

Enantioselective Polymerization of Epoxides: A Highly Active and Selective Catalyst for the Preparation of Stereoregular Polyethers and Enantiopure Epoxides

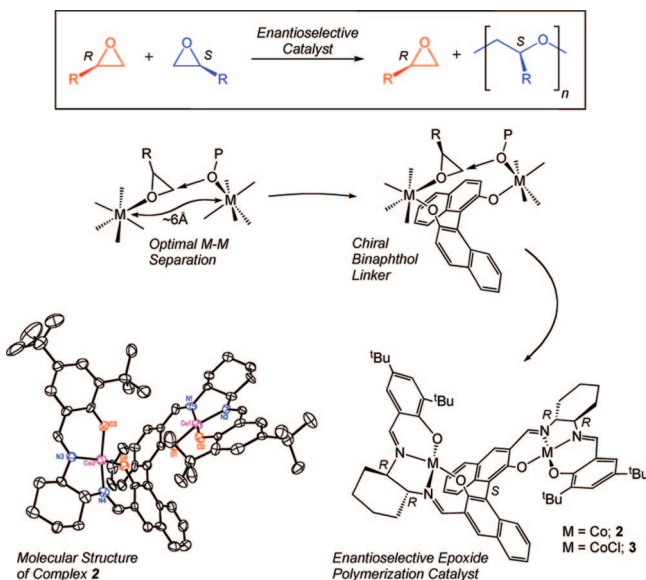
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The development of chiral catalysts for the preparation of enantiopure building blocks¹ and stereoregular macromolecules² are two vibrant areas of stereoselective synthesis. Asymmetric catalysts provide invaluable routes to enantiopure pharmaceutical starting materials and intermediates, while stereoselective polymerization catalysts are the most commercially viable means for the synthesis of isotactic polymers. An interesting intersection of these important subfields of stereoselective synthesis is enantioselective polymerization (also known as stereoelective or kinetic resolution polymerization), where chiral, racemic monomers are kinetically resolved during polymerization.³ Significant advances in enantioselective polymerization of racemic lactones, alkenes, and thiiranes have been achieved.⁴ Although spectacular successes have been reported regarding the kinetic resolution of racemic epoxides by catalytic ring-opening with small molecules,⁵ highly enantioselective polymerization catalysts for the resolution of racemic epoxides do not exist (Scheme 1).^{6–8} Such a reaction would yield two desirable products: enantiopure epoxides and stereoregular polyethers. Thus the development of a catalyst for this transformation became a primary goal of our research.

It has long been postulated that some metal catalyzed epoxide polymerizations occur via a bimetallic reaction where one metal center coordinates the epoxide and another delivers the polymer alkoxide;⁶ recent studies involving homogeneous catalysts have substantiated these hypotheses.⁹ Furthermore, elegant studies by Jacobsen and co-workers have delineated the bimetallic nature of enantioselective epoxide hydrolysis using chiral cobalt salen catalysts.⁵ In theory, epoxide hydrolysis and polymerization differ only in the nature of the nucleophile attacking the coordinated epoxide (hydroxide vs polymer alkoxide). Hypothesizing that a sterically bulky polymer alkoxide would hinder a rate-limiting bimolecular enchainment step in epoxide polymerization, we designed a chiral bimetallic cobalt salen complex to rigidly hold two cobalt centers in the appropriate geometry for epoxide polymerization. Mechanistic studies regarding [(salph)CoOR] (**1**, salph = *N,N'*-bis(3,5-di-*tert*-butylsalicylidine)-1,2-phenylenediamine); R = acyl, alkyl) suggested that a Co...Co separation of ~6 Å is ideal for epoxide polymerization (Scheme 1).¹⁰ A chiral binaphthol linker was selected as a ligand design element as its axial chirality holds metal centers with optimal spacing but also allows some flexibility by rotation about the C_{Nap}–C_{Nap} bond.¹¹ Utilizing imine condensation chemistry, diformylated (*S*)-binaphthol was coupled to the HCl salt of the imine adduct of 3,5-di-*tert*-butylsalicylaldehyde and (*R,R*)-1,2-diaminocyclohexane. Metalation with cobalt acetate gave complex **2** (Scheme 1, M = Co) as a dark red, crystalline solid, which was analyzed by single crystal X-ray

Scheme 1. Design of a Bimetallic, Enantioselective Epoxide Polymerization Catalyst



diffraction.¹² Scheme 1 shows the non-hydrogen atoms of **2** with thermal ellipsoids drawn at the 50% level. Also present in the unit cell was an independent molecule of **2** with a coordinated molecule of ethanol, present during crystallization. Ethanol-free and -bound **2** exhibit Co–Co separations of 5.963 and 5.215 Å, respectively; further analysis reveals the complexes are slightly folded in the solid state, with naphthol–naphthol dihedral angles of 78.0° and 62.2°. Molecular modeling reveals that the Co...Co separation of **2** can readily span the desirable range of 5–7 Å as the molecule pivots about the C_{Nap}–C_{Nap} bond.

Complex **2** and its oxidized form, complex **3** (Scheme 1, M = CoCl), are essentially inactive for propylene oxide polymerization, even at elevated temperatures. Based on our prior success using bis(triphenylphosphine)iminium (PPN) salts as cocatalysts for epoxide/CO₂ copolymerization,¹³ we explored their use for epoxide polymerization in conjunction with **3**. Using 0.025 mol% **3** and 0.050 mol% [PPN][OAc], neat propylene oxide was polymerized almost instantaneously at room temperature. Subsequent reactions were run at 2 M in toluene at 0 °C to avoid a reaction exotherm, except for styrene oxide which could be run in bulk monomer due to a low reaction rate. Subsequent investigation of the enantioselectivity of **3**/[PPN][OAc] for epoxide polymerization by measuring the % ee of the starting epoxide as a function of conversion revealed exceptionally high *s*-factors, with a preference for the *S*-epoxide, and retention of its configuration in the polymer. Due to errors associated with accurately measuring *s* for highly selective catalysts

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Table 1. Enantioselective Polymerization of Racemic Epoxides Catalyzed by **3**/PPN[OAc]: Measurement of s^a

entry	epoxide subs. (R)	[epox]/[3]	time (h)	conv. (%) ^b	ee _(SM) (%) ^c	[mm] (%) ^d	ee _(P) (%) ^e	s -factor ^f	M_n (kg/mol) ^g	M_w/M_n ^g
1	Me	4000	0.25	34	51 (R)	98.6	99.1	370	26.4	1.8
2	Et	1000	0.25	22	29 (R)	98.8	99.2	330	61.4	2.0
3	ⁿ Bu	667	0.33	19	24 (R)	98.6	99.1	260	76.8	2.1
4	Ph	1000	17.0	20	26 (R)	94.4	96.1	63	98.9	1.9

^a General conditions: [PPN][OAc]/[**3**] = 2:1, T_{rxn} = 0 °C; [epoxide] = 2 M in toluene, except for styrene oxide, which was neat. ^b Conversion of epoxide, determined gravimetrically or by ¹H NMR spectroscopy. ^c %ee of the remaining starting material, determined by chiral gas chromatography for entries 1 and 4 and by ¹H NMR spectroscopy using a chiral shift reagent for entries 2 and 3.¹² ^d Isotactic [mm] triad content, determined by ¹³C NMR spectroscopy. ^e %ee of the repeat units in the polymer, calculated using: $ee_{(P)} = (2[mm] + [mr] + [rm] - 1)^{1/2}$. ^f Calculated using $s = k_s/k_R = \ln(1 - c(1 + ee_{(P)}))/\ln(1 - c(1 - ee_{(P)}))$ where c is the conversion of epoxide. ^g Determined by gel-permeation chromatography calibrated with polystyrene standards in 1,2,4-Cl₃C₆H₃ at 140 °C.

Table 2. Enantioselective Polymerization of Racemic Epoxides Catalyzed by **3**/PPN[OAc]: Preparative Reactions^a

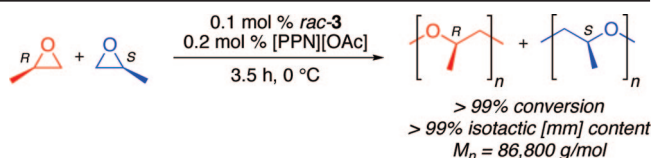
entry	epoxide subs. (R)	[epox]/[3]	time (h)	conv. (%) ^b	yield (%) ^c	ee _(SM) (%) ^d
1	Me	4000	1.5	51	49	>99 (R)
2	Et	1000	52.0	51	49	99 (R)
3	ⁿ Bu	1000	15.0	52	48	>99 (R)
4	Ph	500	15.0	55	45	>99 (R)

^a General conditions: [PPN][OAc]/[**3**] = 2:1 for all reactions; T_{rxn} = 0 °C and [epoxide] = 2 M in toluene for entries 1 and 2, T_{rxn} = 22 °C and neat substrate for entries 3 and 4. ^b Determined gravimetrically after removing residual monomer and solvent *in vacuo*. ^c Yield of recovered epoxide. ^d Determined by chiral gas chromatography for propylene and styrene oxide and by ¹H NMR spectroscopy using a chiral shift reagent for butene and hexene oxide.¹²

based on the % ee of the starting material, we examined the enantiomeric purity of units in the resultant polymer as a function of conversion, which gives significantly higher accuracy (Table 1).¹² As can be seen in entries 1–4, **3**/PPN[OAc] exhibits an unprecedented level of enantioselectivity for the polymerization of epoxides. The catalyst system is highly active for the polymerization of aliphatic epoxides and exhibits s -factors 260–370. The system is also active for styrene oxide. Although the rate and enantioselectivity are significantly slower than those for aliphatic epoxides, the s -factor (63) is well above the threshold for preparative utility.

To fully explore the ability of **3**/PPN[OAc] to prepare enantiopure epoxides, we optimized the kinetic resolution of various substrates (Table 2). Highly active propylene oxide was cleanly resolved (>99% ee; 98% of maximum theoretical yield) in 4 h using 0.025 mol% **3** at 0 °C. Butene and hexene oxides required 0.1 mol% catalyst and longer reaction times but were also resolved in high yield (96–98% of maximum theoretical yield). Due to a lower s -factor, styrene oxide was resolved giving enantiopure epoxide in 90% yield.

Using *rac*-**3** (equimolar mixture of (*R,R,S,R,R*)-**3** and (*S,S,R,S,S*)-**3**), we investigated the isoselective polymerization of racemic epoxides. A wide range of terminal epoxides (alkyl, aryl, alkoxy methyl, fluoroalkyl substituents) undergo rapid polymerization to highly isotactic polyether in >99% yield.¹⁴ Specifically, propylene oxide was quantitatively polymerized to isotactic polymer ([*mm*]

**Figure 1.** Isospecific polymerization of *rac*-propylene oxide catalyzed by *rac*-**3**/PPN[OAc].

>99%) using 0.1 mol % *rac*-**3** at 0 °C for 3.5 h. Therefore, *rac*-**3** represents the first catalyst that exhibits high selectivity for the isospecific polymerization of a range of epoxides.

In conclusion, we report the first highly selective polymerization catalyst for the kinetic resolution of epoxides. The catalyst exhibits exceptional levels of enantioselectivity and activity. The racemic form of the catalyst polymerizes racemic epoxides to highly isotactic polyethers in quantitative yield. Our future studies will focus on the mechanism of action of **3**, with intent to guide efforts to increase stereoselectivity, activity, and substrate scope.

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Supporting Information Available: Experimental procedures for catalyst synthesis and polymerizations, spectroscopic data for polymers, and X-ray data for **2** (CIF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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