# Continuous Enantioselective Kinetic Resolution of Terminal Epoxides Using Immobilized Chiral Cobalt–Salen Complexes

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**Abstract:** Jacobsen's cobalt–salen complex was covalently immobilized on polymer carriers that are part of different technical setups (polymer powder, composite Raschig rings, PASSflow microreactors) and employed for the enantioselective ring opening of terminal epoxides with water and phenols. The polymer-supported catalysts showed good activity and stereoselectivity and could be used repeatedly after a simple reactivation protocol in both batch as well as continuous-flow modes.

**Key words:** catalysis, immobilization, continuous-flow processes, enantioselective synthesis, microreactor, salen

Immobilization of homogeneous catalysts on insoluble supports is widely used to improve the efficiency of chemical processes.[1] Indeed, the use of homogeneous catalysts can be hampered by their high price, air sensitivity, and difficulties when the ligands and their degradation byproducts as well as residual metals have to be removed during workup. These aspects may preclude application of transition-metal-catalyzed reactions on a large scale. Heterogenization of homogeneous catalysts allows easy removal of the active species by simple filtration from the reaction media. Of particular interest is the combination of a heterogenized homogeneous catalyst incorporated in a flow-through device. So far, flow-through processes are restricted to production processes despite the fact that they assure facile automation, reproducibility, safety, and process reliability. Only recently have chemists begun to focus on the development of flow-devices for laboratory use and hence for industrial applications.[2]

In this context, chiral salen–metal complexes such as (*R*,*R*)-**3** (Scheme 1) are among the most versatile catalysts as they can be utilized in the synthesis of a plethora of chiral building blocks (important for the fine chemical industry) and intermediates starting from alkenes and epoxides, respectively.[3] Jacobsen and co-workers[4] have developed a synthetic protocol for the immobilization of salen complexes on hydroxymethylpolystyrene resin as well as on silica beads by employing unsymmetrically substituted salen ligands such as (*R*,*R*)-**1**; various immobilized versions of chiral salen complexes have since been reported.[5]

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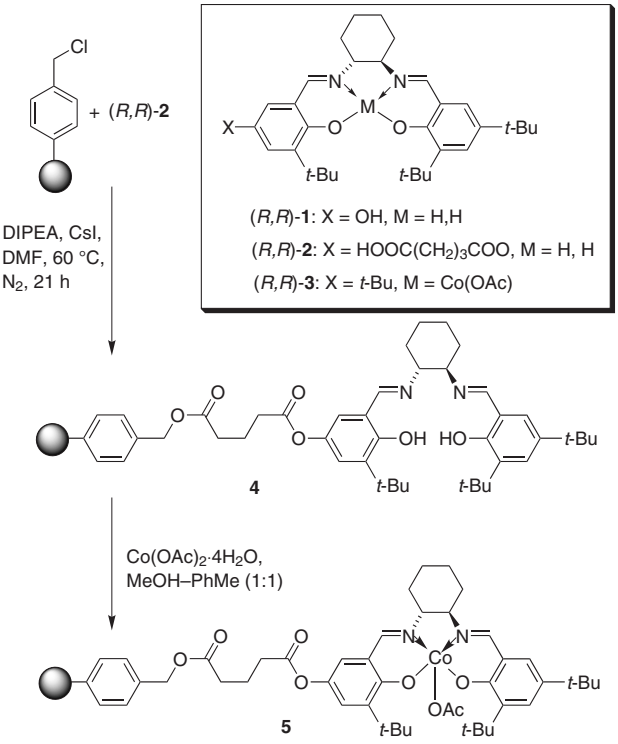


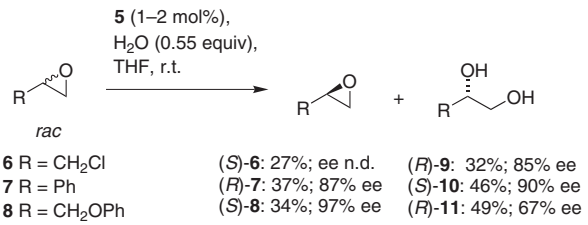

**Scheme 1** Covalent immobilization of the salen ligand on the polymer carrier.

Herein, we report on the immobilization of chiral Jacobsen's cobalt–salen complex **3** on chloromethylpolystyrene (powder), which was prepared by precipitation polymerization as previously described.[6] Additionally, the catalyst was loaded onto in the same material, which is part of a monolithic glass/polymer composite material shaped in the form of industrially utilized Raschig rings (Figure 1). Finally, we incorporate the salen complex inside a PASSflow microreactor, which contains the same composite material. The utility of these immobilized species was demonstrated in the kinetic resolution of terminal epoxides.

Firstly, we immobilized ligand **1** on the model polystyrene resin powder bearing active benzyl chloride groups. The immobilization of chiral ligand (*R*,*R*)-**2** [prepared by acylation of ligand (*R*,*R*)-**1** with glutaric anhydride] was achieved as shown in Scheme 1 and afforded resin **4** (loading ca. 0.35 mmol/g).[7] Treatment with cobalt(II) acetate afforded catalyst **5**.


**Figure 1** Covalent immobilization of the salen ligand on the polymer carrier (the same approach was applied for polystyrene resin, Raschig rings, and PASSflow microreactor).

The functionalized polymer was active in the hydrolytic kinetic resolution of various terminal epoxides **6**–**8** and exerted similar stereoselectivities for both products to those reported for the homogeneous catalyst (*R*,*R*)-**3**[8] (Scheme 2).




**Scheme 2** Hydrolytic kinetic resolution of terminal epoxides (yields refer to isolated products).

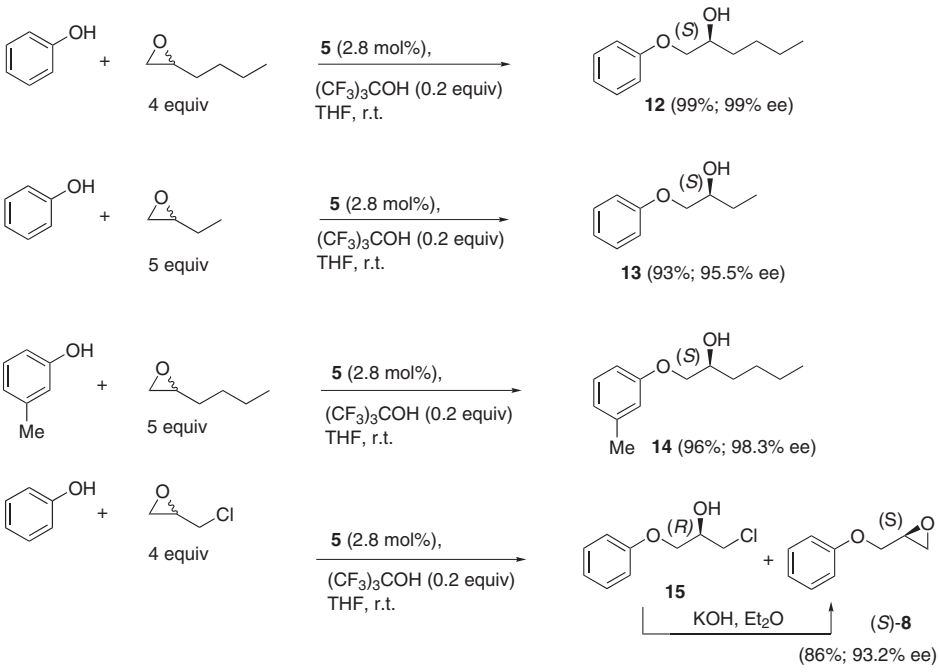
Functionalized polymer **5** was also utilized in the kinetic resolution of terminal epoxides initiated by nucleophilic ring opening with phenols affording phenyl ethers **12**–**15** with selectivity very close to that for the homogeneous catalyst (*R*,*R*)-**3**[9] (Scheme 3). In this case, addition of a catalytic amount of perfluoro-*tert*-butyl alcohol accelerated the reaction dramatically.[4]

In the case of epichlorohydrin, two products were formed in 1:1 ratio after complete consumption of phenol. These products were identified as (*R*)-1-chloro-3-phenoxypropan-2-ol (**15**) and (*S*)-glycidyl phenyl ether [(*S*)-**8**], the latter is formed after ring closure of chlorohydrin **15**. Complete conversion of **15** to (*S*)-glycidyl phenyl ether [(*S*)-**8**, 86%, 93.2% ee] was achieved in the presence of solid potassium hydroxide in diethyl ether.

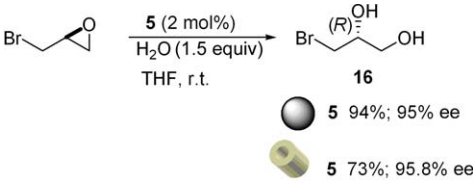
It is noteworthy, that catalyst **5** retains its activity after multiple use. The same portion of catalyst **5** was successfully employed for at least seven different stereoselective ring-opening reactions of racemic terminal epoxides using either water or phenols as nucleophiles (Schemes 2 and 3). After each transformation, the immobilized catalyst **5** was washed successively according to the protocol described in the experimental section.

The stereoselectivity of the Jacobsen catalysts is not absolute, and for the hydrolytic kinetic resolution of terminal epoxides according to Scheme 2, the results (yields and enantiomeric excess of the products) are essentially dependent on the substrate-to-water ratio and the reaction time. In contrast, these factors are not important when epibromohydrin is the substrate, as it undergoes dynamic kinetic resolution according to Scheme 4 as a result of its relatively rapid racemization under the conditions employed.[10]

For this reason, this transformation is a convenient model reaction for the rapid evaluation of the efficiency of various immobilized Jacobsen catalysts. The reaction of racemic epibromohydrin with water (1.5 equiv) in tetrahydrofuran in the presence of catalyst **5** (2 mol%)




**Scheme 3** Stereoselective ring opening of epoxides with phenols (yields refer to isolated products).




**Scheme 4** Dynamic kinetic resolution of epibromohydrin.

gave (*R*)-3-bromopropane-1,2-diol (**16**) in 94% yield and 95% ee (Scheme 4), which correlates well with the results (93% yield and 96% ee) reported for the homogeneous catalysis.[10]

In the next step, we used the same catalytic species except that it was incorporated according to Scheme 1 on the porous glass/polymer composite material shaped as a Raschig ring resembling the situation inside the PASSflow microreactors. In this case, a certain degree of catalyst site isolation can be expected, which will effect the efficiency of the catalytic process because a cooperative bimetallic mechanism has been discussed.[4] However, with these Raschig rings the dynamic kinetic resolution of epibromohydrin was carried out on a 10-mmol scale to yield (*R*)-3-bromopropane-1,2-diol (**16**) in 73% isolated yield and with 95.8% ee.

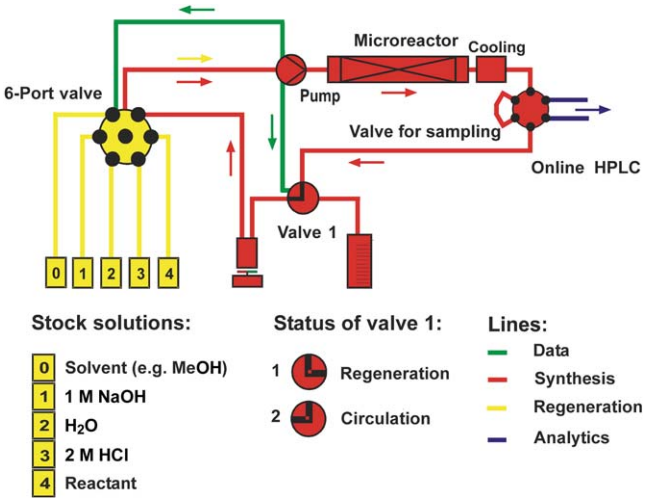



**Figure 2** PASSflow setup.

Recently, we developed a novel continuous-flow reactor device, called PASSflow, which is composed of this monolithic megaporous glass/polymer composite material. Shaped as a rod, it is incorporated inside a tube and casing.[6b] The polymer can be functionalized including grafting of catalytic species. This flow device was incorporated into a setup that is depicted in Figures 2 and 3. Both, stoichiometric and catalytic transformations can be efficiently conducted under continuous-flow conditions. Importantly, reactions can be scaled up without major optimization, which makes this setup ideal for industrial applications.[6,11–13]

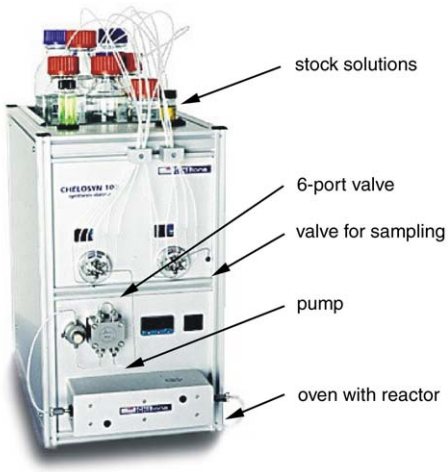
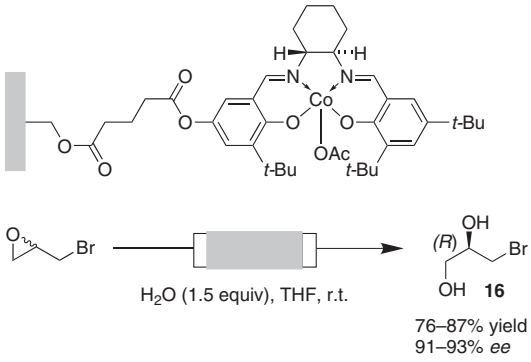



**Figure 3** PASSflow machine.

Thus, we immobilized the salen ligand **1** inside the PASSflow reactor bearing benzyl chloride groups. This was accomplished by the circulation of an *N*,*N*-dimethylformamide solution of ligand (*R*,*R*)-**2** in the presence of *N*,*N*-diisopropylethylamine and cesium iodide through the reactor at 60 °C for 28 hours. After loading with cobalt(II) acetate, the functionalized flow-through reactor was used for the dynamic kinetic resolution of epibromohydrin under flow-through conditions (Scheme 5).

Four successive runs were performed with the same reactor, the reactor being reactivated after each run by washing with toluene–acetic acid (9:1). Three runs performed on the 1-mmol scale were completed within 20 hours for each run and afforded (*R*)-diol **16** in 76–87% yield with constant enantiomeric purity of 91–93% ee. The fourth run was carried out in a 10-mmol scale and required six days for completion, (*R*)-diol **16** was collected in 76% yield and in 93% ee. Thus, no substantial loss of activity or reduced enantioselectivity of the Co–salen complex inside the PASSflow reactor was observed during these four experiments.

In summary, we have demonstrated that Jacobsen's cobalt–salen complex can be successfully immobilized on different polymeric phases (powder, composite Raschig




**Scheme 5** Dynamic kinetic resolution of epibromohydrin under continuous-flow conditions using a PASSflow microreactor.

rings, and inside a PASSflow reactor) thus allowing the kinetic resolution of terminal epoxides under batch or continuous-flow conditions. The flow setup has great potential for scaling up the reaction and, hence, for application in the industrial production of chiral building blocks.

NMR spectra were recorded with a Bruker DPX-400 spectrometer at 400 MHz ($^1$H NMR) and at 100 MHz ($^{13}$C NMR) in $CDCl_3$ using TMS as the internal standard. MS spectra (EI) were obtained at 70 eV with a type VG Autospec apparatus (Micromass). GC analyses were conducted using a Hewlett-Packard HP 6890 Series GC System equipped with a SE-54 capillary column (25 m, Macherey-Nagel) and a FID detector 19231 D/E. Analytical TLC was performed using pre-coated silica gel 60 $F_{254}$ plates (Merck, Darmstadt), and the spots were visualized with UV light at 254 nm or by staining with $H_2SO_4$/4-methoxybenzaldehyde in EtOH. Flash column chromatography was performed on Merck silica gel 60 (230–400 mesh). Commercially available reagents and anhyd solvents were used as received. Most compounds prepared were isolated after filtration and removal of the solvent. Pure homogeneous product samples were collected after flash chromatography and purity was analyzed by TLC, GC, and NMR analyses. Characterization was achieved by appropriate spectroscopic methods ($^1$H and $^{13}$C NMR, IR, HRMS). Additionally, for known compounds the physical (e.g., mp, optical rotation) and spectroscopic data were compared with those in the literature. Chiral GC analyses were conducted using the Hewlett-Packard 5890 Series II Gas Chromatograph with $H_2$ as a carrier gas and the chiral capillary column β-Hydrodex-PM (50 m × 0.25 mm, Macherey-Nagel) at a column head pressure of 20 psi. Chiral HPLC analyses were performed on the LaChrom HPLC System (Merck-Hitachi) interfaced with D-7000 HPLC-System-Manager (Merck) software for data analysis using chiral HPLC column Chiralcel OD-H (25 × 0.46 cm, Diacel Chemical Industries, LTD). Optical rotations were measured on a Perkin-Elmer Polarimeter 341.

Salen ligand (*R*,*R*)-**1** was prepared according the literature method.[4] The preparation of the polymeric phase as powder as well as glass/polymer composite materials is given in the literature.[6]

### Preparation of Catalyst 5

Glutaric anhydride (137 mg, 1.2 mmol) was added to a soln of salen ligand (*R*,*R*)-**1** (506 mg, 1 mmol) and DMAP (146 mg, 1.2 mmol) in $CH_2Cl_2$ (5 mL). The mixture was stirred at r.t. for 22 h and then concentrated in vacuo. Flash chromatography (silica gel, $CH_2Cl_2$–MeOH, 95:5) afforded salen glutarate monoester (*R*,*R*)-**2** as a yellow foam; yield: 411 mg (66%).

$^1$H NMR (400 MHz, $CDCl_3$): δ = 1.23 (s, 9 H), 1.37 (s, 9 H), 1.39 (s, 9 H), 1.0–2.10 (m, 10 H), 2.49 (t, *J* = 7.14 Hz, 2 H), 2.60 (t, *J* = 7.27 Hz, 2 H), 3.31 (m, 2 H), 6.75 (d, *J* = 2.8 Hz, 1 H), 6.91 (d, *J* = 2.8 Hz, 1 H), 6.97 (d, *J* = 2.4 Hz, 1 H), 7.30 (d, *J* = 2.4 Hz, 1 H), 8.22 (s, 1 H), 8.29 (s, 1 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 24.42, 29.29, 29.58, 31.56, 33.26, 33.35, 34.18, 35.04, 35.09, 72.36, 72.59, 117.91, 118.35, 121.46, 122.85, 126.11, 127.07, 136.55, 138.76, 140.13, 142.57, 158.11, 158.34, 164.79, 166.04, 171.98.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{37}H_{53}N_2O_6$: 621.3904; found: 621.3914.

Polyvinyl benzyl chloride resin (50 mg, 0.32 mmol) was added to the soln of salen glutarate monoester (*R*,*R*)-**2** (93 mg, 0.15 mmol), CsI (39 mg, 0.15 mmol), and DIPEA (19.4 mg, 0.15 mmol) in anhyd DMF (2 mL). The mixture was stirred at 60 °C under $N_2$ for 24 h and filtered. The collected solid was washed with $H_2O$, MeOH, and $CH_2Cl_2$ and dried in vacuo to afford resin **4** (64 mg) as a light-yellow powder. The loading of salen ligand was calculated to be 0.37 mmol/g according to weight increase and 0.34 mmol/g according to elemental analysis (0.94% N).

This resin (56 mg) was stirred with a soln of $Co(OAc)_2 \cdot 4\,H_2O$ (10 mg, 0.04 mmol) in MeOH–toluene (1:1, 1 mL) under $N_2$ for 2 h. Then, the resin was filtered, washed with MeOH, $CH_2Cl_2$, toluene–AcOH (9:1), $CH_2Cl_2$, MeOH, and $CH_2Cl_2$, and dried in vacuo to give catalyst **5** (56 mg) as a greenish-brown powder.

After each transformation, the immobilized catalyst **5** was washed successively with MeOH, $CH_2Cl_2$, toluene–AcOH (9:1), $CH_2Cl_2$, MeOH, and $CH_2Cl_2$ and dried in vacuo before use in further experiments.

### (*S*)-Epichlorohydrin [(*S*)-6] and (*R*)-3-Chloropropane-1,2-diol [(*R*)-9]

A suspension of catalyst **5** (47 mg, 2 mol%), epichlorohydrin (**6**, 92.5 mg, 1 mmol) and $H_2O$ (10 μL, 0.55 mmol) were stirred in anhyd THF (0.3 mL) at r.t. for 24 h. $CH_2Cl_2$ (10 mL) was added and the mixture was filtered. The filtrate was washed with $H_2O$ (3 × 2 mL) and dried ($MgSO_4$). Careful rotary evaporation (400 mbar, r.t.) afforded (*S*)-epichlorohydrin [(*S*)-**6**]. The combined aqueous solns were evaporated in vacuo (65 mbar, 60 °C) to yield (*R*)-3-chloropropane-1,2-diol [(*R*)-**9**].

### (*S*)-Epichlorohydrin [(*S*)-6]

Yield: 25 mg (27%) (ee could not be determined with the available chiral columns).

$[\alpha]_D^{20}$ +15.1 (*c* 1.1, $CH_2Cl_2$) {Lit.[14] $[\alpha]_D^{23}$ +20.4 (*c* 1.02, $CH_2Cl_2$)}.

### (*R*)-3-Chloropropane-1,2-diol [(*R*)-9]

Yield: 35 mg (32%); 85% ee [β-Hydrodex-PM, 100 °C, $t_R$ = 6.99, 7.33 min, as the acetonide prepared using 1% w/v CSA–$Me_2C(OMe)_2$].

$[\alpha]_D^{20}$ –6.0 (*c* 1.1, MeOH) {Lit.[8b] $[\alpha]_D^{20}$ –1.24 (neat)}.

$^1$H NMR (200 MHz, DMSO-$d_6$): δ = 3.25–3.42 (m, 2 H), 3.43–3.57 (m, 1 H), 3.58–3.70 (m, 2 H), 4.72 (t, *J* = 5.65 Hz, 1 H), 5.11 (d, *J* = 5.14 Hz, 1 H).

### (*R*)-Styrene Oxide [(*R*)-7] and (*S*)-1-Phenylethane-1,2-diol [(*S*)-10]

A suspension of catalyst **5** (40 mg, 1.1 mol%), styrene oxide (**7**, 120 mg, 1 mmol) and $H_2O$ (9.9 μL, 0.55 mmol) was gently stirred in anhyd THF (0.2 mL) at r.t. for 72 h. The mixture was filtered, and the resin was rinsed with THF (2 × 1 mL) and $CH_2Cl_2$ (2 × 1 mL). The combined filtrates were concentrated in vacuo. Flash chromatography of the residue (silica gel, hexane–EtOAc, gradient from 5:1 to 1:2) afforded (*R*)-**7** and (*S*)-**10**.

### (*R*)-Styrene Oxide [(*R*)-7]

Colorless liquid; yield: 44 mg (37%); 87% ee [chiral GC analysis, chiral capillary column β-Hydrodex PM, 100 °C, isothermal, $t_R$ = 14.45 min (major), 15.13 min (minor)].

$[\alpha]_D^{20}$ +20.3 (*c* 0.3, $CH_2Cl_2$) {Lit.[8b] $[\alpha]_D^{23}$ +28.6 (neat)}.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 2.81 (dd, *J* = 5.4, 2.5 Hz, 1 H, PhCHC*H*H), 3.16 (dd, *J* = 5.4, 4.0 Hz, 1 H, PhCHCH*H*), 3.87 (dd, *J* = 4.0, 2.5 Hz, 1 H, PhC*H*$CH_2$), 7.30–7.40 (m, 5 H, Ph).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 51.33, 52.51, 125.65, 128.33, 128.65, 137.75.

LR-MS: *m*/*z* = 120 ($M^+$).

### (*S*)-1-Phenylethane-1,2-diol [(*S*)-10]

White solid; yield: 64 mg (46%); mp 62–64 °C; 90% ee [chiral GC, β-Hydrodex PM, 140 °C, isothermal, $t_R$ = 9.53 min (minor), 9.88 min (major), as the acetonide prepared using 1% w/v CSA–$Me_2C(OMe)_2$].

$[\alpha]_D^{20}$ +39.2 (*c* 1.11, EtOH) {Lit.[8b] $[\alpha]_D^{23}$ +38.4 (*c* 4.38, EtOH)}.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 2.83 (br s, 1 H, OH), 3.22 (br s, 1 H, OH), 3.55–3.80 (m, 2 H, $CH_2$), 4.79 (dd, *J* = 8.0, 3.5 Hz, 1 H, PhC*H*$CH_2$), 7.30–7.45 (m, 5 H, Ph).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 68.15, 74.83, 126.20, 128.12, 128.66, 140.64.

LR-MS: *m*/*z* = 138 ($M^+$).

**(*S*)-Glycidyl Phenyl Ether [(*S*)-8] and (*R*)-3-Phenoxypropane-1,2-diol [(*R*)-11]**

A suspension of catalyst **5** (55 mg, 1.5 mol%), glycidyl phenyl ether (**8**, 150 mg, 1 mmol), and $H_2O$ (9.9 μL, 0.55 mmol) were stirred in anhyd THF (0.2 mL) at r.t. for 67 h. The mixture was filtered, and the resin was rinsed with THF (2 × 1 mL) and $CH_2Cl_2$ (2 × 1 mL). The combined filtrates were concentrated in vacuo. Flash chromatography of the residue (silica gel, hexane–EtOAc, 5:1, then 1:2) afforded (*S*)-**8** and (*R*)-**11**.

**(*S*)-Glycidyl Phenyl Ether [(*S*)-8]**

Colorless liquid; yield: 51 mg (34%); 97% ee (chiral HPLC, Chiralcel OD-H, 10% *i*-PrOH–hexane, 214 nm, 1 mL/min, $t_R$ = 6.72, 11.95 min).

$[\alpha]_D^{20}$ +4.8 (*c* 1.77, $CHCl_3$) {Lit.[8b] $[\alpha]_D^{23}$ +5.2 (*c* 7.5, $CHCl_3$)}.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 2.77 (dd, *J* = 5.0, 2.7 Hz, 1 H, CHC*H*$HO_{epoxy}$), 2.92 (dd, *J* = 4.8, 4.2 Hz, 1 H, CHC*H*$HO_{epoxy}$), 3.37 (dddd, 5.6, 4.0, 2.9, 2.9 Hz, 1 H, $OCH_2CHCH_2O_{epoxy}$), 3.97 (dd, *J* = 11.0, 5.6 Hz, 1 H, PhOC*H*HCH), 4.22 (dd, *J* = 11.0, 3.3 Hz, 1 H, PhOCH*H*CH), 6.97–7.05 (m, 3 H, Ph), 7.22–7.35 (m, 2 H, Ph).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 44.9, 50.3, 68.8, 114.8, 121.4, 129.7, 158.7.

LR-MS: *m*/*z* = 150 ($M^+$).

**(*R*)-3-Phenoxypropane-1,2-diol [(*R*)-11]**

Viscous colorless liquid that crystallizes at standing; yield: 82 mg (49%); 67% ee (chiral HPLC, Chiralcel OD-H, 10% EtOH–hexane, 260 nm, 1 mL/min, $t_R$ = 10.67, 16.91 min).

$[\alpha]_D^{20}$ –6.6 (*c* 1.9, EtOH) {Lit.[8b] $[\alpha]_D^{23}$ –10.0 (*c* 1.9, EtOH)}.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 3.20 (br s, 1 H, O*H*), 3.58 (br s, 1 H, O*H*), 3.65–3.73 (m 1 H, C*H*HOH), 3.77–3.87 (m, 1 H, CH*H*OH), 3.98 (d, *J* = 5.3 Hz, 2 H, PhOC$H_2$), 4.06–4.13 (m, 1 H, C*H*OH), 6.88 (dd, *J* = 8.7, 0.9 Hz, 2 H, Ph), 6.95 (dd, *J* = 7.3, 7.3 Hz, 1 H, Ph), 7.26 (dd, *J* = 8.7, 7.3 Hz, 2 H, Ph).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 63.8, 69.1, 70.3, 114.7, 121.4, 129.7, 158.5.

LR-MS: *m*/*z* = 168 ($M^+$).

**(*S*)-1-Phenoxyhexan-2-ol (12)**

Phenol (18.4 mg, 0.196 mmol), 1,2-epoxyhexane (80.1 mg, 0.8 mmol), $(CF_3)_3COH$ (5.6 μL, 0.04 mmol), and catalyst **5** (20 mg, 2.8 mol%) were stirred in anhyd THF (100 μL) at r.t. After complete consumption of phenol (17 h, GC monitoring), the mixture was filtered, the resin was rinsed with $CH_2Cl_2$ (4 × 1 mL), and the filtrates were concentrated in vacuo to give pure **12** as a colorless oil; yield: 38 mg (>99%); >99% ee (chiral GC, β-Hydrodex PM, 120 °C, isothermal, $t_R$ = 131.4, 134.6 min).

$[\alpha]_D^{20}$ +19.1 (*c* 1.45, $CH_2Cl_2$) {Lit.[9] $[\alpha]_D^{25}$ +18.7 (*c* 1.25, $CH_2Cl_2$)}.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 0.94 (t, *J* = 7.0 Hz, 3 H, $CH_2CH_3$), 1.25–1.60 (m, 6 H, 3 $CH_2$), 2.40 (d, *J* = 3.4 Hz, 1 H, CHO*H*), 3.84 (dd, *J* = 9.2, 7.5 Hz, 1 H, PhOC*H*HCH), 3.99 (dd, *J* = 9.2, 2.4 Hz, 1 H, PhOCH*H*CH), 3.98–4.05 (m, 1 H, C*H*OH), 6.90–6.99 (m, 3 H, Ph), 7.25–7.33 (m, 2 H, Ph).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 14.1, 22.8, 27.8, 32.9, 70.3, 72.3, 114.7, 121.2, 129.6, 158.8.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{12}H_{18}O_2$: 194.1307; found: 194.1307.

**(*S*)-1-Phenoxybutan-2-ol (13)**

Phenol (18.8 mg, 0.2 mmol), 1,2-epoxybutane (72.1 mg, 1 mmol), $(CF_3)_3COH$ (5.6 μL, 0.04 mmol), and catalyst **5** (20 mg, 2.8 mol%) were stirred in anhyd THF (100 μL) at r.t. for 24 h. The mixture was filtered, the resin was washed with THF (2 × 1 mL) and $CH_2Cl_2$ (4 × 1 mL) and the combined filtrates were concentrated in vacuo. Flash chromatography of the residue (silica gel, hexane–EtOAc, 5:1) afforded **13** as a colorless liquid; yield: 31 mg (93%); 95.5% ee (chiral GC, β-Hydrodex PM, 120 °C, isothermal, $t_R$ = 44.37, 46.15 min).

$[\alpha]_D^{20}$ +24.6 (*c* 2.04, $CH_2Cl_2$).

$^1$H NMR (400 MHz, $CDCl_3$): δ = 1.04 (t, *J* = 7.5 Hz, 3 H, $CH_2CH_3$, 1.63 (dq, *J* = 7.5, 6.6 Hz, 2 H, $CHCH_2CH_3$), 2.39 (br s, 1 H, O*H*), 3.84 (dd, *J* = 8.9, 7.3 Hz, 1 H, PhOC*H*HCH), 3.90–3.96 (m, 1 H, C*H*OH), 3.99 (dd, *J* = 8.9, 3.0 Hz, 1 H, PhOCH*H*CH), 6.92 (dd, *J* = 8.7, 0.9 Hz, 2 H, Ph), 6.97 (dd, *J* = 7.4, 7.4 Hz, 1 H, Ph), 7.30 (dd, *J* = 8.7, 7.4 Hz, 2 H, Ph).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 10.0, 26.3, 71.6, 72.0, 114.7, 121.2, 129.6, 158.8.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{10}H_{14}O_2$: 166.0994; found: 166.0986.

**(*S*)-1-(3-Methylphenoxy)hexan-2-ol (14)**

*m*-Cresol (21.6 mg, 0.2 mmol), 1,2-epoxyhexane (100.2 mg, 1 mmol), $(CF_3)_3COH$ (5.6 μL, 0.04 mmol), and catalyst **5** (20 mg, 2.8 mol%) were stirred in anhyd THF (100 μL) at r.t. for 24 h. Then, the mixture was filtered, the resin was rinsed with THF (2 × 1 mL) and $CH_2Cl_2$ (4 × 1 mL), and the filtrates were concentrated in vacuo. Flash chromatography of the residue (silica gel, hexane–EtOAc, 5:1) afforded **14** as a colorless liquid; yield: 40 mg (96%); 98.3% ee [chiral HPLC, Chiralcel OD-H, 3% EtOH–hexane, 210 nm, 1 mL/min, $t_R$ = 14.29 min (minor), 24.51 min (major)].

$[a]_D^{20}$ +19.8 (*c* 1.54, $CH_2Cl_2$) {Lit.[9] $[a]_D^{25}$ +19.5 (*c* 1.87, $CH_2Cl_2$)}.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 0.94 (t, *J* = 7.1 Hz, 3 H, $CH_2CH_3$), 1.35–1.44 and 1.45–1.62 (2 m, 6 H, 3 $CH_2$), 2.34 (s, 3 H, $C_6H_4CH_3$), 2.38 (d, *J* = 3.3 Hz, 1 H, CHO*H*), 3.82 (dd, *J* = 9.1, 7.4 Hz, 1 H, ArOC*H*HCH), 3.97 (dd, *J* = 9.1, 2.6 Hz, 1 H, ArOCH*H*CH), 3.96–4.02 [m, 1 H, $CH_2CH$(OH)$CH_2$], 6.72 (dd, *J* = 8.3, 2.1 Hz, 1 H, Ar), 6.75 (s, 1 H, Ar), 6.79 (d, *J* = 7.5 Hz, 1 H, Ar), 7.17 (dd, *J* = 7.8, 7.8 Hz, 1 H, Ar).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 14.1, 21.6, 22.8, 27.8, 32.9, 70.3, 72.3, 111.6, 115.6, 122.1, 129.4, 139.7, 158.8.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{13}H_{20}O_2$: 208.1463; found: 208.1463.

**(*S*)-Glycidyl Phenyl Ether [(*S*)-8] and (*R*)-1-Chloro-3-phenoxypropan-2-ol (15)**

Phenol (18.8 mg, 0.2 mmol), epichlorohydrin (**6**, 74 mg, 0.8 mmol), $(CF_3)_3COH$ (5.6 μL, 0.04 mmol), and catalyst **5** (20 mg, 2.8 mol%) were stirred in anhyd THF (100 μL) at r.t. After 24 h GC analysis indicated complete consumption of phenol and the presence of two products in ca. 1:1 ratio. The mixture was filtered, and the resin was rinsed with $CH_2Cl_2$ (4 × 1 mL). The filtrates were concentrated in vacuo. Flash chromatography of the residue (silica gel, hexane–EtOAc, 5:1) afforded (*S*)-glycidyl phenyl ether [(*S*)-**8**] (12 mg, 40%) and (*R*)-1-chloro-3-phenoxypropan-2-ol (**15**) (18 mg, 48%).

**(*R*)-1-Chloro-3-phenoxypropan-2-ol (15)**

$^1$H NMR (200 MHz, $CDCl_3$): δ = 2.58 (d, *J* = 5.9 Hz, 1 H), 3.70–3.85 (m, 3 H), 4.08–4.18 (m, 2 H), 6.90–7.05 (m, 3 H), 7.25–7.35 (m, 2 H).

LR-MS: *m*/*z* = 186 ($M^+$, $Cl^{35}$), 188 ($M^+$, $Cl^{37}$)].

**(*S*)-Glycidyl Phenyl Ether [(*S*)-8]**

(*R*)-**15** (17.5 mg) and solid KOH (20 mg) were stirred in $Et_2O$ (6 mL) at r.t. for 2.5 h. Filtration of the mixture and removal of the solvent in vacuo provided pure (*S*)-**8** (14 mg). Total yield of (*S*)-glycidyl phenyl ether [(*S*)-**8**] (26 mg, 86%); 93.2% ee (chiral HPLC, Chiralcel OD-H, 10% *i*-PrOH–hexane, 210 nm, 1 mL/min, $t_R$ = 8.08, 13.31 min).

$[\alpha]_D^{20}$ +4.5 (*c* 0.4, $CHCl_3$) {Lit.[8b] $[\alpha]_D^{23}$ +5.2 (*c* 7.5, $CHCl_3$)}.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 2.77 (dd, *J* = 4.8, 2.5 Hz, 1 H, CHC*H*HO$_{epoxy}$), 2.91 (dd, *J* = 4.7, 4.2 Hz, 1 H, CHCH*H*O$_{epoxy}$), 3.36 (dddd, *J* = 5.6, 4.0, 2.8, 2.8 Hz, 1 H, $CH_2CHCH_2O_{epoxy}$), 3.97 (dd, *J* = 11.0, 5.6 Hz, 1 H, PhOC*H*HCH), 4.22 (dd, *J* = 11.0, 3.2 Hz, 1 H, PhOCH*H*CH), 6.90–6.99 (m, 3 H, Ph), 7.27–7.32 (m, 2 H, Ph).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 44.9, 50.3, 68.8, 114.8, 121.4, 129.7, 158.7.

LR-MS: *m*/*z* = 150 ($M^+$).

**Preparation of Catalyst 5 Loaded on Raschig Rings and Dynamic Kinetic Resolution of Epibromohydrin**

Six glass/polymer composite Raschig rings (bearing ca. 1 mmol of benzyl chloride groups) were gently shaken with a soln of (*R*,*R*)-**2** (207 mg, 0.333 mmol), DIPEA (68.5 μL, 0.4 mmol), and CsI (104 mg, 0.4 mmol) in DMF (7 mL) at 60 °C under $N_2$ for 72 h. After decantation of the soln, the rings were shaken for 5 min with DMF (10 mL) followed by decantation. This procedure was repeated with DMF (11 × 10 mL), $H_2O$ (2 × 10 mL), MeOH (2 × 10 mL), and $CH_2Cl_2$ (2 × 10 mL). After drying in vacuo, the rings were shaken with a soln of $Co(OAc)_2{\cdot}4\,H_2O$ (174 mg, 0.7 mmol) in MeOH–toluene (1:1) under $N_2$ for 6 h, then washed with MeOH (2 ×), $CH_2Cl_2$ (2 ×), toluene–AcOH (9:1, 3 ×) and finally with $CH_2Cl_2$ (2 ×), MeOH (2 ×), and $CH_2Cl_2$ (2 ×). After drying in vacuo, these rings were gently shaken in a soln of epibromohydrin (1.37 g, 10 mmol) and $H_2O$ (0.27 mL, 15 mmol) in THF (6 mL) at r.t. for 20 h. The soln was decanted, the rings were washed with THF (5 mL) and $CH_2Cl_2$ (2 × 5 mL), and the combined organic solns were concentrated in vacuo. The residue was taken up in $CH_2Cl_2$ (10 mL) and extracted with $H_2O$ (3 × 5 mL). The aqueous soln was washed with $CH_2Cl_2$ (5 mL) and concentrated in vacuo to yield (*R*)-3-bromopropane-1,2-diol (**16**) as a colorless viscous liquid; yield: 1.134 g (73%); 95.8% ee [chiral GC, β-Hydrodex PM, 100 °C, isothermal, $t_R$ = 10.92 min (minor), 11.12 min (major), as the acetonide prepared using 1% w/v CSA–$Me_2C(OMe)_2$].

$[a]_D^{20}$ –4.4 (*c* 9.5, MeOH) {Lit.[15] $[a]_D^{25}$ –3.94 (*c* 5.07, $CHCl_3$)}.

$^1$H NMR (200 MHz, DMSO-$d_6$): δ = 3.25–3.70 (m, 5 H, $CH_2CHCH_2$), 4.72 (t, *J* = 5.6 Hz, 1 H, $CH_2OH$), 5.13 (d, *J* = 4.9 Hz, 1 H, CHO*H*).

$^{13}$C NMR (100 MHz, DMSO-$d_6$): δ = 37.4, 63.4, 70.9.

**Preparation of Catalyst 5 Loaded Inside a PASSflow Reactor and Dynamic Kinetic Resolution of Epibromohydrin in Continuous-Flow Mode**

A homogeneous soln of salen glutarate monoester (*R*,*R*)-**2** (105 mg, 0.169 mmol), CsI (43.9 mg, 0.169 mmol), and DIPEA (21.8 mg, 0.169 mmol) in anhyd DMF (5 mL) was allowed to circulate (2 mL/min) through the PASSflow reactor for 28 h (containing ca. 0.4 mmol active benzyl chloride groups), the reactor was heated at 60 °C (external thermostat). The reactor was washed with DMF (10 mL), $H_2O$ (10 mL), MeOH (10 mL), and MeOH–toluene (1:1). Then, a soln of $Co(OAc)_2{\cdot}4\,H_2O$ (87.2 mg, 0.35 mmol) in MeOH–toluene (1:1; 3 mL) was pumped (2 mL/min) through the reactor in circulating mode at r.t. for 1 h. Finally, the reactor was washed with MeOH (10 mL), $CH_2Cl_2$ (10 mL), toluene–AcOH (9:1, 20 mL), $CH_2Cl_2$ (10 mL), MeOH (10 mL), and $CH_2Cl_2$ (10 mL) and dried in vacuo over $P_2O_5$.

This loaded and dried reactor was flushed with anhyd THF (20 mL). Then, a soln of epibromohydrin (137 mg, 1 mmol) and $H_2O$ (27 μL, 1.5 mmol) in anhyd THF (0.5 mL) was pumped (2 mL/min) through the reactor in circulating mode at r.t. for 20 h (GC monitoring). After the complete consumption of epibromohydrin, the reactor was washed with THF (10 mL) and $CH_2Cl_2$ (10 mL). The combined organic solns were concentrated in vacuo (65 mbar, 60 °C) to give (*R*)-3-bromopropane-1,2-diol (**16**) as a clear viscous liquid; yield: 118 mg (76%); 91% ee. Analytical data are described above.

The PASSflow reactor was washed with toluene–AcOH (9:1, 10 mL) followed by anhyd THF (20 mL) and used in the next runs according to the procedure described above.

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