

Enhanced Cooperativity in Hydrolytic Kinetic Resolution of Epoxides using Poly(styrene) Resin-Supported Dendronized Co-(Salen) Catalysts

Poorva Goyal,^{a,b} Xiaolai Zheng,^b and Marcus Weck^{a,b,*}

^a Department of Chemistry and Molecular Design Institute, New York University, New York, NY 10003-6688, USA
Fax: (+1)-212-260-7905; phone: (+1)-212-992-7968; e-mail: marcus.weck@nyu.edu

^b School of Chemistry and Biochemistry, Georgia Institute of Technology, Atlanta, GA 30332-0400, USA

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Abstract: Excellent enantioselectivities and isolated yields have been achieved for the hydrolytic kinetic resolution of epoxides using a resin-supported dendronized R,R-(salen)Co catalyst with catalyst loadings as low as 0.04 mol%, the lowest metal loadings of any heterogeneous resin-supported (salen)Co catalyst reported to date. In addition, the supported catalysts can be recycled and reused with comparable enantioselectivities. It is hypothesized that the high catalytic activity can be attributed to the flexible

linker and the dendronized framework supporting the (salen)Co moieties on the resin thereby promoting cooperativity between two metal centers. This work opens up new opportunities for the design of highly active resin-supported catalysts that catalyze transformations through a bimetallic pathway.

Keywords: asymmetric catalysis; cobalt; epoxides; hydrolytic kinetic resolution; salen ligand

Introduction

Recent years have seen a tremendous growth in the development of methods for heterogenizing homogeneous catalysts in an attempt to combine the advantages of both homogeneous and heterogeneous catalysts.^[1–7] This is mainly motivated by the need of the industry for libraries of enantiomerically pure compounds as potential leads in drug discovery and to reduce metal contamination in products and the waste stream.^[8] Among the methods of choice for heterogenizing homogeneous catalysts is the covalent attachment of catalysts to insoluble organic polymers or resins.^[1,9] The advantages of using insoluble polymer supports include easy separation of the metal catalysts from the products, easy recyclability of the oftentimes expensive metal catalysts by simple filtration, as well as the potential use of resin-supported catalysts in continuous flow processes.^[5,10] One major limitation to the use of resin-supported catalysts is the limited tunability of the resin-supported materials in regard to activity and selectivity. In most cases, resin-supported catalysts are less active and selective than their homogeneous counterparts.^[11–14] Therefore, new strategies to immobilize catalysts on insoluble polymer supports that allow for the tuning of catalytic activity and enantioselectivity as well as for easy recyclability of the catalyst for repeated re-use are warranted. In

this manuscript we present such a strategy and describe a recyclable and resin supported (salen)Co catalyst system that is highly active and selective for the hydrolytic kinetic resolution of epoxides with significantly lower (up to 80%) catalyst loadings.

Chiral metallosalen catalysts discovered by Jacobsen and Katsuki^[15–19] have emerged as a powerful and ubiquitous family of catalysts for numerous asymmetric organic transformations including the epoxidation of olefins,^[20,21] the hydrolytic kinetic resolution of epoxides,^[22–28] other epoxide ring-opening reactions,^[29] hetero Diels–Alder reactions,^[30] and conjugate addition reactions.^[31,32] Among these reactions, the hydrolytic kinetic resolution (HKR) of racemic epoxides by (salen)Co catalysts is of particular interest, since enantiopure epoxides are versatile intermediates for asymmetric organic syntheses in the pharmaceutical and fine chemical industries. A variety of groups have reported the immobilization of (salen)Co catalysts on polymer supports or membranes,^[25–28,33–46] but only two reports^[45,46] describe the use of insoluble polymer resins as supports. However, these resin-supported catalysts require high catalyst loadings in HKR when compared to soluble and optimized polymer-supported catalysts.^[26,40]

It has been postulated that the HKR of epoxides using (salen)Co catalysts follows a bimetallic pathway where two catalytic centers with proper proximity are

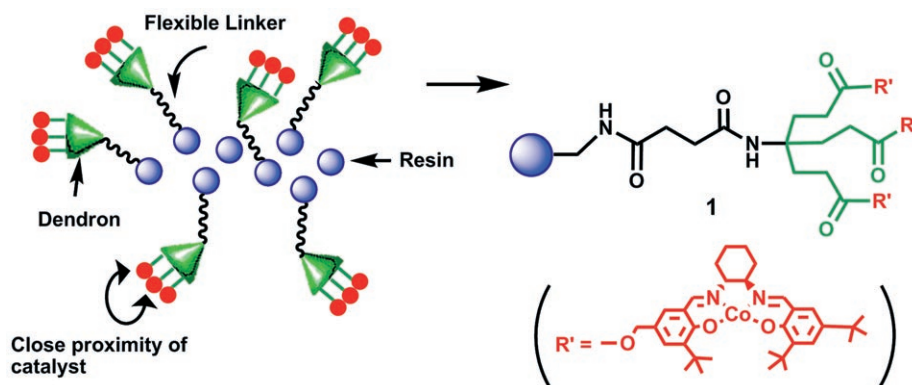


Figure 1. Schematic representation of the resin-supported catalyst design and structure.

needed for the catalysis to occur.^[47–51] Examples of promoting high local concentrations of (salen)Co for beneficial effects on catalytic activity for HKR have been shown previously on dendrimers,^[38] polymers^[25,26,41–44] and silica.^[49] In contrast to soluble supports, it is more difficult to generate cooperative activation on a solid material due to the absence of elaborate control over the proper proximity and relative conformation of active centers on a surface, porous material or insoluble polymer.^[49] In this contribution, we present a new strategy to address these shortcomings by employing a dendron to immobilize (salen)Co catalysts on the resin (Figure 1).

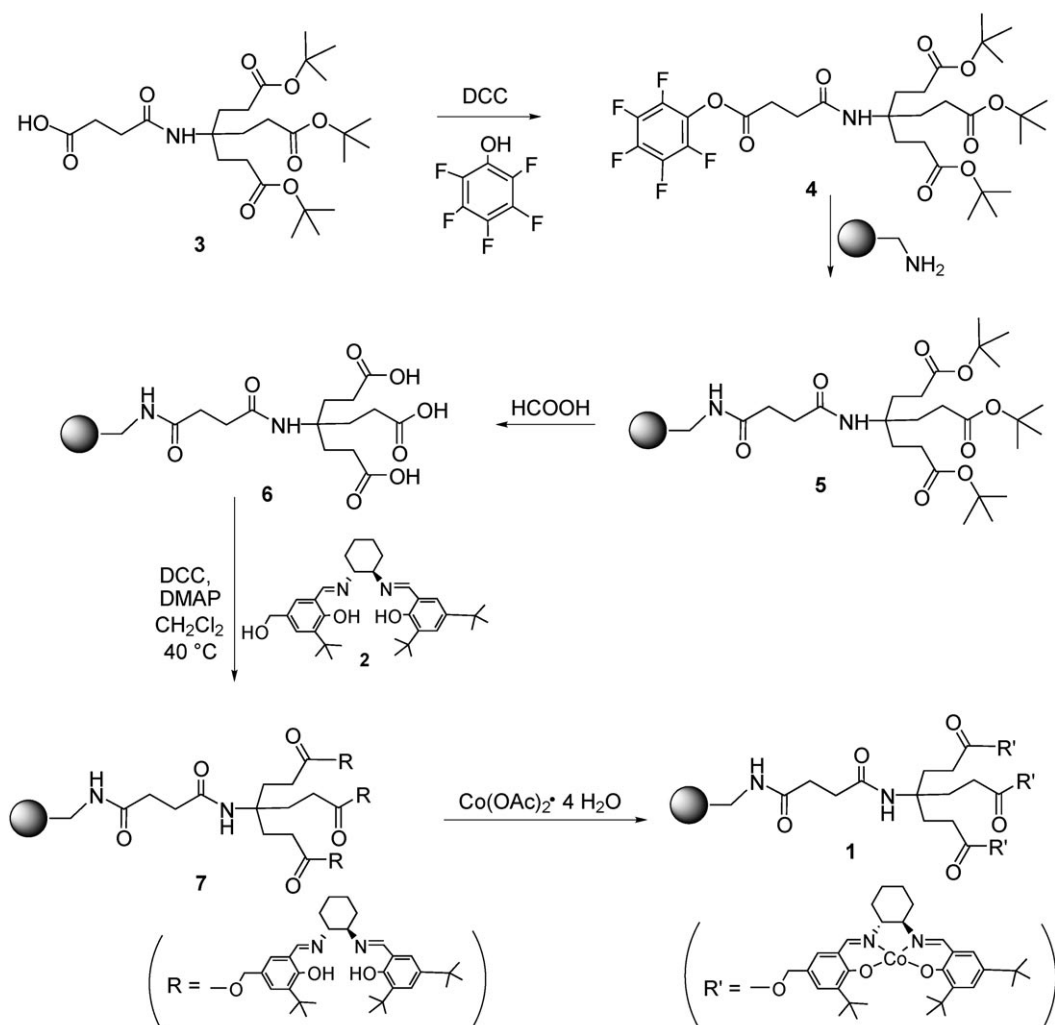
The three components of our system are a cross-linked poly(styrene) resin, a dendron-based linker and a (salen)Co catalyst. Poly(styrene) resin was an attractive choice for the backbone owing to its ease of commercial availability and its chemical inertness. Commercially available generation one dendron^[52] exhibits a branched structure and allows for the covalent attachment of up to three catalytic moieties along the dendron periphery, forcing them in close proximity to each other thereby promoting cooperative interactions between them. The resulting catalytic system upon activation shows high activities and enantioselectivities in the HKR of a variety of terminal epoxides with catalyst loadings as low as 0.04 mol% and allows for easy catalyst separation from product mixtures by simple filtration. The recovered catalysts are demonstrated to retain their activity and enantioselectivity upon recycling.

Results and Discussion

The first step towards the synthesis of the resin-supported catalysts involved a one-pot synthesis of unsymmetrical salen ligand **2**, using a procedure developed by our group.^[53] Resin catalyst **1** was then synthesized following the synthetic protocol outlined in Scheme 1. Acid terminated dendron **3** was synthe-

sized in 74% yield by reacting an aminotriester dendron^[52] with succinic anhydride using pyridine as the solvent. This step was carried out to create a long spacer between the dendron branch points and the resin surface thereby installing a higher degree of flexibility to the systems. Dendron linker **3** was then reacted with pentafluorophenol and DCC to obtain the activated ester dendron **4** in 56% yields which was then coupled with aminomethylated poly(styrene) resin (1.4 mmol g^{−1} of amine loading) to obtain the dendron linker immobilized poly(styrene) resin **5**. The immobilization was also supported by appearance of a new signal in ¹³C solid-state NMR spectra at 27 ppm, corresponding to the primary methyl carbons, and at 80 ppm corresponding to the *tert*-butyl tertiary carbon. The *tert*-butyl ester groups on **5** were then hydrolyzed by stirring the resin in formic acid for 20 h. The complete removal of protecting groups was identified by the disappearance of the signals at 80 ppm in the ¹³C solid-state NMR spectra and at 27.4 ppm corresponding to the primary methyl carbons. Elemental analysis of the oxygen content on **6** showed that 0.899 mmol g^{−1} of the hydrolyzed dendron linker was attached to the resin. Resin **6** was then coupled to salen ligand **2** using DCC and DMAP coupling conditions to yield **7**.

Formation of the product was supported by the appearance of a new signal in the ¹³C solid state NMR spectrum at 119 ppm corresponding to the aromatic carbon next to the imine (C–CH₂–N=) and a broad signal between 63–79 ppm corresponding to the overlap of signals of the cyclohexane carbon attached to the nitrogen (–C–N) and the benzyl carbon (–CH₂–O). Elemental analysis of the oxygen content corresponded to an estimated^[54] 90.1% of salen ligand coupled to the terminal acid sites of the dendron on the resin **7**. Resin **7** was then metallated with cobalt(II) acetate tetrahydrate in methanol to yield target resin **1**. The loading of cobalt on resin **1** was determined by elemental analysis of cobalt content to be 0.561 mmol g^{−1}.

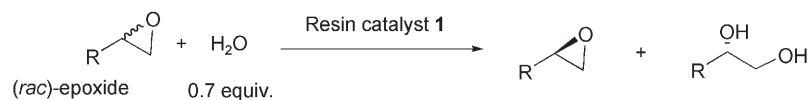


Scheme 1. Synthesis of poly(styrene) resin supported dendronized (salen)Co complexes.

With resin catalyst **1** in hand, we investigated its catalytic activity in the hydrolytic kinetic resolution (HKR) of a small library of epoxides (Table 1). Prior to the catalysis, the Co(II) centers were oxidized to the corresponding Co(III) active species under air

through the addition of excessive acetic acid. The oxidation process was followed by a color change from deep red to dark brown which is well documented in the literature.^[25] We investigated the HKR of the following structurally diverse racemic epoxide sub-

Table 1. HKR of racemic terminal epoxides.



Entry	R	Catalyst Loading [mol%] ^[a]	Time [h]	ee [%] ^[b]	Yield [%] ^[c]
1	CH ₂ Cl	0.04	3	> 99	46
2	<i>n</i> -Bu	0.04	2	> 99	47
3	CH ₂ OAllyl	0.04	7	> 99	45
4	Ph	0.06	22	> 99	40

^[a] Catalyst loadings are reported on a per cobalt basis relative to racemic epoxide.

^[b] Enantiomeric excess of the remaining epoxide was determined by GC analysis using a Chiraldex G-TA column.

^[c] Isolated yield based on racemic epoxides; theoretical maximum yield = 50%.

Table 2. Recycling of resin catalyst **1** in the HKR of (*rac*)-1,2 epoxyhexane.

$ \begin{array}{c} \text{H}_3\text{C}-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{O} \\ \\ \text{O} \end{array} + \text{H}_2\text{O} \xrightarrow[0.7 \text{ equiv.}]{0.04 \text{ mol\% Resin catalyst } \mathbf{1}} \begin{array}{c} \text{H}_3\text{C}-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{O} \\ \\ \text{O} \end{array} + \begin{array}{c} \text{H}_3\text{C}-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{OH} \\ \\ \text{OH} \end{array} $ (<i>rac</i>)-epoxyhexane (R) (S)			
Cycle	Reaction Time [h]	Yield [%] ^[a]	<i>ee</i> [%] ^[b]
1	2	47	> 99
2	2	45	> 99
3	2	45	> 99
4	3	42	98
5	3.5	44	98

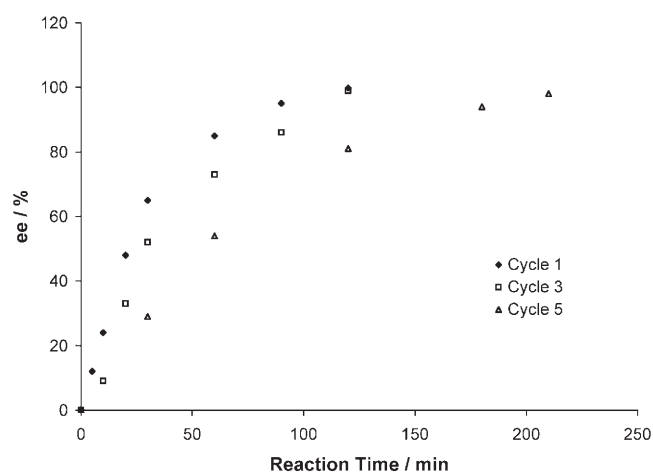
^[a] Isolated yield based on racemic epoxides; theoretical maximum yield = 50%.

^[b] Determined by GC analysis using a chiraldex G-TA column.

strates: (*rac*)-epichlorohydrin, (*rac*)-allyl glycidyl ether, (*rac*)-1,2-epoxyhexane and (*rac*)-styrene oxide (Table 1). The resolution of (*rac*)-epichlorohydrin was complete within 3 h at ambient temperature using 0.04 mol% cobalt loading of **1**, affording the (*S*)-enantiomer in >99% *ee* and 46% isolated yield. Using the same catalyst loading, (*rac*)-allyl glycidyl ether was resolved in 7 h to give the remaining enantiomer in >99% *ee* and 45% isolated yields. The resolution of (*rac*)-1,2-epoxyhexane was complete in 2 h with the enantiomeric excess of the remaining epoxide higher than 99% and 47% isolated yield. The resolution of the conjugate epoxide, (*rac*)-styrene oxide, took nearly 22 h and a catalyst loading of 0.06 mol% for completion. While we still obtained the remaining epoxide with *ees* above 99% we isolated the enantiopure epoxide with lower yields (40%) when compared to the other substrates (Table 1).

A key motivation to develop resin-immobilized salen complex lies in its potential for easy recovery and reuse for subsequent reactions. Therefore, we investigated the recyclability of **1** for the HKR reaction of (*rac*)-1,2 epoxyhexane. The HKR was carried out using the reaction conditions described above. After complete conversion of the *S*-epoxide to the corresponding diol, we separated and purified the resin easily from the reaction mixture by simple filtration and washing with dichloromethane. The collected resin catalyst **1** was reactivated with acetic acid and then reused under strictly identical conditions as for the first cycle. Using this protocol, we reused **1** in five consecutive catalyses. The results of the recycling experiment are shown in Table 2. While, the enantioselectivity of the reused catalyst remained almost the same after 5 cycles, the catalytic activity fell marginally. The reaction time had to be extended to 3.5 h for the fifth cycle to obtain an *ee* of 98%. This result clearly demonstrates the high recyclability of the resin supported dendronized catalyst **1** for the HKR of racemic epoxides.

In order to gain a better understanding of the catalytic properties of the activated resin catalyst **1**, we investigated the kinetics of recycling of **1** for the HKR of (*rac*)-1,2-epoxyhexane for the 1st, 3rd and 5th cycles. The kinetic experiments were carried out at room temperature with 0.7 equiv. of water and a catalyst loading of 0.04 mol%. The kinetic plot of *ee* versus the reaction time is presented in Figure 2. Chiral GC analysis showed that the reaction proceeded to completion in 2 h in the presence of resin-supported catalyst **1** for the 1st cycle. While the catalytic activity of the third recycle is comparable to the first cycle, it fell significantly for the fifth cycle. For the fifth cycle, the resolution took about 3.5 h to be completed with 98% *ee* of the remaining epoxide. These results demonstrate that the resin-supported catalyst can be recycled with comparable activities several times. Multiple recycling events start to lower the activity of the supported catalysts. Nevertheless, even after 5 catalytic cycles **1** does indeed retain its excellent selectivity. To investigate whether the lower activities are a result of cobalt leaching off the resin into the solvent, we mea-

**Figure 2.** Plot of *ee* vs. reaction time in the hydrolytic kinetic resolution of *rac*-1,2 epoxyhexane.

sured the cobalt loading of the resin before the first (cobalt loading 3.31%) and after the fifth catalytic cycle (cobalt loading 3.28%) using elemental analysis. The resin loadings for both experiments are identical within experimental errors suggesting that cobalt leaching is not the source of the decreased catalyst activity.

The aforementioned data sufficiently demonstrate that the new resin catalyst **1** possesses high activity, enantioselectivity and reusability in the HKR of epoxides. As outlined in the introduction, two earlier reports have investigated the HKR of terminal epoxides with resin-supported (salen)Co catalysts.^[45,46] In comparison to these known resin-supported (salen)Co complexes, **1** is significantly more active. Prior to this work, the best resin supported Co-salen catalyst for the HKR was a system reported by Jacobsen and co-workers.^[46] Their system is based on the direct immobilization of Co(salen) complexes onto poly(styrene) resins. In comparison to the reported study, the HKR using catalyst **1** proceeds in significantly (up to 80%) lower catalyst loadings (routinely 0.04 mol% were used in this study while the lowest catalyst loadings reported in the literature was 0.25 mol% catalyst) and with shortened or equally fast resolution times for the HKR of terminal epoxides. HKR of epichlorohydrin took around 3 h with both the Jacobsen's catalyst^[46] and our system, while the HKR of 1,2 epoxyhexane took only 2 h with our catalyst **1** whereas the literature reported 4 h.^[46] We suggest that the enhanced activities of our resin-supported dendronized catalyst **1** as evidenced by the lower catalyst loadings and/or shortened reaction times can be attributed to the dendronized framework that potentially provides a favorable geometry for the two metal centers to interact with each other by increasing the local catalyst concentration and facilitating the intramolecular bimetallic transition state.

Conclusions

We have developed a poly(styrene) resin-supported R,R-(salen)Co catalyst for the hydrolytic kinetic resolution of terminal epoxides. The resin supported dendronized catalyst shows high catalytic activities and enantioselectivities for the HKR of a library of terminal epoxides. Catalyst loadings as low as 0.04 mol% for the HKR resulted in *ees* often above 99% with outstanding isolated yields. Such low catalyst loadings, high *ees*, and excellent yields have not been achieved before using any resin-supported (salen)Co catalyst. We hypothesize that the high catalyst activity stems from our unique dendron design that allows for close proximity of two catalytic sites to each other. A second advantage of the resin-supported catalysts is that it can be recycled easily by filtration. This work

opens new opportunity for the design of efficient insoluble polymer-supported catalysts for reactions that involve bimolecular transition state or cooperative interactions between catalytic centers and might potentially allow for the employment of such catalysts in continuous flow reaction chambers.

Experimental Section

General

All starting materials were obtained from commercial suppliers and used without further purification unless otherwise stated. Aminomethylated poly(styrene) resin with 50–100 mesh and 1.4 mmol g⁻¹ loading was purchased from Nova-biochem. All air- or moisture-sensitive reactions were performed using oven-dried or flame-dried glassware under an inert atmosphere of dry argon or nitrogen. Dichloromethane was dried by passing through columns of activated copper and alumina successively. Chlorobenzene was distilled under an atmosphere of argon prior to use. DMF was purchased anhydrous and dried further using 5 Å molecular sieves. Analytical thin layer chromatography (TLC) was performed using Silica XHL pre-coated (250 µm thickness) glass-backed TLC plates from Sorbent Technologies. Compounds were visualized using UV light or phosphomolybdic acid stains. Flash column chromatography was performed using silica gel 60 Å (230–400 mesh) from Sorbent Technologies. All NMR spectra were acquired on a Varian Mercury 400 MHz spectrometer (¹H, 400.0 MHz; ¹³C, 100.6 MHz). Chemical shifts are expressed in parts per million (δ), coupling constants (*J*) are reported in Hertz (Hz), and splitting patterns are reported as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), or broad (br). Mass spectra were recorded with a VG 7070 EQ-HF hybrid tandem mass spectrometer. Cross-polarization magic angle spinning (CP-MAS) ¹³C solid-state NMR spectra were collected on a Bruker DSX-500 MHz instrument. Samples were packed in 7 mm zirconia rotors and spun at 12.5 kHz. Typical ¹³C CP-MAS parameters were 4000 scans, a 90° pulse length of 5 µs and a recycle time of 5 s. Enantiomeric excesses (*ee*) were determined by capillary gas-phase chromatography (GC) analysis on a Shimadzu GC 14 A instrument equipped with an FID detector and a Chiraldex G-TA column (30 m × 0.25 mm) with helium as a carrier gas.

Synthesis of Dendron 3

To a round-bottomed flask equipped with a magnetic stir bar was added aminotriester^[52] (10 g, 0.024 mol), succinic anhydride (3.61 g, 0.036 mol) and pyridine (48 mL). The reaction mixture was stirred for 3 days following by the removal of pyridine under vacuum. The reaction mixture was redissolved in dichloromethane and washed with water and brine. The collected organic layers were then dried with MgSO₄ and the solvent was removed under vacuum. The product was purified by flash column chromatography (1:1 CH₂Cl₂/EtOAc) to afford the product as a white solid; yield: 9.2 g (74.1%). ¹H NMR (400 MHz, CDCl₃): δ = 1.44 (s, 27H), 1.97 (t, 6H, *J* = 5.4 Hz), 2.22 (t, 6H, *J* = 5.3 Hz), 2.49 (t, 2H, *J* = 4.6 Hz), 2.67 (t, 2H, *J* = 4.8 Hz), 6.63 (br s, 1H);

^{13}C NMR (400 MHz, CDCl_3): δ = 27.5, 29.7, 29.9, 30.2, 58.9, 80.9, 163.5, 171.9, 172.4; HR-MS (ESI+); m/z = 516.31 (100.0%), calcd. for $\text{C}_{26}\text{H}_{45}\text{NO}_9$ [$M+1$]: 515.31; anal. calcd. for $\text{C}_{26}\text{H}_{45}\text{NO}_9$: C 60.56, H 8.80, N 2.72; found: C 60.52, H 8.85, N 2.70.

Synthesis of Dendron 4

To a round-bottomed flask equipped with a magnetic stir bar and a reflux condenser was added **3** (2 g, 0.0038 mol), DCC (1.03 g, 0.0050 mol) and pentafluorophenol (1.71 g, 0.0093 mol) in DMF (30 mL). The reaction mixture was stirred at room temperature for 16 h, during which a precipitate formed. The precipitate was filtered off and the DMF was removed under vacuum at 55 °C to afford a crude mixture. The product was then subjected to flash column chromatography (9:1 hexane/EtOAc) to afford **4** as a white solid; yield: 1.50 g (56.8%). ^1H NMR (400 MHz, CDCl_3): δ = 1.44 (s, 27H), 1.97 (t, 6H, J = 5.4 Hz), 2.22 (t, 6H, J = 5.7 Hz), 2.56 (t, 2H, J = 4.5 Hz), 3.10 (t, 2H, J = 4.8 Hz), 6.23 (s, 1H); ^{13}C NMR (400 MHz, CDCl_3): δ = 27.5, 29.7, 29.9, 30.2, 58.9, 80.9, 138.1, 140.1, 142.4, 143.4, 163.5, 171.9, 172.4; HR-MS (ESI+); m/z = 682.30 (100.0%), calcd. for $\text{C}_{32}\text{H}_{44}\text{F}_5\text{NO}_9$ [$M+1$]: 681.29; anal. calcd. for $\text{C}_{32}\text{H}_{44}\text{F}_5\text{NO}_9$: C 56.38, H 6.51, N 2.05; found: C 56.42, H 6.49, N 2.01.

Synthesis of Resin 6

Aminomethylated poly(styrene) HL (Novabiochem, 1.4 mmol g^{-1} , 300 mg, 0.42 mmol), **4** (572.2 mg, 0.84 mmol) and anhydrous DMF (10 mL) were charged to a Schlenk flask and stirred at 100 °C in an argon atmosphere for 20 h. Filtration and rinsing with anhydrous DMF and CH_2Cl_2 followed by drying under high vacuum overnight yielded the orange-colored resin **5**. Resin **5** (378 mg) was suspended in 95% HCOOH (12 mL) and stirred at room temperature for 20 h. The reaction mixture was then filtered through a frit and washed with DMF and CH_2Cl_2 . The solid was dried on high vacuum to yield the orange resin **6**. Elemental analysis of oxygen showed that 0.899 mmol g^{-1} hydrolyzed linker was immobilized on the resin.

Synthesis of Resin 7

Resin **6** (87 mg, 0.078 mmol of dendron) and CH_2Cl_2 (15 mL) were added under an atmosphere of argon to a flame-dried round-bottomed flask equipped with a magnetic stir bar. Then, the salen ligand **2**^[51] (306.2 mg, 0.588 mmol), DCC (242.6 mg, 1.176 mmol) and DMAP (86.2 mg, 0.705 mmol) were added to the reaction mixture. The reaction mixture was allowed to reflux for 3 days. The solvent was removed under vacuum. The resin was suspended in DMF and centrifuged for multiple times, each time removing the supernatant and re-suspending the resin in a fresh DMF solution to remove the urea adducts and excess reagents. The resin was then filtered through a medium coarseness frit and washed with excess dichloromethane, DMF and methanol. The yellow solid was collected and dried on high vacuum for 2 days to give resin material **7**.

Synthesis of Resin 1

Resin **7** (66.5 mg) was dissolved in CH_2Cl_2 (2 mL) in a vial and stirred under an argon atmosphere (in glove box). A solution of cobalt(II) acetate tetrahydrate (15.69 mg, 0.063 mmol) in methanol (2 mL) was added to the mixture and the reaction mixture was stirred at room temperature for 2–3 days. The color of the resin changed from yellow to deep red. The reaction mixture was then diluted with methanol, stirred for 4–5 mins and suction filtered on a frit washing continuously with methanol. The washed red resin material was collected in a vial and dried over high vacuum to give resin **1**. Elemental analysis of cobalt showed that 0.561 mmol g^{-1} Co was loaded on the resin.

General Procedure for HKR of Terminal Epoxides

Resin catalyst **1** (3.56 mg, 0.002 mmol on basis of cobalt, 0.04 mol%) was dissolved in CH_2Cl_2 (1 mL) in a vial and stirred. To this, 0.1 mL glacial acetic acid was added to activate the catalyst and the reaction mixture was stirred in open air for 30 min. The reaction mixture was then evacuated under vacuum to remove excess acetic acid and dichloromethane and then pumped on high vacuum for 5 min. To the resulting resin, the desired racemic epoxide (5 mmol) was added along with chlorobenzene (50 μL , internal standard) and the vial was immersed in a water bath at room temperature. Water (0.7 equiv., 63 μL) was then injected to start the reaction. Samples (4 μL) were removed from the reaction mixture at each designated time interval and diluted with anhydrous diethyl ether (3 mL) and passed through a plug of silica gel in a pasteur pipet to remove water and the resin catalyst. The conversion and the enantiomeric excesses were calculated by the GC analysis.

General Procedure for Recycling of Resin Catalyst 1

The used resin catalyst **1** was separated and purified from the reaction mixture by filtration over a fine frit and repeated washing with dichloromethane (5–10 mL). The collected resin catalyst **1** was then reused for HKR under strictly identical conditions as for the first cycle.

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