Polymer-Supported Chiral Co(Salen) Complexes: Synthetic Applications and Mechanistic Investigations in the Hydrolytic Kinetic Resolution of Terminal Epoxides

ARTICLE *in* JOURNAL OF THE AMERICAN CHEMICAL SOCIETY · APRIL 1999

Impact Factor: 12.11 · DOI: 10.1021/ja984410n

2 AUTHORS, INCLUDING:

Eric Jacobsen
Harvard University
280 PUBLICATIONS **27,599** CITATIONS

SEE PROFILE

Polymer-Supported Chiral Co(Salen) Complexes: Synthetic Applications and Mechanistic Investigations in the Hydrolytic Kinetic Resolution of Terminal Epoxides

D. Allen Annis and Eric N. Jacobsen*

Contribution from the Department of Chemistry and Chemical Biology and the Institute of Chemistry and Cell Biology, Harvard University, Cambridge, Massachusetts 02138

Received December 22, 1998

Abstract: This paper describes the synthesis of polystyrene- and silica-bound chiral Co(salen) complexes and their application in asymmetric catalysis. A general method for the covalent attachment of salen complexes to both types of support has been devised, and the corresponding immobilized cobalt derivatives are shown to be efficient and highly enantioselective catalysts for the hydrolytic kinetic resolution (HKR) of terminal epoxides. These systems provide practical solutions to certain technical difficulties associated with the isolation of reaction products from the HKR. Removal of the supported catalyst by filtration and repeated recycling is demonstrated with no loss of reactivity or enantioselectivity. The enantioselective addition of phenols to terminal epoxides mediated by this catalyst system provides a facile, high-yielding synthesis of the corresponding enantioenriched aryl ethers. The immobilized catalysts have been adapted to a continuous flow process for the generation of reaction products in high yield and ee, requiring only very simple techniques for product purification. The mechanism by which these catalysts perform highly efficient and enantioselective epoxide ring opening has been addressed using a silica-bound Co(salen) complex. A dramatic corrrelation between the degree of catalyst site-isolation and reaction rate has been observed, consistent with a cooperative bimetallic mechanism in these reactions.

Introduction

The covalent attachment of homogeneous catalysts to insoluble polymer supports has been studied widely as an attractive strategy for extending the practical advantages of heterogeneous catalysis to homogeneous systems.[1] The potential benefits of heterogenization include facilitation of catalyst separation from reagents and reaction products, simplification of methods for catalyst recycle, and the possible adaptation of the immobilized catalyst to continuous-flow processes. The use of polymer-supported reagents in combinatorial synthesis is also a topic of growing interest.[2] The possibility of promoting selective reactions between libraries of reacting partners with subsequent separation of catalyst by mechanical means renders polymer-bound catalysts worthy of investigation in this regard.[3] Ideally, attachment of catalysts to a solid support can also provide insight into reaction mechanism, particularly with respect to issues of intercatalyst interaction.[4]

Whereas immobilization of achiral catalysts onto polymer supports has enjoyed growing application,[5] the development of practical polymer-immobilized asymmetric catalysts has proven highly challenging.[6] Immobilization often results in catalysts with lower enantioselectivities or efficiencies than the solution-phase counterparts. Also, the practical advantages gained by covalent attachment to a support are often outweighed by the added complexity associated with synthesizing the appropriately modified chiral ligands.[7]

The recently developed chiral, salen-based catalysts for the enantioselective ring-opening of meso epoxides and kinetic resolution of terminal epoxides[8] are appealing candidates for immobilization on solid support. The catalysts are readily prepared from inexpensive components, and are amenable to

(1) For a recent review see: Shuttleworth, S. J.; Allin, S. M.; Sharma, P. K. *Synthesis* **1997**, 1217−1239.

(2) (a) Kaldor, S. P.; Siegel, M. G. *Curr. Opin. Chem. Biol.* **1997**, *1*, 101. (b) Thompson, L. A.; Ellman, J. A. *Chem. Rev.* **1996**, *96*, 555−600.

(3) For a discussion of the relevance of absolute stereocontrol in library synthesis, see: Annis, D. A.; Helluin, O.; Jacobsen, E. N. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1907−1909.

(4) (a) Collman, J. P.; Belmont, J. A.; Brauman, J. I. *J. Am. Chem. Soc* **1983**, *105*, 7288−7294. (b) Tollner, K.; Popovitv-Biro, R.; Lahav, M.; Milstein, D. *Science* **1997**, *278*, 2100−2102.

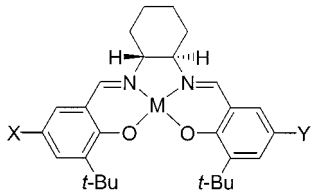
(5) See ref 1 and also: (a) Kobayashi, S.; Nagayama, S. *J. Am. Chem. Soc.* **1998**, *120*, 2985−2986. (b) Nagayama, S.; Endo, M.; Kobayashi, S. *J. Org. Chem.* **1998**, *63*, 6094−6095. (c) Kobayashi, S.; Nagayama, S. *J. Org. Chem.* **1996**, *61*, 2256−2257.

(6) For recent examples and related efforts, see: (a) Han, H.; Janda, K. D *Tetrahedron Lett.* **1997**, *38*, 1527−1530. (b) Wan, K. T.; Davis, M. *Nature* **1994**, *370*, 449−450. (c) Lohray, B. B.; Nandanan, E.; Bhushan, V. *Tetrahedron Asym.* **1996**, *7*, 2805−2808. (d) Altava, B.; Burguete, M. I.; Escudar, B.; Luis, S. V.; Salvador, R. V. *J. Org. Chem.* **1997**, *62*, 3126−3134. (e) Nanadanan, E.; Sudalai, A.; Ravindranathanan, T. *Tetrahedron Lett.* **1997**, *38*, 2577−2580. (f) Huang, W. S.; Hu, Q. S.; Zheng, X. F.; Anderson, J.; Pu, L. *J. Am. Chem. Soc.* **1997**, *119*, 4313−4314. (g) Kamahori, K.; Ito, K.; Itsuno, S. *J. Org. Chem.* **1996**, *61*, 8321−8324. (h) Han, H.; Janda, K. D. *J. Am. Chem. Soc.* **1996**, *118*, 7632−7633. (i) Salvadori, P.; Pini, D.; Petri, A. *J. Am. Chem. Soc.* **1997**, *119*, 6929−6930. (j) Vidal-Ferran, A.; Bampos, N.; Moyano, A.; Pericas, M. A.; Riera, A.; Sanders, J. K. M. *J. Org. Chem.* **1998**, *63*, 6309−6318.

(7) It should be noted, however, that these problems are at least partly avoided in the recently developed methods for immobilizing chiral catalysts noncovalently within membranes or polymer matrixes. See: (a) Vancelecom, I. F. J.; Tas, D.; Parton, R. F.; Van de Vyver, V.; Jacobs, P. A. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1346−1348. (b) Janssen, K. B. M.; Laquiere, I.; Dehaen, W.; Parton, R. F.; Vankelecom, I. F. J.; Jacobs, P. A. *Tetrahedron Asym.* **1997**, *8*, 3481−3487.

(8) (a) Water: Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science* **1997**, *277*, 936−938. (b) Trimethylsilyl azide: Martinez, L. E.; Leighton, J. L.; Carsten, D. H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1995**, *117*, 5897−5898. Schaus, S. E.; Larrow, J. F.; Jacobsen., E. N. *J. Org. Chem.* **1997**, *62*, 4197−4199. Larrow, J. F.; Schaus, S. E.; Jacobsen., E. N. *J. Am. Chem. Soc.* **1996**, *118*, 7420−7421. (c) Carboxylic acids: Jacobsen, E. N.; Kakiuchi, F.; Konsler, R. G.; Larrow, J. F.; Tokunaga, M. *Tetrahedron Lett.* **1997**, *38*, 773−776. (d) Thiols: Wu, M.; Jacobsen, E. N. *J. Org. Chem.* **1998**, *63*, 5252−5254.

10.1021/ja984410n CCC: $18.00
Published on Web 04/20/1999



(*R,R*)-**1**: X = Y = *t*-Bu, M = Co
(*R,R*)-**2**: X = Y = *t*-Bu, M = H, H
(*R,R*)-**3**: X = OH, Y = *t*-Bu, M = H, H
(*R,R*)-**4**: X = Y = OH, M = H, H

Figure 1.

modification for attachment to a solid support.[9,10] These systems have been demonstrated to be quite efficient, even at large (>100 kg) scale,[11] and the catalysts are recyclable without loss of selectivity or reactivity. Moreover, mechanistic studies indicate that the epoxide ring-opening reactions proceed through a mechanism involving cooperative interaction between catalyst units,[12] so enforcement of a high local concentration of catalyst by attachment to a high-loading support may be beneficial to their reactivity.

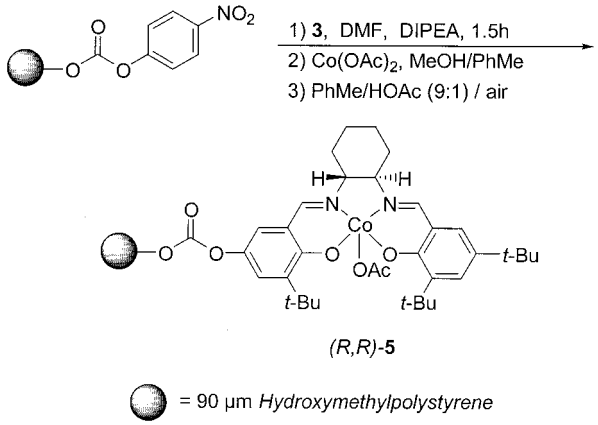
Herein we report the synthesis of polystyrene- and silica-bound chiral Co(salen) complexes and their application to the kinetic resolution of terminal epoxides. These systems allow highly simplified catalyst separation from product mixtures, and recovered catalysts are demonstrated to retain full activity and enantioselectivity. In addition, the effects on reactivity of varying catalyst loading on the solid support have provided a new tool for studying the mechanism of epoxide ring-opening.

Results and Discussion

A. Synthesis and Applications of Polystyrene-Bound Chiral Co(Salen) Complexes. The Co(salen) complex **1**, derived from the chiral salen ligand **2**, has been demonstrated to be a highly efficient and enantioselective catalyst for the hydrolytic kinetic resolution (HKR) of terminal epoxides.[8a]

With the goal of accessing variants of **1** covalently linked to polymer supports, we have developed an effective method for the covalent attachment of the corresponding mono-phenol **3** to polystyrene beads (Scheme 1). Compound **3** has been utilized previously for the construction of soluble dimeric catalysts.[13] In that context, it was shown that tethering the catalyst through the 5-substituent of the salicaldehyde has no adverse effect on the enantioselectivity of the asymmetric ring-opening of terminal epoxides.

Scheme 1



(*R,R*)-**5**

= 90 μm *Hydroxymethylpolystyrene*

Addition of commercial 90 μm beads of hydroxymethylpolystyrene, derivatized as the corresponding 4-nitrophenyl carbonate, to a solution of **3** in DMF in the presence of diisopropylethylamine afforded the carbonate-linked immobilized ligand as bright yellow beads. These were rinsed thoroughly with CH_2Cl_2 and dried in vacuo, and metal insertion was accomplished by adding a solution of $Co(OAc)_2$ in MeOH/toluene. Oxidation to the Co(III) state occurred upon rinsing the resulting beads with AcOH/toluene in air. Complex **5** was isolated as dark red beads after thorough rinsing and drying in vacuo; elemental analysis indicated incorporation of 160 μmol Co(salen) per gram of resin.

An alternative, and more practical, synthesis of **5** by resin capture of **3** generated from a crude ligand preparation is outlined in Figure 2. Synthesis of the salen ligand precursor by utilization of an excess of di-*tert*-butyl salicaldehyde relative to 2,5-dihydroxy-3-*tert*-butylbenzaldehyde yielded a statistical 6:1 ratio of **3** to diphenolic ligand **4**. Addition of the carbonate-derived polystyrene resin to the mixture allowed for the selective capture of the hydroxy-terminated ligands **3** and **4**, while the soluble tetra-*tert*-butyl-substituted ligand **2** was washed away from the polymer-bound product. Complex **5** prepared in this manner displayed identical reaction rates and enantioselectivy to material prepared using purified **3**, but required no chromatographic purification of unsymmetrical salen ligands for its preparation. Incorporation of a minor amount of the diphenolic ligand **4** in the resin-bound catalyst, to the extent that it does occur, has no apparent deleterious effect on catalyst reactivity or enantioselectivity.

Polystyrene-bound complex **5** was examined for its efficacy in the hydrolytic kinetic resolution of epichlorohydrin, **6**. This substrate is susceptible to chloride-catalyzed racemization,[14,15] and its isolation from catalyst by distillation of HKR product mixtures can lead to diminution of epoxide ee, particularly when carried out at large scale.[16] Therefore, an improved method for the removal of the catalyst prior to the isolation of enantioenriched **6** could hold practical significance, and attachment of the catalyst to a solid support could allow for such a separation by simple filtration. The results of a series of experiments in which polystyrene-bound complex **5** was used and recycled four times in the HKR of **6** are summarized in Figure 3. Complete consumption of the reactive enantiomer occurred within 3 h

(9) Synthesis of **2**: Larrow, J. F.; Jacobsen, E. N.; Gao, Y.; Hong, Y.; Nie, X.; Zepp, C. M. *J. Org. Chem.* **1994**, *59*, 1939.

(10) Several previous efforts to immobilize (salen)Mn-based epoxidation catalysts have been described. However, the tendency of (salen)Mn complexes to undergo decomposition under conditions of catalysis limits the attractiveness of immobilization strategies for these particular systems. See ref 7a and: (a) Minutolo, F.; Pini, D.; Salvadori, P. *Tetrahedron Lett.* **1996**, *37*, 3375−3378. (b) De, B. B.; Lohray, B. B.; Sivaram, S.; Dhal, P. K. *Tetrahedron: Asymm.* **1995**, *6*, 2105−2108. (c) Das, B. C.; Iqubal, J. *Tetrahedron Lett.* **1997**, *38*, 2903−2906. (d) Chang, S. Ph.D. Thesis, Harvard University, 1996. (e) Ogunwumi, S. G.; Bein, T. *J. Chem. Soc., Chem. Commun.* **1997**, 901. (f) Angelino, M. D.; Laibinis, P. E. *Macromolecules* **1998**, *22*, 7581−7587. (g) Canali, L.; Cowan, E.; Gibson, C. L.; Sherrington, D. C.; Deleuze, H. *J. Chem. Soc., Chem. Commun.* **1998**, 2561−2562. (h) Minutolo, F.; Pini, D.; Petri, A.; Salvadori, P. *Tetrahedron: Asymm.* **1996**, *7*, 2293−2302.

(11) Pettman, R. B. *Spec. Chem.* **1997**, 118−120.

(12) Hansen, K. B.; Leighton, J. L.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1996**, *118*, 10924−10925.

(13) Konsler, R. G.; Karl, J.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 10780−10781.

(14) Schaus, S. E.; Jacobsen, E. N. *Tetrahedron Lett.* **1996**, *37*, 7937−7940.

(15) Furrow, M. E.; Schaus, S. E.; Jacobsen, E. N. *J. Org. Chem.* **1998**, *63*, 6776−6777.

(16) Cummins, J.; Waldram, D.; Bone. S.; ChiRex Inc., Dudley, U.K. Private communication.

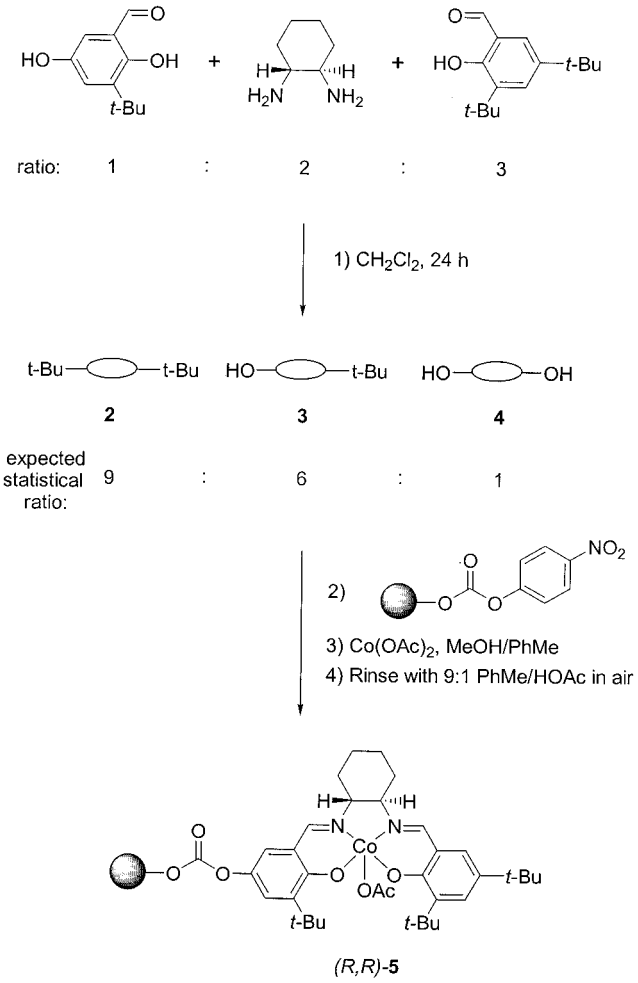
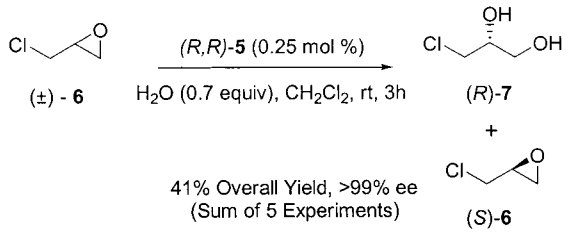


Figure 2. Resin-capture synthesis of polystyrene-bound chiral Co(salen) complexes.



cycle	conversion[a] (%)	ee **6** (%)	ee **7** (%)	k_{rel}
1	52	>99	92.4	133
2	51	>99	95.0	206
3	51	>99	93.6	159
4	51	>99	93.4	154
5	52	>99	93.0	145

[a] Estimated based on the ee of recovered epoxide and diol product (see experimental section).

Figure 3.

using as low as 0.25 mol % catalyst loadings. The catalyst was recoverable by simple filtration, and the filtrate and combined dichloromethane rinsings could be extracted with water to remove the diol product **7**. Use of the polymer-supported catalyst in this reaction thus avoided the necessity of catalyst separation by distillation. The catalyst, reoxidized between cycles by rinsing

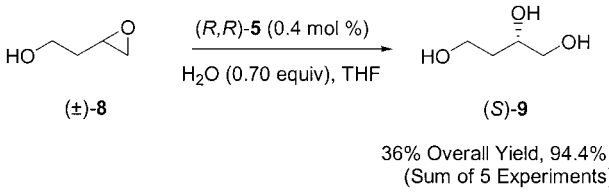


Figure 4. HKR of 4-hydroxy-1-butene oxide with solid-phase catalyst **5**.

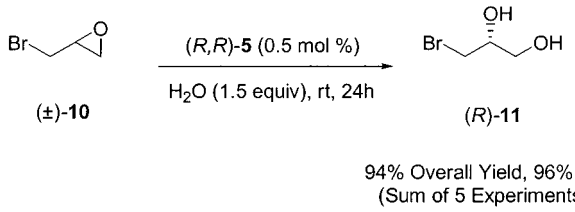


Figure 5. Dynamic kinetic resolution of epibromohydrin with polymer-bound catalyst **5**.

under air with 9:1 toluene/acetic acid, was recyclable with no apparent loss of reactivity or selectivity (cycles 2−5). Combination of the crude organic-soluble products of the recycle experiments and concentration under reduced pressure provided *R*-**6** in 99% ee and in 41% isolated yield based on racemate used.

Another illustration of practical advantages conferred by the use of immobilized catalyst **5** was provided through the HKR of epoxy alcohol **8** (Figure 4). The ring-opened product, triol **9**, is a direct precursor to 3-hydroxytetrahydrofuran,[17] a component of the HIV protease inhibitor VX-478.[18] While **9** can be accessed in high enantiomeric purity via HKR using catalyst **1**, its isolation from catalyst residue is difficult due to foaming upon distillation.[19] Utilization of polymer-bound complex **5** provided a straightforward solution to this problem. Five reaction cycles were performed with a single catalyst batch, and the filtrates and washings from each run were combined. The enantioselectivity for this substrate is lower than that observed for most terminal epoxides; however, high ee product could be accessed by stopping the reaction at moderate (ca. 40%) conversion of starting material. The resulting crude product mixture contained epoxide **8** in 59% ee and triol **9** in 94.4% ee. Filtration and removal of volatile materials in vacuo yielded **9** in 36% isolated yield, 94.4% ee, and > 98% chemical purity.

The recently reported dynamic hydrolytic kinetic resolution of epibromohydrin, **10**, catalyzed by complex **1**, represents an appealing case for the application of an insoluble catalyst. Starting material is converted quantitatively to a single, nonvolatile product, so the use of catalyst **5** would allow product isolation by simple filtration and solvent removal. Results of the dynamic HKR of racemic **10** by catalyst **5** are shown in Figure 5. The reaction was repeated with the same catalyst batch through five cycles. The products obtained from each reaction were combined and the solvents used for rinsing the beads were removed in vacuo. Diol **11** was thus isolated in 94% overall yield, 96% ee, and in 90% chemical purity, the only detectable impurity being 1,3-dibromo-2-propanol.

Very recently complex **1** has been discovered to be an efficient catalyst for the kinetic resolution of terminal epoxides by the addition of phenols.[20] As numerous epoxide−phenol

(17) Tandon, V. K.; van Leusen, A. M.; Wynberg, H. *J. Org. Chem.* **1983**, *48*, 2767−2769.
(18) Kim, E. E.; Baker, C. T.; Dwyer, M. D.; Murcko, M. A.; Rao, B. G.; Tung, R. D.; Navia, M. A. *J. Am. Chem. Soc.* **1995**, *117*, 1181−1182.
(19) Hansen, K. B. Ph.D. Thesis, Harvard University, 1998.
(20) Ready, J. M.; Jacobsen, E. N. Submitted for publication.

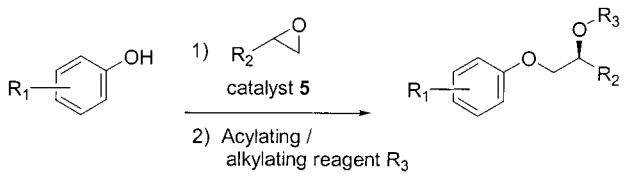


Figure 6. A possible application of the enantioselective ring-opening of epoxides by phenols to the combinatorial synthesis of novel compounds.

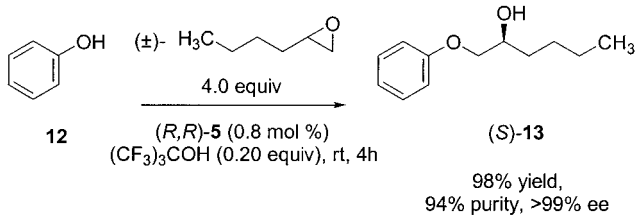
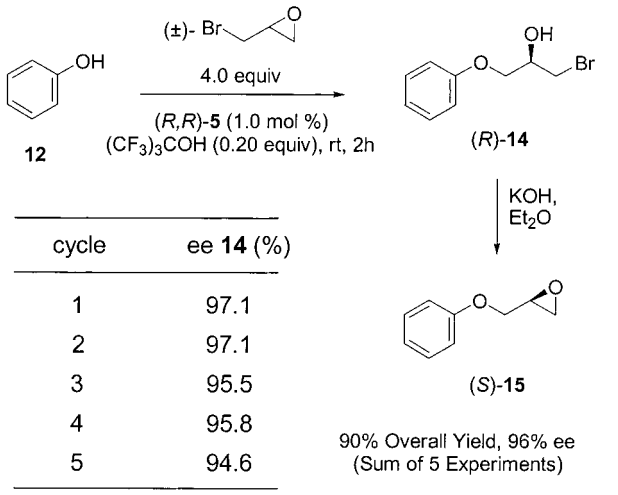


Figure 7.



cycle	ee **14** (%)
1	97.1
2	97.1
3	95.5
4	95.8
5	94.6

Figure 8.

combinations can be envisioned, with subsequent derivatization steps providing additional diversity, simplified purification afforded by the use of polymer-bound catalysts could enable the facile combinatorial synthesis of libraries of stereochemically defined ring-opened products (Figure 6).

The addition of phenol, **12**, to 1-hexene oxide was examined as a model system to test the efficacy of immobilized catalyst **5** for phenol additions to epoxides (Figure 7). In the presence of low loadings of **5**, this reaction provided excellent yields of the ring-opened product **13** in very high enantiomeric excess. Addition of tris(trifluoromethyl)methanol, a volatile, nonnucleophilic protic acid additive, was found to accelerate this reaction with no reduction in enantioselectivity or yield, presumably by helping to maintain the catalyst in the Co^{III} oxidation state. By carrying out the reactions to low conversion of epoxide (ca. 25%), the ring-opened product was obtainable in very high ee.[21]

To further explore the utility of polymer-bound catalysts for the enantioselective ring-opening of terminal epoxides by phenols, epibromohydrin was evaluated as a substrate for the reaction (Figure 8). Though the reaction proceeded with high efficiency and enantioselectivity, the bromohydrin product **14** was found to undergo ring-closure slowly to the phenyl glycidyl ether **15** under the conditions of the ring-opening reaction.

(21) Kagan, H. B. in *Topics in Stereochemistry*; Eliel, E. L., Wilen, S. H., Eds.; Wiley: New York, 1987; Vol. 14, pp 249−330.

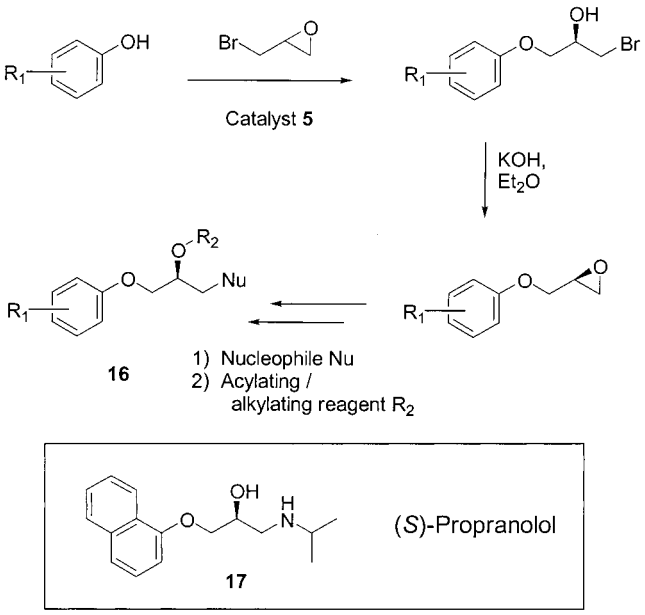


Figure 9. A possible application of the enantioselective ring-opening of epibromohydrin with phenols in combinatorial synthesis.

However, the crude reaction mixture could be converted quantitatively to **15** after catalyst removal by filtration by the addition of solid KOH. Subsequent filtration and removal of volatile materials provided the epoxide product in high yield, >99% purity and excellent enantiomeric excess without further purification. Further elaboration of the aryl glycidyl ether provides a straightforward strategy for the synthesis of combinatorial libraries of the general structure **16**, an example of which includes the antihypertensive agent Propranolol, **17** (Figure 9).

B. Synthesis and Applications of Silica-Bound Chiral Co(Salen) Complexes. We have also explored the use of silica as an insoluble support for the covalent attachment of chiral Co(salen) complexes. With the attributes of inflexibility and noncompressibility, silica provides a stationary phase amenable to incorporation in continuous flow reactors, as well as a surface upon which site isolation of supported catalysts may be more carefully defined than on a flexible polymer backbone such as polystyrene. The preparation of ligand **19**, suitable for attachment to a silica surface, is shown in Figure 10.

The bifunctional tether **18**, bearing one end reactive toward silica and the other appropriately functionalized for attachment to the ligand **3**, was prepared in three steps without need for chromatographic purification starting from 10-undecylenic acid. Carbodiimide-mediated coupling to **3** afforded **19** as a yellow oil, which could be purified chromatographically with good recovery. Attachment of the silyl ether to silica using the conditions of Pirkle[22] provided the silica-bound ligand as a yellow powder after filtration and rinsing. Addition of a solution of $Co(OAc)_2$ in methanol/toluene yielded silica-bound Co(salen) complex **20** as a red-brown powder.

The efficacy of complex **20** in the HKR reaction was tested using styrene oxide, **21**, as a model substrate (Figure 11). The HKR of **21** using silica-bound catalyst **20** was found to be efficient and highly enantioselective. Using only 0.7 mol % catalyst, in 3 h the reaction had proceeded to nearly complete conversion of the reactive enantiomer of the starting material, forming the diol product **22** in excellent ee. The k_{rel} for this particular substrate was calculated to be 58 based on the ee of

(22) Pirkle, W. H.; Welch, C. J.; Lamm, B. *J. Org. Chem.* **1992**, *57*, 3854−3860.

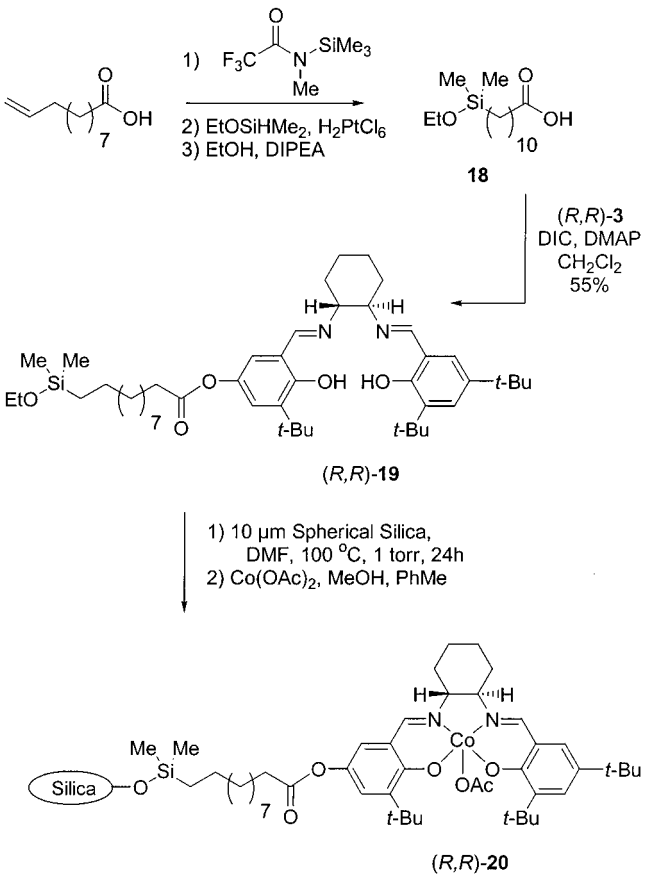


Figure 10.

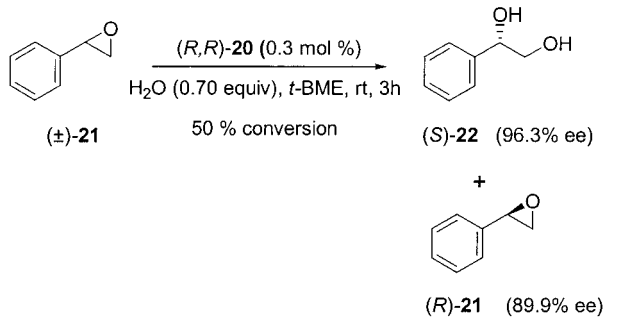


Figure 11. HKR of styrene oxide with silica-bound Co(salen) complex (*R,R*)-**20**.

the recovered epoxide. The ee of the diol product is elevated relative to the unreacted epoxide as a result of ring-opening at the benzylic position of the less reactive enantiomer of epoxide. This affords the same enantiomer of diol as does reaction at the terminal position of the more reactive epoxide enantiomer.

C. Application of Silica-Bound Co(Salen) to a Continuous-Flow System for HKR. Continuous-flow reaction systems incorporating an immoibilized catalyst can have clear practical advantages relative to homogeneous systems.[23] Epoxy alcohol **8** was selected as a model substrate for evaluating this methodology in the HKR with catalyst **20**. This particular substrate has the property that all reaction components (substrate, water, product), with the exception of the catalyst, are miscible under the reaction conditions.[24] The reaction was first examined in a batchwise manner. The HKR of **8** was found to proceed in the presence of silica-bound catalyst **20** with reactivity and

(23) (a) Kamahori, K.; Ito, K.; Itsuno, S. *J. Org. Chem.* **1996**, *61*, 8321−8324. (b) Itsuno, S.; Ito, K.; Maruyama, T.; Kanda, N.; Hirao, A.; Nakahama, S. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 3329−3331.

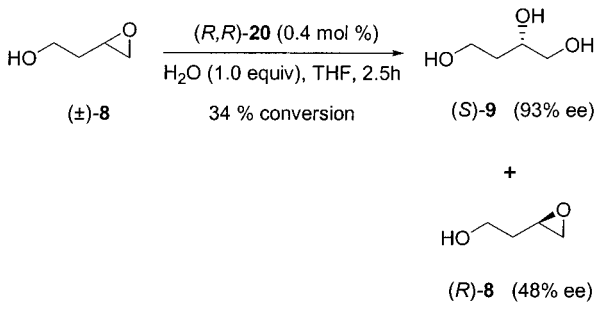


Figure 12. HKR of 4-hydroxy-1-butene oxide with silica-bound Co-(salen) complex (*R,R*)-**20**.

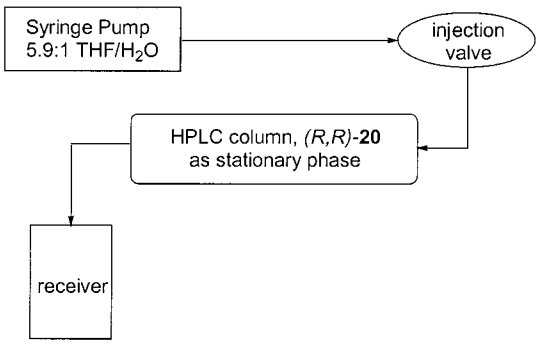
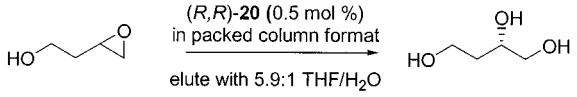


Figure 13. Continuous-flow apparatus for the HKR of **8** over silica-bound catalyst **20**.



Cycle	Conversion (%)	*ee* **8** (%)	*ee* **9** (%)	k_{rel}	yield **9** (%)
1	36	54.0	94.7	63	34
2	39	61.1	94.2	63	39

Figure 14. Continuous-flow HKR of 4-hydroxy-1-butene oxide over silica-bound Co(salen) complex (*R,R*)-**20**.

enantioselectivity comparable to the polystyrene-bound catalyst variant, affording product in 93% ee at 34% conversion of epoxide (Figure 12).

A simple apparatus for the continuous-flow HKR of **8** over a packed bed of catalyst **20** was constructed using a standard laboratory syringe pump as a solvent delivery device, an HPLC injector valve equipped with an injection loop for loading reagents into the reactant stream, a stainless steel HPLC column packed with **20** as the catalyst bed, and a receiver flask for the collection of product. A schematic diagram of the apparatus is shown in Figure 13.

The results of this continuous-flow HKR of **8** over silica-bound catalyst **20** are summarized in Figure 14. A solution of **8** in 5.9:1 THF/water was injected into a solvent stream of 5.9:1 THF/water and passed through the column containing **20**. The column was then rinsed with additional THF/water and the combined eluates were concentrated in vacuo, removing excess solvent and remaining starting material, to yield the desired triol **9** in good yield and high enantiomeric excess. The column could

(24) While only select epoxide substrates form a single phase in the HKR and are thus amenable to continuous flow processes, the ring-opening of epoxides by phenols occurs in a single-phase reaction mixture. Application of continuous flow processes to this class of asymmetric transformation holds considerable promise and is currently under investigation.

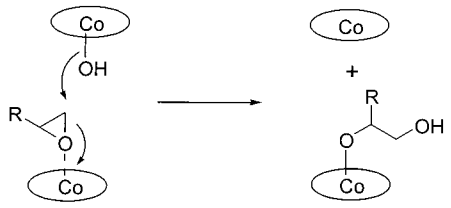


Figure 15. Proposed cooperative mechanism for the hydrolytic kinetic resolution of terminal epoxides.

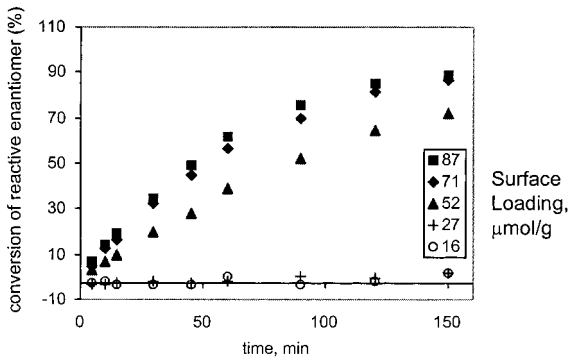


Figure 16. Plot of epichlorohydrin conversion vs time in the HKR using various loadings of catalyst on the silica surface.

be regenerated by elution of a small volume of acetic acid/toluene; a second cycle of the HKR of **8** yielded product **9** with ee and yield comparable to the first cycle. Given the straightforward preparation of the immobilized catalyst **20**, and the effectiveness and experimental ease of its use in the synthesis of enantioenriched products, such catalysts could hold promise for the practical preparation of chiral building blocks in a continuous-flow manner.

D. Mechanistic Investigation of the HKR of Terminal Epoxides Using Silica-Bound Chiral Co(Salen) Complexes. Preliminary studies into the mechanism of the hydrolytic kinetic resolution of terminal epoxides using Co(salen) complex **1** indicate that the reaction rate exhibits a second-order dependence on catalyst concentration.[8a] By analogy to the mechanism of the Cr(salen)-catalyzed enantioselective ring-opening of meso epoxides by hydrazoic acid,[12] the kinetic behavior exhibited by the Co(salen) catalyst in the HKR suggests a cooperative mechanism for epoxide ring-opening such as that illustrated in Figure 15.

A direct means of examining the degree of catalyst cooperativity is to assess the effect of site-isolation of the catalyst on an inflexible solid support.[4] Batches of catalyst **20** were prepared with various loadings of Co(salen) on the silica surface, and the rates of the HKR of styrene oxide and epichlorohydrin were determined using these different catalyst batches. The enantioselectivity of the reaction was not affected by variation of the catalyst loading. Kinetic profiles for epichlorohydrin conversion as a function of different batches of **20** are shown in Figure 16. Analysis of the kinetic data reveals clearly that there is a minimum loading of catalyst on the silica surface required for the reaction to proceed.

The probability that any catalyst on the silica surface can interact with any other catalyst was calculated according to the method of Collman[4a] from the loading level of Co(salen) on the silica surface (established by elemental analysis), an estimation made by molecular modeling of the length of the tether between the silica surface and the salen ligand, and the surface area of the silica particulate used in the synthesis. A plot of the rates of the HKR of epichlorohydrin and styrene oxide, corrected for the absolute amount of catalyst present in each experiment, versus the probability that any catalyst can interact with any other catalyst is shown in Figure 17.

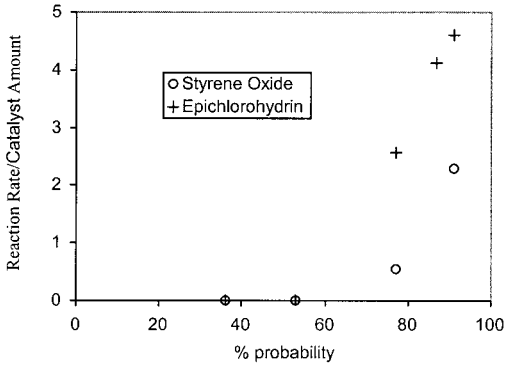


Figure 17. Plot of the rate of the HKR of styrene oxide and epichlorohydrin vs the probability of catalyst interaction on the silica surface.

A remarkable correlation between reaction rate and site isolation is evident from this analysis. While there is essentially no observable reaction at lower catalyst concentrations on the silica surface, increasingly higher rates of reaction are observed for systems wherein high surface loading allows, and ultimately favors, the interaction of bound catalysts. These results lend strong support to a cooperative bimetallic mechanism. It is interesting to note that, in the case of polystyrene-bound catalyst **5**, the flexibility of the support appears to facilitate intercomplex interactions, as the reactions proceed with rates comparable to the solution-phase catalyst **1** and to the high-loading silica-bound catalyst **20**.

Conclusions

This work demonstrates the synthetic applicability and mechanistic utility of polymer-supported chiral Co(salen) complexes. The benefits usually postulated to be associated with immobilization of soluble catalysts—facilitated product purification, catalyst recycling, and adaptation to continuous flow methodology—have all been realized in the solid-supported chiral Co(salen) complexes **5** and **20**. Use of these catalyst systems proved particularly advantageous in the HKR of substrates such as epichlorohydrin **6** and epoxyalcohol **8** where purification had proven problematic with homogeneous catalysts. However, the immobilized salen complexes are likely to hold more general utility with possible large scale applications using immobilized catalyst beds and small scale applications to library synthesis. These are the subject of ongoing investigation.

Experimental Section

General. Tetrahydrofuran, toluene, and TBME were distilled from sodium/benzophenone ketyl prior to use. Commercially available starting materials were used as received or distilled over calcium hydride. Analytical thin-layer chromatography was performed on EM Reagent 0.25 mm silica gel 60-F plates. Flash chromatography was performed using EM silica gel 60 (230−400 mesh).

Gas chromatographic (GC) analyses were conducted on Hewlett-Packard HP5890 Series II gas chromatographs equipped with the following commercially available capillary columns: HP-5 (30 m × 0.25 mm × 0.25 μm film; Hewlett-Packard), Cyclodex-B (30 m × 0.25 mm × 0.25 μm film; J & W Scientific), and Chiraldex γ-TA (20 m × 0.25 mm × 0.25 μm film; Advanced Separation Technologies, Inc.).

Infrared spectra were recorded on a Mattson Galaxy Series FTIR 3000 spectrometer. ^{1}H NMR spectra were recorded on a Bruker DMX-500, AM-500, AM-400, or AM-300 spectrometer. Chemical shifts are

reported in ppm downfield from tetramethylsilane as an internal standard. ^{13}C NMR spectra were recorded on a Bruker AM-500 (125 MHz) or AM-400 (100 MHz) spectrometer with broadband proton decoupling. Chemical shifts are reported in ppm downfield from tetramethylsilane with the solvent reference as the internal standard (deuteriochloroform: δ 77.0 ppm). Fast atom bombardment (FAB) mass spectra were obtained on a JEOL AX-505 or SX-102 high-resolution magnetic sector mass spectrometer by the Harvard University Mass Spectrometry Laboratory. HPLC analysis was performed on a Hewlett-Packard Series 1050 quaternary pump HPLC system equipped with an HP 1050 diode array detector.

Synthesis of (R,R)-3. (a) 3-*tert*-Butyl-2,5-dihydroxybenzaldehyde: A tetrabutylammonium fluoride solution (1.0 M in THF, 30.5 mL, 30.5 mmol, Aldrich) was added dropwise to a solution of 3-*tert*-butyl-2-hydroxy-5-triisopropylsiloxybenzaldehyde[25] (9.0 g, 25.4 mmol) in 60 mL of THF at −78 °C and allowed to warm to room temperature over 3 h. The reaction mixture was poured into 100 mL of water and extracted (100 mL × 3) with diethyl ether. The organic layers were combined, washed with saturated aqueous ammonium chloride (100 mL × 2), dried over magnesium sulfate, and concentrated. The product was purified by silica gel chromatography (diethyl ether/hexanes, 1:4) to give 3.5 g (71% yield) of product as a yellow solid. Mp (open capillary) 181−183 °C; IR (KBr) 3400 (b), 2968, 2877, 1596, 1645, 1589, 1495, 1263, 1154 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.07 (s, 1H), 7.22 (d, J = 1.6 Hz, 1H), 7.13 (d, J = 1.4 Hz, 1H), 1.52 (s, 9H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 196.3, 153.1, 149.6, 138.4, 122.9, 115.4, 101.8, 34.4, 28.9; HRMS (FAB) calcd for $C_{11}H_{14}O_3Si$ $[M]^+$ 194.0943, found 194.0935.

(b) Dissymmetric salen ligand 3: To a solution of 3,5-di-*tert*-butylsalicylaldehyde (2.25 g, 9.6 mmol) and 3-*tert*-butyl-2,5-dihydroxybenzaldehyde (0.62 g, 3.2 mmol) in CH_2Cl_2 (20 mL) was added (*R*)-1,2-diaminocyclohexane (0.73 g, 6.4 mmol). The reaction mixture was stirred at room temperature for 12 h, then concentrated to yield a yellow foam. (This product was used without further purification in the synthesis of **5** by resin-capture.) The mixture of salen ligands could be separated by silica gel chromatography (gradient elution: diethyl ether/hexanes, 1:20 to 1:1) to give **3** (1.15 g, 95% theoretical yield) as a yellow foam. IR (film) 3316 (b), 2954, 2864, 1630, 1598, 1465, 1440 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.35 (s, 1H), 8.12 (s, 1H), 7.42 (d, J = 2.3, 1H), 7.05 (d, J = 2.3, 1H), 6.87 (d, J = 2.3, 1H), 6.44 (d, J = 2.3, 1H), 3.29 (m, 2H), 1.89 (m, 4H), 1.71 (m, 4H), 1.52 (s, 9H), 1.42 (s, 9H), 1.32 (s, 9H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 166.0, 165.2, 158.9, 154.6, 147.0, 140.0, 138.6, 136.8, 127.3, 126.2, 118.4, 118.3, 117.8, 114.9, 72.1, 72.0, 35.1, 34.9, 34.1, 33.2, 33.0, 31.7, 31.5, 29.6, 29.4, 24.3; HRMS (FAB) calcd for $[C_{32}H_{46}N_2O_3 + H]^+$ 507.3587, found 507.3583.

Synthesis of (R,R)-5. Hydroxymethyl polystyrene (Advanced Chemtech, 2% cross-linked 90 μm beads, 0.8 mmol/g, 0.50 g, 0.4 mmol), 4-nitrophenyl chloroformate (322 mg, 1.6 mmol), and DMAP (49 mg, 0.4 mmol) were combined, suspended in CH_2Cl_2 (5 mL), and shaken at room temperature for 1 h. Filtration and rinsing with anhydrous CH_2Cl_2 followed by drying in vacuo yielded colorless beads. The IR spectrum (KBr pellet) revealed a strong absorbance at 1765 cm^{-1}. To a suspension of this material in anhydrous DMF (5.0 mL) was added (*R,R*)-**3** (304 mg, 0.59 mmol), DMAP (49 mg, 0.4 mmol), and DIPEA (0.14 mL, 0.8 mmol). The resulting yellow suspension was shaken at room temperature for 1.5 h, then filtered and rinsed sequentially with DMF, CH_2Cl_2, MeOH, and CH_2Cl_2 and dried in vacuo to yield the product as yellow beads. The IR spectrum (KBr pellet) contained strong absorbances at 1755 and 1630 cm^{-1}. Preparation of the polystyrene-bound salen by resin capture was performed exactly as above except the mixture of isomers obtained in the preparation of **3** (outlined above) was used.

Cobalt insertion into the polystyrene-bound ligand was accomplished by adding a solution of $Co(OAc)_2 \cdot 4H_2O$ (199 mg, 0.8 mmol) in 5 mL 1:1 MeOH/toluene to the resin beads (0.50 g) with gentle stirring at room temperature. The beads turned dark red over a 2-min period. After 1 h the beads were filtered and rinsed sequentially with MeOH, CH_2Cl_2, 9:1 toluene/HOAc, CH_2Cl_2, MeOH, and CH_2Cl_2 and then dried in vacuo to yield the product as very dark red beads. The IR spectrum (KBr pellet) contained strong absorbances at 1755 and 1630 cm^{-1}. Elemental analysis indicated 0.94% Co, corresponding to a final loading of 0.16 mmol/g of Co.

HKR of Epichlorohydrin 6 with Polystyrene-Bound Co(Salen) Complex 5. To complex **5** (160 mg, 26 μmol) was added CH_2Cl_2 (0.78 mL), **6** (0.78 mL, 10 mmol), and H_2O (0.126 mL, 7.0 mmol). The reaction was gently stirred for 3 h. An aliquot taken for GC analysis indicated **6** to be present in >99% ee (CD γ-TA, 40 °C, t_R = 8.5, 10.6 min); 92.4% ee of **7** (Cyclodex B, 75 °C, t_R = 7.4, 8.0 min, as the acetonide prepared using 1% w/v camphorsulfonic acid in dimethoxypropane). The conversion was calculated from measurement of the ee of the starting material and product, having established that no racemization occurs under these reaction conditions, to be 52%, indicating a k_{rel} of 133.[26] The reaction was filtered, and the polymer beads were rinsed with 10 mL of CH_2Cl_2. The combined filtrates were washed with water (3 × 2 mL), dried over $MgSO_4$, filtered, and concentrated by rotary evaporation, carefully controlling the pressure at 400 mbar, to yield 0.38 g of **6** (41%) with ee >99%. The polymer beads were rinsed sequentially with MeOH, CH_2Cl_2, 9:1 toluene/HOAc, CH_2Cl_2, MeOH, and CH_2Cl_2 and dried in vacuo prior to recycle.

HKR of 4-Hydroxy-1-butene Oxide 8 with Polystyrene-Bound Co(Salen) Complex 5. To a solution of **8**[27] (50 mg, 0.57 mmol) in 50 μL of THF was added **5** (18 mg, 2.8 μmol) and H_2O (7.2 μL, 0.40 mmol) and the reaction was gently stirred at room temperature for 2.5 h. An aliquot taken for GC analysis indicated **8** to be present in 73% ee (γ-TA, 75 °C, t_R = 9.0, 11.9 min). The ee of product **9** was established by first converting the triol to 3-hydroxytetrahydrofuran by concentrating the aliquot in vacuo to remove remaining **8**, adding catalytic *p*-toluenesulfonic acid, and heating the sample at 100 °C for 1 h. The ee of the cyclized product was determined to be 94% (Cyclodex B, 90 °C, t_R = 6.6, 6.8 min, as the acetate prepared using acetyl chloride/pyridine in CH_2Cl_2), corresponding to a conversion of 44%, and k_{rel} of 71. The reaction was filtered and the polymer beads rinsed with MeOH into a tared flask. The beads were then rinsed sequentially with MeOH, CH_2Cl_2, 9:1 toluene/HOAc, CH_2Cl_2, MeOH, and CH_2Cl_2 and dried in vacuo prior to recycle. After five recycles, the combined filtrates were concentrated in vacuo to yield **9** as a colorless oil (108 mg, 36% yield, 94.4% ee). The ee of **8** in the combined filtrate was determined to be 59%, corresponding to an overall conversion of 38%, and k_{rel} of 63.

Dynamic HKR of Epibromohydrin 10 with Polystyrene-Bound Co(Salen) Complex 5. To complex **5** (16 mg, 2.6 μmol) was added THF (43 μL), **10** (43 μL, 0.50 mmol), and H_2O (13.5 μL, 0.75 mmol). The reaction was gently stirred at room temperature for 24 h. An aliquot taken for GC analysis indicated complete consumption of **10** and **11** to be present in 96% ee (Cyclodex B, 75 °C, t_R = 15.6, 17.0 min, as the acetonide prepared using 1% w/v camphorsulfonic acid in dimethoxypropane). The reaction was filtered and the polymer beads rinsed with CH_2Cl_2 into a tared flask. The beads were then rinsed sequentially with MeOH, CH_2Cl_2, 9:1 toluene/HOAc, CH_2Cl_2, MeOH, and CH_2Cl_2 and dried in vacuo prior to recycle. After five recycles, the combined filtrates were concentrated in vacuo to yield **11** as a colorless oil (352 mg, 94% yield, 96.4% ee) in 90% purity by ^{1}H NMR, the remainder being 1,3-dibromo-2-propanol.

Reaction of Phenol and 1-Hexene Oxide Catalyzed by Polystyrene-Bound Co(Salen) Complex 5. To a solution of phenol (11 mg, 0.11 mmol) in 1-hexene oxide (53 μL, 0.44 mmol) was added **5** (5.5 mg, 0.88 μmol) and F_9-*tert*-butyl alcohol (3.1 μL, 22 μmol). The reaction was gently stirred at room temperature for 4 h. An aliquot taken for GC analysis indicated complete consumption of phenol and **13** to be

(25) Finney, N. S.; Pospisil, P. J.; Chang, S.; Palucki, M.; Konsler, R. G.; Hansen, K. B.; Jacobsen, E. N. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1720.

(26) Reaction conversion was calculated using the equation:[21]

$$\text{conversion} = \frac{ee_{sm}/ee_{prod}}{1 + (ee_{sm}/ee_{prod})}$$

k_{rel} was calculated using the equation:

$$k_{rel} = \frac{\ln[(1 - \text{conversion}) \times (1 + ee_{prod})]}{\ln[(1 - \text{conversion}) \times (1 - ee_{prod})]}$$

(27) Feringa, B. L.; Lange, B. D. *Tetrahedron* **1988**, *44*, 7213−7222.

present in >99% ee (Cyclodex B, 120 °C, t_R = 63.9, 66.0 min). The reaction was filtered, the polymer beads were rinsed with CH_2Cl_2, and the filtrates were concentrated in vacuo to yield **13** as a colorless oil (22.3 mg, 98% yield, >99% ee) in 94% purity by ^{1}H NMR, the remainder being 1,2-hexanediol.

Reaction of Phenol and Epibromohydrin Catalyzed by Polystyrene-Bound Co(Salen) Complex 5. To a solution of phenol (20 mg, 0.21 mmol) in epibromohydrin (73 μL, 0.85 mmol) was added **5** (13.3 mg, 2.1 μmol) and F_9-*tert*-butyl alcohol (5.9 μL, 42 μmol). The reaction was gently stirred at room temperature for 2 h. An aliquot taken for GC analysis indicated complete consumption of phenol. HPLC analysis indicated **14** to be present in 97.1% ee (Chiralcel OD, 9:1 hexanes/2-propanol, t_R = 11.0, 19.6 min). The reaction was filtered, and the polymer beads were rinsed with ether into a tared flask. The beads were then rinsed sequentially with MeOH, and CH_2Cl_2 9:1 toluene/HOAc, CH_2Cl_2, MeOH, CH_2Cl_2, and dried in vacuo prior to recycle. After five recycles, powdered KOH (100 mg) was added to the combined ether filtrates (ca. 50 mL). The reaction was stirred at room temperature at which time GC analysis indicated complete conversion of **14** to phenyl glycidyl ether **15**. Filtration and concentration yielded 142 mg (90%) of **15** in >99% purity by ^{1}H NMR and 96.6% ee (Chiralcel OD, 9:1 hexanes/2-propanol, t_R = 8.0, 13.3 min).

Synthesis of (R,R)-19. Carboxylic acid 18: To a solution of 1-undecylenic acid (0.50 g, 2.7 mmol) in 1.5 of mL CH_2Cl_2 was added *N*-methyl-*N*-(trimethylsilyl)trifluoroacetamide (MSTFA, 1.0 g, 5.0 mmol) with stirring at room temperature. The reaction gently warmed, and was stirred 1 h then concentrated at the rotary evaporator to yield a slightly yellow oil. The oil dissolved in 1.5 mL of CH_2Cl_2 and ethoxydimethylsilane (0.75 mL, 5.4 mmol) and H_2PtCl_6 (ca. 10 mg in 50 μL of 2-propanol) were added with stirring. The reaction was heated to reflux for 1 h then concentrated at the rotary evaporator to yield a slightly yellow oil. To 400 mg (ca. 1.1 mmol) of this product was added 5.5 mL of EtOH and 0.39 mL of DIPEA. The solution was stirred at room temperature for 1 h to selectively deprotect the trimethylsilyl ester in the presence of the ethoxysilane, then was concentrated in vacuo to yield **18** as a slightly yellow oil which was used without further purification. To this was added 11 mL of CH_2Cl_2, DMAP (6 mg, 49 μmol), DIPEA (0.39 mL, 2.2 mmol), diisopropylcarbodiimide (DIC, 0.19 mL, 1.2 mmol), and (*R,R*)-**3** (139 mg, 0.27 mmol). The reaction was stirred at room temperature for 10 h, then diluted with 20 mL of CH_2Cl_2 and extracted with aqueous NH_4Cl. The organic phase was dried over $MgSO_4$, filtered, and concentrated to yield a yellow oil which was purified by flash chromatography over silica gel (1:4 ethyl acetate/hexanes) to yield **19** as a yellow film (118 mg, 55% based on **3**). R_f = 0.50 (10% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$) δ 8.30 (s, 1H), 8.23 (s, 1H), 7.32 (d, J = 2.5 Hz, 1H), 6.98 (d, J = 2.5 Hz, 1H), 6.93 (d, J = 2.5 Hz, 1H), 6.76 (d, J = 2.5 Hz, 1H), 3.65 (q, J = 6.5 Hz, 2H), 3.33 (m, 2H), 2.49 (m, 2H), 2.0−1.1 (m, 60 H), 0.10 (s, 6H). ^{13}C NMR ($CDCl_3$) 171.2, 165.9, 164.6, 158.3, 158.0, 141.5, 140.0, 138.7, 136.5, 127.0, 126.0, 122.7, 121.3, 118.3, 117.8, 72.6, 72.2, 35.0, 34.9, 34.8, 34.1, 33.3, 33.2, 33.1, 31.5, 29.2−29.7, 24.3, 16.4, −2.0. Exact mass (FAB, NBA + NaI) calcd for $[C_{47}H_{76}N_2O_5Si + Na]^+$ 799.5422, found 799.5452.

Synthesis of (R,R)-20. To a solution of **19** (74 mg, 95 μmol) in 1.5 mL of 2:1 CH_2Cl_2/DMF was added 320 mg of 10 μm spherical silica (YMC Inc.) having a surface area of 350 m^2/g. The slurry was stirred and concentrated in vacuo to a yellow powder, which was then heated at 100 °C at 1 Torr with gentle stirring for 20 h. The product was filtered and rinsed sequentially with CH_2Cl_2, MeOH, and CH_2Cl_2 and dried in vacuo to yield a bright yellow powder. Carbon analysis indicated a loading of 4.67% C, corresponding to 87 μmol of ligand/g. To 50 mg of the silica-bound ligand was added a solution of $Co(OAc)_2 \cdot 4H_2O$ (50 mg, 0.20 mmol) in 0.83 mL of 1:1 MeOH/toluene. The reaction was stirred at room temperature for 0.5 h, filtered, rinsed sequentially with MeOH, CH_2Cl_2, 9:1 toluene/HOAc, CH_2Cl_2, MeOH, and CH_2Cl_2, and dried in vacuo to yield **20** as a green powder.

HKR of Styrene Oxide 21 with Silica-Bound Co(Salen) Complex 20. To complex **20** (15 mg, 1.4 μmol) was added tBME (50 μL), **21** (50 μL, 0.44 mmol), and H_2O (5.5 μL, 0.31 mmol). The reaction was gently stirred at room temperature for 3 h. An aliquot taken for GC analysis indicated 50% conversion, with **21** present in 88.9% ee and **22** in 96.3% ee (Cyclodex B, 75 °C for 25 min, then 10°/min to 120 °C, hold 12 min, t_R (**21**) = 20.0, 21.2 min and t_R (**22**) = 34.0, 35.0 min as the acetonide prepared using 1% w/v camphorsulfonic acid in dimethoxypropane). A k_{rel} of 51 was calculated from the reaction conversion as measured by GC and from the ee of **21**.[28]

HKR of 4-Hydroxy-1-butene Oxide 8 with Silica-Bound Co(Salen) Complex 20. To a solution of **8** (10 mg, 0.10 mmol) in 10 μL of THF was added **20** (5.0 mg, 0.44 μmol) and H_2O (2.0 μL, 0.10 mmol) and the reaction was gently stirred at room temperature for 2.5 h. An aliquot taken for GC analysis (as described for the HKR of **8** with catalyst **4**) indicated **8** to be present in 48% ee and **9** in 93% ee, corresponding to a conversion of 34% and k_{rel} of 44.

Continuous-Flow HKR of 4-Hydroxy-1-butene Oxide 8. A 2.0 mm i.d. × 25 mm (internal volume = 79 μL) stainless steel HPLC guard column equipped with 4.5 μm end frits was dry packed with ca. 30 mg (2.6 μmol) of **20**. The catalyst bed was wetted with 5.0 mL of 5.9:1 THF/H_2O at 35 μL/min, then 100 μL of a 5.1 M solution of **8** in THF/H_2O (corresponding to 45 mg, 0.51 mmol **8**) was eluted through the column with 350 μL of THF/H_2O at 20 μL/h. The column was then washed with another 350 μL of THF/H_2O at 35 μL/min, and collected eluate was analyzed by GC (as described for the HKR of **8** with catalyst **5**) to indicate **8** to be present in 54% ee and **9** in 95% ee, corresponding to a conversion of 36% and k_{rel} of 63. Removal of the volatiles in vacuo yielded 18.6 mg (34%) of **9**. The catalyst bed was reoxidized by eluting a small volume of 200 μL of 9:1 toluene/HOAc with anhydrous THF at 35 μL/min, then rinsing the column with 1.0 mL of THF/H_2O at 35 μL/min prior to recycle.

Investigation of the Effect of Catalyst Site Isolation on the HKR Reaction. Catalyst **20** was prepared at loading levels of 16, 27, 52, and 87 μmol/g, as established by carbon analysis, by varying the ratio of **15** to silica used in the synthesis. The probability that any catalyst can interact with any other catalyst was determined according to the method of Collman.[29] The tether length r_2/2 was calculated using the molecular modeling program Chem3D[30] to be 22.8 Å, with a base radius r_1/2 of 3.0 Å. The HKR of styrene oxide and epichlorohydrin were conducted with these catalyst batches as described above. Aliquots were periodically taken for GC analysis of reaction conversion and selectivity. Rates of reaction were calculated from plots of ln[conversion] vs time.

Acknowledgment. This research was supported in part by the NCI through the Institute of Chemistry and Cell Biology (ICCB) at Harvard University by the NIH (GM-43214), and by graduate fellowships to D.A.A. from Eli Lilly. The authors also thank Dr. Stefan Peukert for valuable experimental contributions.

JA984410N

(28) Values for k_{rel} were calculated using the equation:[21]

$$k_{rel} = \frac{\ln[(1 - \text{conversion}) \times (1 + \text{ee}_{sm})]}{\ln[(1 - \text{conversion}) \times (1 + \text{ee}_{sm})]}$$

(29) Assuming a random distribution of catalyst moieties on the silica surface, the probability that any one can interact with any other is given by

$$P = NX - \frac{N^2X^2}{2!} + \frac{N^3X^3}{3!} - \frac{N^4X^4}{4!} + ...$$

where N is the total number of surface-bound species, and $X = \pi(r_2^2 - r_1^2)/A$, where r_1/2 is the van der Waals radius of the base of the molecule at the surface, r_2/2 is the length of the molecule, and A is the total area of the surface.[4a]

(30) CambridgeSoft Corporation, 100 CambridgePark Drive, Cambridge, MA 02140.