The preparation of optically active polymers represents an interesting challenge as it involves asymmetric polymerization[1] or polymerization of an enantiopure monomer.[2]

In 1975, Svec et al.[3] reported the preparation of the racemic crosslinked copolymer, poly(glycidyl methacrylate-*co*-ethylene dimethacrylate). The appeal of this material lies in the straightforward modification of the epoxy group. Epoxide derived products have found use in ion exchange chromatography,[4–6] as ion exchange resins,[7–9] as gas chromatography stationary phases,[10] as gas sorbents,[11,12] protecting groups[13] and enzyme immobilization agents.[14] However, to our knowledge, an enantiopure equivalent has not yet been synthesized.

Herein, we present results relating to the synthesis of optically active glycidyl methacrylate monomers by hydrolytic kinetic resolution involving lipase or salen cobalt(III) complexes and their copolymerization with ethylene glycol dimethacrylate. The synthesis of a family of enantiomerically pure amino alcohol copolymers obtained by epoxy ring cleavage of poly(glycidyl methacrylate-*co*-ethyleneglycol dimethacrylate) and their subsequent use as ligands in the asymmetric heterogeneous catalytic hydrogen transfer reduction of acetophenone is also reported.

2. Results and discussion

2.1. Hydrolytic kinetic resolution

Formation of the enantiopure glycidyl methacrylate monomer was initially examined. An alternative to the Sharpless method[15] to obtain optically active epoxides is hydrolytic kinetic resolution. One method uses a hydrolytic enzyme to access optically active epoxy esters. Ladner and Whitesides[16] have shown that lipase from porcine pancreas was able to hydrolyze racemic esters of several saturated epoxy alcohols with useful levels of enantioselectivity. Applied to racemic glycidyl methacrylate, under mild conditions (pH 7.8, $T=25°C$) this lipase (E.C. 3.1.1.3 sigma type II) permits the isolation of (*R*)-glycidyl methacrylate with an e.e. of 70% at 57% conversion ($E=6.5$) (Scheme 1). Nevertheless, this system gave only the (*R*)-enantiomer.

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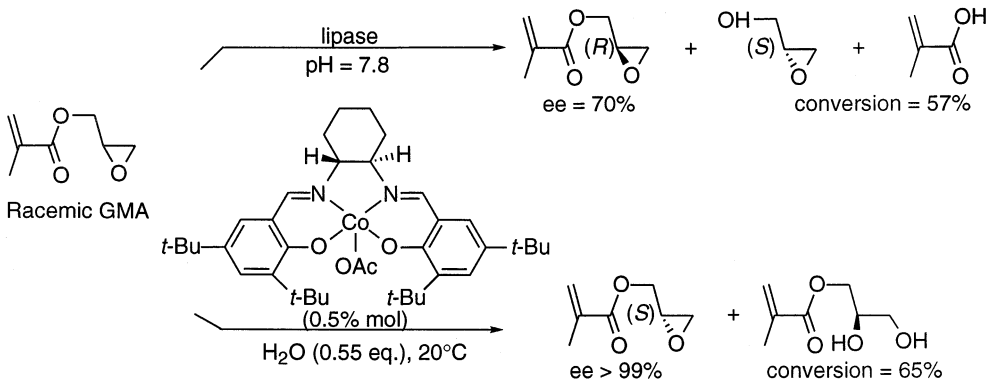
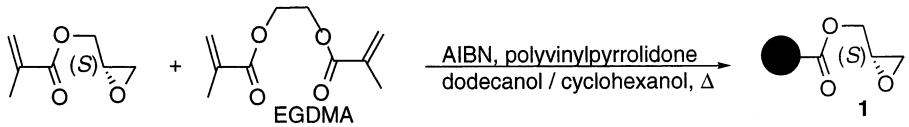


Scheme 1.



Scheme 2.

In order to form (*S*)-glycidyl methacrylate, we used the readily accessible chiral cobalt–salen complexes developed by Jacobsen et al.[17] as catalysts for the asymmetric hydrolysis of saturated terminal epoxides. Thus, hydrolysis of racemic glycidyl methacrylate in the presence of 0.5 mol% of Co(III)-[(*R*,*R*)-salen](OAc) complex, led to the (*S*)-enantiomer with excellent enantioselectivity of up to 99% and 35% yield ($S=15.6$) (Scheme 1). It is noteworthy that under the same conditions, use of the Co(III)–[(*S*,*S*)-salen](OAc) complex afforded the (*R*)-enantiomer in high selectivity and workable yield.

2.2. Polymerization

We performed the copolymerization of (*S*)-glycidyl methacrylate with ethylene glycol dimethacrylate, using radical suspension polymerization with AIBN initiator[3] (Scheme 2).

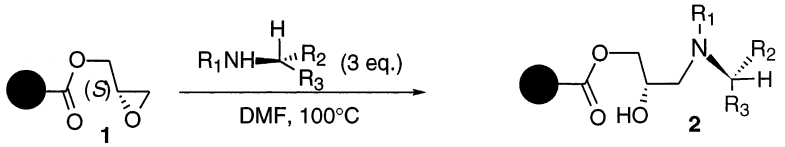
In order to use this copolymer as a polymer supported catalyst, we focussed our attention on the size of spherical polymeric particles, the specific surface area and also the pore sizes. Previously, Svec et al. showed that specific surface area[18] is predominantly affected by the concentration of the inert phase (mixture of alcohols acting as solvent) and the concentration of the crosslinking agent. Whereas porosity and pore size[19] are mainly affected by the volume and the nature of the porogenic component of the inert phase (aliphatic alcohol) and also by the concentration of the crosslinking agent, particle size[3] depends mainly on the rate of stirring during the polymerization reaction. Thus, the compromise chosen was to perform the copolymerization using 70 wt% of ethylene glycol dimethacrylate with a mixture of cyclohexanol and dodecanol (91/9 wt/wt) as an inert solvent mixture and a stirring rate of 200 rpm in a 500 mL glass reactor equipped with a stirring anchor. These conditions gave rise to spherical particles with a specific surface area of between 80 and 100 $m^2\ g^{-1}$ (determined by B.E.T.[20]), 87% of the sample had particle size from 106 to 300 μm (Table 1).

2.3. Functionalization of poly(glycidyl methacrylate-co-ethylene glycol dimethacrylate)

The epoxy functions of polymer **1** were subsequently submitted to ring opening with benzylamine, *N*-benzylmethylamine, (*R*)-α-methylbenzylamine, (*R*)-*N*,α-dimethylbenzylamine, (*S*)-*N*,α-dimethylbenzylamine and methylamine to afford the polyamino alcohols **2a**–**2f**, according to the procedure of Lindsay and Sherrington[8] which favors regioselective attack at the

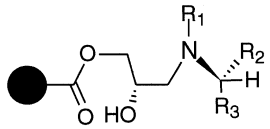
Table 1. Distribution of the particle size of copolymer

Fraction %			
$-\varnothing<106$ μm	$106<\varnothing<300$ μm	$300<\varnothing<500$ μm	500 μm $<\varnothing$
≈0	87	13	≈0



Scheme 3.

Table 2. Functionalization ratio of the epoxy polymer **1**



Run	Polymer	R_1	R_2	R_3	Amine configuration	Functionalization	
						Ratio (%)	mmol/g
1	**2a**	H	H	Ph		69	1.20
2	**2b**	Me	H	Ph		71	1.22
3	**2c**	H	Me	Ph	*R*	70	1.21
4	**2d**	Me	Me	Ph	*R*	59	0.94
5	**2e**	Me	Ph	Me	*S*	60	0.95
6	**2f**	H	H	Me		36	0.76

Table 3. Ruthenium catalyzed transfer hydrogenation of acetophenone

Run	Polymer	R_1	R_2	R_3	Time (h)	% Conversion	% e.e. (*R*)
1	**2a**	H	H	Ph	3	94	70
2	**2b**	Me	H	Ph	22	7	29
3	**2c**	H	Me	Ph	22	94	45
4	**2d**	Me	Me	Ph	22	11	34
5	**2e**	Me	Ph	Me	22	7	23
6	**2f**	H	H	Me	1	95	65

less hindered position of the epoxide ring (Scheme 3). To determine the level of functionalization of the final polymers **2**, elemental analysis for nitrogen content was completed. The results indicate that, in all cases, the contents of amino alcohol units are, respectively, 70% for **2a**–**2c**, 60% for **2d** and **2e** and 36% for **2f** (Table 2) of the initial epoxide functional group.

2.4. Asymmetric hydrogen transfer reduction of acetophenone

Amino alcohols are known to be ligands for asymmetric homogeneous or heterogeneous catalysis for C–C, C–O and C–H bond formations;[21] this prompted us to use polymers **2** as catalytic ligands in the asymmetric hydrogen transfer reduction reaction, which has been studied in our laboratory and is attractive because it avoids the use of pressurized hydrogen which requires special equipment.

Table 3 summarizes the results of the hydrogen transfer reduction of acetophenone (Scheme 4), using ruthenium complexes of amino alcohol polymers **2** synthesized from $[RuCl_2(p\text{-cymene})]_2$ precursor and *iso*-propanol as a hydrogen source. The reaction was carried out under argon with a ratio of acetophenone:Ru:ligand:*t*-BuOK of 20:1:4:5.

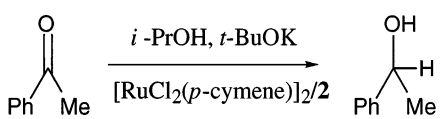
As shown in Table 3, amino alcohol ligands derived from primary amine (runs 1, 3 and 6) gave the best conversions and the best e.e.s. However, α-substituted primary amine (run 3) led to a lower e.e. of 45% compared to unsubstituted amines (runs 1 and 6), which gave products with e.e.s of 70 and 65%, respectively. In contrast, amino alcohol ligands from secondary amine (runs 2 and 4) led to the lowest conversions with enantioselectivities of about 30%. The chirality of the amino α-substituent had no influence on the enantioselectivity.

An attempt to recycle the ruthenium complex **2a** led to a marked decrease in activity from 94 to 27% and lowered selectivity from 70 to 54%.

3. Conclusions

We have synthesized enantiopure poly(glycidyl methacrylate-*co*-ethylene glycol dimethacrylate) and subsequently transformed it into amino alcohol derivatives for use as a ruthenium ligand in the asymmetric hydrogen transfer reduction of acetophenone leading to encouraging results in terms of activity and enantioselectivity.

In order to ascertain the scope and limitations of these new catalytic systems different substrates and metals will be investigated for transfer hydrogenation reactions. The catalytic properties of such polymeric ligands



Scheme 4.

in other reactions will also be examined. Additionally appropriate derivatization **1** will allow its use in solid-phase combinatorial chemistry and chiral chromatography.

4. Experimental

4.1. General

For the hydrolytic kinetic resolution of glycidyl methacrylate and hydrogen transfer reduction of acetophenone, enantiomeric excess and conversion values were determined by GC on a Supelco β dex 225 (30 m×0.25 mm) chiral column, using a Shimadzu GC-14A apparatus equipped with FID connected to a Shimadzu C-R6A integrator. ^{1}H and ^{13}C NMR spectra were recorded with an AM200 (^{1}H: 200 MHz, ^{13}C: 50 MHz) using TMS as internal standard and $CDCl_3$ as solvent.

Polarimetric measurements were performed on a Perkin–Elmer 241 instrument, at ambient temperature, at 589 nm, at a concentration of grams per 100 mL.

Elemental analyses were carried out by CNRS (Service Central d'Analyse-Département Analyse Élémentaire), Solaize, France. Granulometric analyses were obtained using a Coulter LS230 (small volume module). B.E.T. measurements were performed on an automatic home made 'Institut de Recherche sur la Catalyse' apparatus, at a (N_2) temperature of −196°C. Before any measurement, the support was heated to 240°C for 3 h in vacuo. The Roberts' model was used to determine the pore size.

4.2. Hydrolytic kinetic resolution with lipase

A mixture of racemic glycidyl methacrylate (10 g, 70.3 mmol) and bidistilled water (80 mL) was added to lipase (10 g) (E.C.3.1.1.3, sigma type II, from porcine pancreas). The reaction mixture was allowed to stir vigorously maintaining the pH of the reaction at 7.8 by addition of 1.4 M NaOH with a pH controller, for 24 h (conversion 57%). After filtration of the crude product over silica gel (300 g), which was washed once with DCM (300 mL), the organic layer was washed with 10% aqueous $NaHCO_3$ (25 mL) and twice with bidistilled water (15 mL). The resulting organic extracts were dried over a mixture of $Na_2SO_4/NaHCO_3$ (90/10 wt/wt) then concentrated to yield (*S*)-glycidyl methacrylate (3.11 g, 21.9 mmol, 31.2%) e.e. = 70%; $[\alpha]_D = -20.6$ ($c = 0.564$, CH_2Cl_2); ^{1}H NMR: 1.95 (s, 3H), 2.6–2.7 (m, 1H), 2.8–2.9 (m, 1H), 3.25 (m, 1H), 4.0–4.1 (m, 1H), 4.4–4.5 (m, 1H), 5.62 (s, 1H), 6.18 (s, 1H); ^{13}C NMR: 18.3, 44.6, 49.4, 65.2, 126.2, 135.9, 167.0.

4.3. Hydrolytic kinetic resolution with salen

Acetic acid (76 μL, 1.336 mmol) was added to a solution of (1*R*,2*R*)-1,2-diaminocyclohexane *N*,*N*′ bis (3,5-di*tert*butylsalicylidene) cobalt(II) (0.457 g, 0.668 mmol) dissolved in toluene (12 mL). After stirring for 1 h at room temperature, the solvent was removed in vacuo. The black residue obtained was cooled to 0°C, and treated with (±)-glycidyl methacrylate (19 g, 133 mmol) followed by very slow addition of bidistilled water (1.2 g, 66 mmol, 0.55 equiv.). The reaction mixture was allowed to stir for 24 h at room temperature.

The product was separated from the diol by silica gel column chromatography (Merck 60, 40–60 μm). (*S*)-glycidyl methacrylate (6.65 g, 46.55 mmol, yield 35 %) e.e. = 99.8%; $[\alpha]_D = +29.3$ ($c = 0.564$, CH_2Cl_2).

4.4. Copolymerization

A solution of AIBN (204 mg) in a mixture of (*S*)-glycidyl methacrylate (6.13 g) and ethylene glycol dimethacrylate (14.30 g) (30/70 wt/wt) was added to a solution of cyclohexanol (24.64)/dodecanol (2.43) (91/9 wt/wt). This mixture was then added to a solution of polyvinylpyrrolidone (1.5 g) in water (150 mL). The reaction mixture, formed in this way, stirred at 200 rpm, was heated at 70°C for 2 h then, at 80°C for 6 h. After 2 h at room temperature, the spherical particles formed were washed 4–5 times with ethanol 95%, dried by means of a vacuum oven and sifted to afford **1**. Calcd: C, 60.17; H, 7.06; O, 32.77. Found: 59.75; H, 7.40; O, 32.85%. Functional: 2.11 mmol/g.

4.5. Typical polyamino alcohol synthesis

Under argon, 3 equivalents of amine were added to a suspension the chiral copolymer (1 mmol/g of epoxide) in anhydrous DMF (2 mL) under mechanical stirring (180 rpm). Then the reaction mixture was heated at 100°C for 22 h.

Elemental analyses:
2a: Calcd: C, 62.64; H, 7.24; O, 28.45; N, 1.67. Found: C, 61.05; H, 7.15; O, 30.1; N, 1.15%; functional: 69%, 1.20 mmol/g.
2b: Calcd: C, 64.07; H, 7.48; O, 26.10; N, 2.36. Found: C, 62.39; H, 7.67; O, 28.23; N, 1.71%; functional: 71%, 1.22 mmol/g.
2c: Calcd: C, 64.07; H, 7.48; O, 26.10; N, 2.36. Found: C, 61.70; H, 7.50; O, 29.15; N, 1.66%; functional: 70%, 1.21 mmol/g.
2d Calcd: C, 64.57; H, 7.63; O, 25.49; N, 2.30. Found: C, 62.40; H, 7.75; O, 28.50; N, 1.35%; functional: 59%, 0.94 mmol/g.
2e Calcd: C, 64.57; H, 7.63; O, 25.49; N, 2.30. Found: C, 61.75; H, 7.41; O, 29.45; N, 1.38%; functional: 60%, 0.95 mmol/g.
2f Calcd: C, 58.85; H, 7.62; N, 2.78. Found: C, 58.45; H, 7.25; N, 1.01%; functional: 36%, 0.76 mmol/g.

4.6. Typical reduction procedure of acetophenone

Under argon, the polyamino alcohol **2** and $[RuCl_2(p\text{-cymene})]_2$ (**2**/Ru ratio = 4:1) in suspension in *iso*-propanol (2 mL for 3.7 mg of $[RuCl_2(p\text{-cymene})]_2$) were stirred and heated at 80°C for 30 min. The reaction mixture and the polymer underwent a color change

from colorless to red and were cooled to room temperature. Acetophenone was added (acetophenone/Ru ratio: 20/1), then a solution of potassium *tert*-butoxide (0.03 mol/L) is added (Ru/base ratio: 1/5). The reaction times and e.e. are summarized in Table 3.

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