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Highly Selective Hydrolytic Kinetic Resolution of Terminal Epoxides Catalyzed by Chiral (salen)Co^{III} Complexes. Practical Synthesis of Enantioenriched Terminal Epoxides and 1,2-Diols

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Abstract: The hydrolytic kinetic resolution (HKR) of terminal epoxides catalyzed by chiral (salen)Co^{III} complex 1·OAc affords both recovered unreacted epoxide and 1,2-diol product in highly enantioenriched form. As such, the HKR provides general access to useful, highly enantioenriched chiral building blocks that are otherwise difficult to access, from inexpensive racemic materials. The reaction has several appealing features from a practical standpoint, including the use of H₂O as a reactant and low loadings (0.2–2.0 mol %) of a recyclable, commercially available catalyst. In addition, the HKR displays extraordinary scope, as a wide assortment of sterically and electronically varied epoxides can be resolved to ≥99% ee. The corresponding 1,2-diols were produced in good-to-high enantiomeric excess using 0.45 equiv of H₂O. Useful and general protocols are provided for the isolation of highly enantioenriched epoxides and diols, as well as for catalyst recovery and recycling. Selectivity factors (k_{rel}) were determined for the HKR reactions by measuring the product ee at ca. 20% conversion. In nearly all cases, k_{rel} values for the HKR exceed 50, and in several cases are well in excess of 200.

Introduction

The importance of epoxides in organic synthesis arises partly from the occurrence of the strained three-membered ring unit in a number of interesting natural products¹ but more so because the ring opening of epoxides allows straightforward elaboration to useful new functionality, often with generation of new carbon–carbon bonds. Indeed, reactions of epoxides with nucleophiles, Lewis acids, radicals, reducing agents, oxidizing agents, acids, and bases have all been well documented and utilized in synthesis.² Further, the stereospecific manner in which epoxides generally react renders these compounds attractive chiral building blocks for asymmetric synthesis.

Since those epoxides that are produced naturally are typically complex compounds available only in limited amounts, Nature's chiral pool has not proven to be a useful direct source of optically active epoxides for use in organic synthesis. Instead, enantioenriched epoxides have been accessed indirectly from the chiral pool via multistep procedures.³ These, however, tend to be inherently inefficient, and the range of epoxides available by this approach is also quite limited. As a consequence, the preparation of enantioenriched epoxides has long stood as a most significant target for asymmetric synthesis. In particular, the identification of catalytic asymmetric olefin oxidation methods has been an area of active research for several decades, and the advances made in this field have increased greatly the number of enantiomerically enriched epoxides available for use in organic synthesis.

Among available methods for the preparation of enantioenriched epoxides, the Sharpless epoxidation reaction has arguably had the most profound impact of any asymmetric

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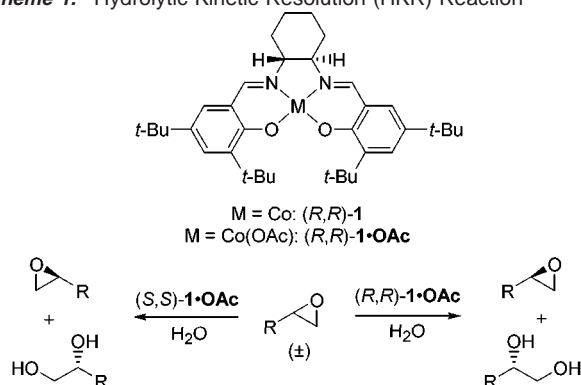
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catalytic reaction discovered thus far, providing general access to highly enantioenriched epoxyalcohols.⁴ More recently, the epoxidation of unfunctionalized conjugated olefins by chiral (salen)Mn^{III} complexes has enabled the practical synthesis of certain classes of enantiomerically enriched epoxides.⁵ A highly complementary strategy for epoxidation of simple olefins involving chiral dioxirane intermediates has expanded the range of chiral epoxides now accessible in enantioenriched form to a significant extent.⁶ Indirect routes to enantiopure epoxides involving asymmetric catalytic dihydroxylation or reduction reactions have also proven highly valuable in specific contexts.⁷

Despite these considerable advances in asymmetric catalytic synthesis of epoxides, to date no general methods have been identified for the direct preparation of highly enantioenriched 1-oxiranes, arguably the most valuable class of epoxides for organic synthesis.⁸ The utility of terminal epoxides as chiral building blocks is perhaps best illustrated by the fact that the few examples for which effective catalytic approaches exist have found extensive use in asymmetric synthesis. In particular, glycidol and a number of its derivatives are available in enantiomerically enriched form using the Sharpless epoxidation technology⁹ or by enzymatic kinetic resolution methods,¹⁰ and these compounds have become widely used starting materials for target-oriented synthesis.¹¹ Epichlorohydrin has been rendered commercially available in bulk by microbial resolution of (±)-2,3-dichloro-1-propanol,¹² and it, too, has found widespread application.

Pursuant to our own efforts directed toward the development of catalysts for the enantioselective nucleophilic ring opening of meso epoxides,¹³ we became interested in the possibility of developing analogous methodology for the kinetic resolution of 1,2-epoxides. One of the most attractive features of kinetic resolution processes in general is the fact that the enantiomeric

Scheme 1. Hydrolytic Kinetic Resolution (HKR) Reaction



composition of unreacted substrate can be controlled by adjusting the degree of conversion, and virtually enantiopure material can be obtained at appropriately high conversions.¹⁴ This is an important consideration in the present case, since low-molecular weight terminal epoxides are typically liquids at room temperature and are not readily derivatized as salts, and therefore it is not a straightforward matter to upgrade their enantiomeric composition by crystallization. However, in the absence of straightforward substrate racemization protocols, kinetic resolutions have the significant disadvantage of a 50% maximum yield of substrate recovery. With a specific interest in devising a practical method for obtaining highly enantioenriched terminal epoxides, we deemed that the following criteria must be met in order for a kinetic resolution approach to be viable:¹⁵

(1) The racemic epoxides must be inexpensive or easily accessible from inexpensive commercial starting materials.

(2) The catalyst for the resolution must be readily available in both enantiomeric forms. In the optimal case, the catalyst would be used in small quantities in the resolution and would be recyclable.

(3) The nucleophile used for the ring opening should be inexpensive and easily handled.

(4) The resolved epoxides must be obtained in good yield and very high enantiopurity and must be easily separated from the ring-opened products.

(5) Ideally, although not necessarily, the ring-opened byproducts should also be valuable chiral building blocks and be obtainable in high enantiomeric excess.

To this end, we communicated recently the discovery that the (salen)Co complex **1** catalyzed the efficient hydrolytic kinetic resolution (HKR) of a variety of terminal epoxides (Scheme 1).^{16–18} This new method appeared to hold considerable promise with regard to meeting all of the criteria outlined above. First,

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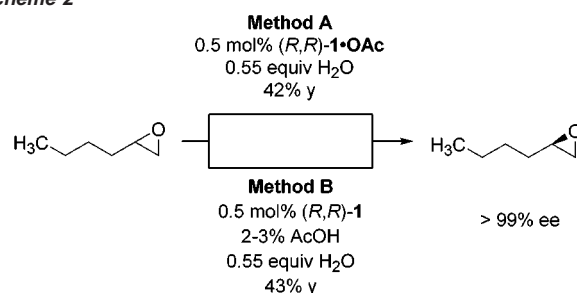
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racemic 1,2-epoxides are generally available directly from commercial suppliers at low cost or are obtainable in one step from inexpensive α -olefins or aldehydes. In fact, certain racemic epoxides, such as propylene oxide, epichlorohydrin, styrene oxide, and butadiene monoepoxide, are commodity chemicals and are no more expensive than common organic solvents. Second, the ligands for catalyst **1** had previously been commercialized and manufactured on a ton scale in the context of (salen)Mn epoxidation catalysts.¹⁹ The cobalt analogues (*R,R*)-**1** and (*S,S*)-**1** proved equally accessible, and these are also now available in bulk.²⁰ Third, water is perhaps the ideal reagent for effecting the resolution reaction: it is inexpensive and safe, and the rate of the ring-opening reaction can be controlled simply by modulating the rate of addition of water to the epoxide–catalyst mixture.²¹ Fourth, for those examples that were described in the preliminary report, highly enantioenriched epoxides were recovered from the HKR. Finally, the HKR provided useful enantioenriched 1,2-diols, including many that are otherwise not readily accessible using existing asymmetric dihydroxylation methods.²²

The HKR has seen rapid adoption as the method of choice for the preparation of a variety of terminal epoxides in enantioenriched form, and a number of applications in target-oriented synthesis have been reported already.²³ In addition, the commercial manufacture of enantioenriched propylene oxide, epichlorohydrin, and styrene oxide using HKR methodology has been implemented, thereby reducing the cost of these useful chiral building blocks.²⁰ We have sought to elucidate fully the synthetic potential of this reaction by establishing its substrate scope and outlining optimized procedures for the isolation of resolved epoxides and 1,2-diol products in high enantiomeric excess. In that regard, we set as a common criterion for all substrates the isolation of resolved epoxide in >99% ee. We also aimed to develop general protocols for the HKR that would allow the straightforward evaluation of previously unexamined

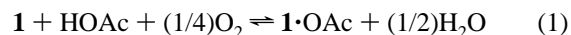
Scheme 2



substrates. As a result of these efforts, we have discovered that the HKR is an extraordinarily general reaction, allowing efficient kinetic resolution of virtually any type of terminal epoxide. Our findings are described herein.

Results and Discussion

(I) Preparation of Catalyst and General Experimental Considerations. Both enantiomers of the (salen)Co^{II} complex **1** are available commercially on research or commercial scale,²⁰ or they can be prepared from the commercially available ligands using Co(OAc)₂ (see Experimental Section). The Co(II) complex **1** is catalytically inactive, however, and it must be subjected to one-electron oxidation to produce a (salen)Co^{III}X complex (X = anionic ligand) prior to the HKR. This may be done conveniently by aerobic oxidation in the presence of a mild Brønsted acid. Water alone was found not to mediate the oxidation reaction, but a screen of additives revealed that acetic acid was effective and that the corresponding Co(III) precatalyst **1**·OAc is convenient for use in HKR reactions both in terms of its preparation and reactivity (eq 1).²⁴



Two useful methods for the generation of complex **1**·OAc have been developed. Method A involves isolation of **1**·OAc as a crude solid prior to the HKR. The Co(II) complex **1** is dissolved in toluene to generate a ca. 1 M solution, and acetic acid (2 equiv) is added. The resulting solution is stirred open to air at room temperature for 30 min, during which time the color of the mixture changes from orange to dark brown. All volatile materials are removed in vacuo, affording **1**·OAc as a brown solid residue that can be used without further purification. Method B involves in situ generation of **1**·OAc under HKR conditions by suspension of the Co(II) complex **1** in epoxide or epoxide/solvent and addition of HOAc under an aerobic atmosphere.

Catalyst obtained by both methods was examined for each of the epoxides described in this study. For certain substrates such as 1-hexene oxide, catalyst prepared by either method leads to essentially identical results (Scheme 2). In these situations, in situ catalyst generation (method B) is preferable since the

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- (24) The identity of the counterion can influence reactivity, enantioselectivity, and catalyst lifetime in the HKR. With the goal of defining general protocols for HKR of the broadest range of substrates, we carried out all reactions with catalyst **1**·OAc. However, other derivatives of **1** have been found to display greater reactivity toward certain epoxides, and this is revealed most dramatically in the HKR of relatively unreactive substrates. For example, the HKR of methyl glycidate required use of 2 mol % **1**·OAc to provide recovered epoxide in 99% ee in 24 h (Table 4, entry 4). In contrast, use of the *p*-nitrobenzoate complex **1**·O₂CC₆H₄(NO₂) at the 0.9 mol % level led to >99% ee epoxide within the same time frame (C. P. Stevenson, work in progress). The synthetic implications and mechanistic basis for these effects are under investigation and will be described separately.

Table 1. Hydrolytic Kinetic Resolution (HKR) of Aliphatic Terminal Epoxides^a

entry	epoxide substituent	cat. loading ^b (mol %)	cat. oxidation method	solvent ^c	reaction time (h)	isolated yield ^d (%)
1	CH ₃	0.2	A		18	46
2	(CH ₂) ₃ CH ₃	0.5	B		18	43
3	(CH ₂) ₁₁ CH ₃	0.5	A	<i>i</i> -PrOH	24	42
4	(CH ₂) ₂ CH=CH ₂	0.5	B	THF	18	43
5	CH ₂ Ph	0.5	B	THF	18	46
6	<i>c</i> -C ₆ H ₁₁	0.5	B	THF	18	44
7	<i>t</i> -C ₄ H ₉	2.0	A	(±)1,2-hexanediol	48	41

^a Reactions were carried out with 0.55 equiv of H₂O relative to racemic epoxide. Water was added dropwise to a solution of catalyst and epoxide at 0 °C, and the reaction mixture was allowed to warm to room temperature with continuous stirring for the indicated time. ^b Catalyst loading based on racemic epoxide. ^c In those cases where solvent was included (entries 3–7), 1:1 (v/v) ratio was used relative to epoxide. ^d Isolated yield of >99% ee epoxide based on racemic material (theoretical maximum = 50%).

procedure avoids an extra solvent removal step. On the other hand, catalyst prepared by method A was found to be more effective with less reactive substrates (vide infra) and was applicable to all substrates examined. Therefore, if HKR did not afford epoxide in >99% ee with catalyst prepared by method B after optimization of solvent and catalyst loading, then catalyst prepared by method A was employed.

Aside from the method of generation of **1**•OAc, the only reaction parameters in the HKR that required optimization for individual substrates were catalyst loading and choice of solvent. With few exceptions, epoxide of >99% ee could be obtained using 0.55 equiv of water relative to racemate. Relatively small epoxides with some degree of water solubility could be resolved effectively without added solvent. However, the HKR of more lipophilic substrates did benefit from inclusion of a water-miscible organic solvent such as tetrahydrofuran (THF), 2-propanol, or 1,2-hexanediol. In general, one volume of solvent relative to racemic epoxides was sufficient to allow efficient HKR. Catalyst loadings of 0.5 mol % or lower relative to racemic epoxide were effective for many substrates, but epoxides bearing sterically hindered or unsaturated substituents often required more catalyst (up to 2 mol %) to attain complete resolution. Reactions were initiated at 0 °C and then allowed to warm to room temperature with continued stirring for 12–18 h.

(II) HKR of Terminal Epoxides. (a) Aliphatic Epoxides.

As illustrated in Table 1, terminal aliphatic epoxides are outstanding substrates for the HKR, and for all substrates examined the epoxide could be recovered in ≥99% ee and in 82–92% of the theoretical yield (41–46% yield based on racemic epoxide). The HKR of propylene oxide proved to be a particularly efficient reaction, requiring only 0.2 mol % catalyst under solvent-free conditions and affording recovered epoxide in high yield (entry 1). The HKR of 1-hexene oxide also proceeded well under solvent-free conditions (entry 2), but more lipophilic epoxides with minimal solubility in water or the diol product required the use of added solvents. For example, the diol product precipitates from the reaction mixture in the HKR of (±)-1,2-epoxytetradecane under solvent-free conditions. This renders mixing extremely difficult in the late stages of the resolution reaction and thereby leads to severely diminished reaction rates. The HKR of this substrate was effected successfully within 24 h using *i*-PrOH as the solvent at high initial concentration of epoxide (25 M), and employing 1 equiv of H₂O

relative to the racemate. Similarly, the HKR of 1,2-epoxy-5-hexene proved difficult to carry to completion under solvent-free conditions, affording only 95% ee epoxide after 24 h. However, using in situ generated catalyst (method B) and THF as solvent (1:1, v/v, THF:H₂O), epoxide could be recovered in 99.5% ee and 86% of the theoretical yield (entry 4). This protocol was equally effective for the HKR epoxypropylbenzene and vinylcyclohexane oxide, affording resolved epoxide in ≥99% ee and 46% and 44% yield, respectively (entries 5,6).

Very hindered aliphatic epoxides such as *tert*-butylethylene oxide proved to be particularly challenging substrates for the HKR, but efficient resolution was ultimately achieved through careful optimization of reaction conditions. Under solvent-free conditions employing up to 2 mol % catalyst generated by either method A or B, no hydrolysis of *tert*-butylethylene oxide was observed at room temperature over the course of several days. A systematic investigation of water-soluble organic solvents (e.g. THF, *i*-PrOH, and 1,2-diols) revealed that the use of 1,2-hexanediol as solvent and 2 mol % **1**•OAc (generated by method A) was effective for inducing resolution of this epoxide to ≥99% ee (entry 7). In general, such moderately lipophilic 1,2-diols have proven quite effective as solvents for the most unreactive substrates in the HKR, presumably because of their ability to effectively solubilize epoxide, water, and diol product.²⁵

(b) Halogenated Epoxides. Three-carbon (C-3) epoxides bearing halide substituents are highly versatile synthetic building blocks because each carbon is functionalized and a potential site of nucleophilic attack. Epichlorohydrin, in particular, is a readily available C-3 unit that is widely employed in organic and polymer synthesis.²⁶ However, this most interesting substrate for the HKR initially proved problematic. It was found to undergo gradual racemization under the reaction conditions, thereby rendering it difficult to recover from HKR reactions in highly enantioenriched form.^{16b} The racemization pathway could be suppressed, however, by carrying out the reaction at 0–4 °C in the presence of THF. Using 0.5 mol % **1**•OAc (generated by method A), the epoxide could be recovered in ≥99% ee and 43% yield (Table 2, entry 1). In contrast, the HKR of (±)-epibromohydrin afforded the epoxide in 41% yield but only 43% ee under the same reaction conditions. In this case, bromide-catalyzed racemization could not be eliminated; however, it could be used to advantage in the dynamic HKR to produce diol (see section III). The HKR of (±)-epifluorohydrin and (±)-1,1,1-trifluoro-2,3-epoxypropane²⁷ proceeded smoothly under solvent-free conditions with no detectable racemization (entries 3 and 4, Table 2).

(c) Epoxides Bearing Ether and Carbonyl Functionality.

The HKR was found to be applicable to a wide variety of ether containing epoxides (Table 3). Benzyl glycidyl ether, *tert*-butyldimethylsilyl glycidyl ether, and phenyl glycidyl ether all underwent resolution in excellent yield employing 0.5 mol % of the in situ generated catalyst **1**•OAc (method B; entries 1–3). 1-Naphthyl glycidyl ether, a useful precursor to propranolol,²⁸

(25) There was no observable difference in the outcome of HKR reactions carried out with racemic or enantiopure diols. This is consistent with the general observation of the absence of product inhibition in the HKR.

(26) Huber, J. E. In *Encyclopedia of Reagents for Organic Synthesis*, Vol. 4; Paquette, L. A. Ed.; Wiley: New York, 1995; p 2326.

(27) For applications of this interesting building block, see: Katagiri, T.; Irie, M.; Uneyama, K. *Org. Lett.* **2000**, 2, 2423, and references therein.

(28) (a) Klunder, J. M.; Ko, S. Y.; Sharpless, K. B. *J. Org. Chem.* **1986**, 51, 3710. (b) For a report on the application of the HKR to aryl glycidyl ethers as a strategy for the synthesis of β-blockers, see ref c.

Table 2. HKR of Halogenated Terminal Epoxides^a

entry	epoxide substituent	solvent ^b	ee (%)	isolated yield ^c (%)
1	CH ₂ Cl	THF	>99	43
2	CH ₂ Br	THF	43	41
3	CH ₂ F		>99	42
4	CF ₃		>99	42

^a Reactions were carried out with 0.55 equiv of H₂O and 0.5 mol % **1**·OAc prepared from **1** by method A. Reactions were initiated at 0 °C and then allowed to proceed at room temperature for 16–18 h. Reagent and catalyst amounts based on racemic epoxide. ^b In those cases where solvent was included (entries 1 and 2), 1:1 (v/v) ratio was used relative to epoxide. ^c Isolated yield based on racemic epoxide (theoretical maximum = 50%).

Table 3. HKR of Ether-Containing Terminal Epoxides^a

entry	epoxide substituent	cat. loading ^b (mol %)	cat. oxidation method	isolated yield ^c (%)
1	CH ₂ OBn	0.5	B	48
2	CH ₂ O(TBS)	0.5	B	47
3	CH ₂ OPh	0.5	B	47
4 ^d	CH ₂ O(1-naphthyl)	0.5	B	38
5	CH ₂ CH ₂ OBn	0.5	B	42
6 ^e	oxiranylf	1.0	A	36

^a Unless noted otherwise, reactions were carried out at 0 °C to room temperature for 16–18 h, with 0.55 equiv of H₂O relative to racemic epoxide and THF (1:1 (v/v) with respect to epoxide) as solvent. ^b Catalyst loading based on racemic epoxide. ^c Isolated yield of >99% ee epoxide based on racemic epoxide (theoretical maximum = 50%). ^d A 48 h reaction time. ^e A 0.6 equiv amount of H₂O used relative to racemic epoxide. ^f The substrate was D,L-butadiene diepoxide (Aldrich).

Table 4. HKR of Terminal Epoxy Esters, Ketones, and Carbamates^a

entry	epoxide substituent	cat. loading ^b (mol %)	cat. oxidation method	isolated yield ^c (%)
1	CH ₂ OCO _n -C ₃ H ₇	0.5	B	46
2	CH ₂ CO ₂ Et	0.5	B	44
3 ^d	CH ₂ NHBoc	2.0	A	36
4 ^e	CO ₂ CH ₃	2.0	A	43
5 ^{d,f,g}	COCH ₃	2.0	A	40
6 ^{e,f}	COCH ₂ CH ₃	2.0	A	41

^a Unless noted otherwise, reactions were carried out at 0 °C to room temperature for 16–18 h, with 0.55 equiv of H₂O relative to racemic epoxide and THF (1:1 (v/v) with respect to epoxide) as solvent. ^b Catalyst loading based on racemic epoxide. ^c Isolated yield of >99% ee epoxide based on racemic material (theoretical maximum = 50%). ^d A 48 h reaction time. ^e A 24 h reaction time. ^f Reaction was carried out under an atmosphere of O₂ (balloon pressure). ^g A 0.7 equiv amount of H₂O used relative to racemic epoxide.

required longer reaction times to attain high ee in the HKR, but was nevertheless resolved successfully (entry 4). The C-4 building block, (2-phenylmethoxymethyl)oxirane (entry 5) was hydrolyzed efficiently using 0.5 mol % **1**·OAc to yield the enantioenriched epoxide in 42% yield. The HKR of commercially available (±)-butadiene diepoxide was also effected successfully, requiring use of 1.0 mol % of **1**·OAc (prepared by method A) and 0.6 equiv of H₂O to afford the recovered diepoxide in >99% ee and 36% isolated yield. This interesting C-4 chiral building block has particular potential for elaboration to a variety of C₂ symmetric diols.

Epoxides containing carbonyl functionalities were also examined as substrates for the HKR (Table 4). The kinetic resolutions of glycidyl butyrate and ethyl 3,4-epoxybutyrate (entries 1 and 2) were effected in a straightforward manner using 0.5 mol % **1**·OAc (method B) in 46 and 44% yield, respectively.

Table 5. HKR of Terminal, Conjugated Epoxides^a

entry	epoxide substituent	cat. loading ^b (mol %)	isolated yield ^c (%)
1	C ₆ H ₅	0.8	44
2	4-ClC ₆ H ₄	0.8	38
3	3-ClC ₆ H ₄	0.8	40
4	3-(CH ₃ O)C ₆ H ₄	0.8	41
5	3-(NO ₂)C ₆ H ₄	0.8	38
6	2-ClC ₆ H ₄	1.5	38
7 ^d	CH=CH ₂	1.5	36
8 ^e	C≡C(TBS)	0.8	41

^a Unless noted otherwise, reactions were carried out at 0 °C to room temperature for 48 h, with 0.55 equiv of H₂O relative to racemic epoxide and THF (1:1 (v/v) with respect to epoxide) as solvent. ^b Catalyst loading based on racemic epoxide. In all cases, **1**·OAc was prepared by method A. ^c Isolated yield of >99% ee epoxide based on racemic material (theoretical maximum = 50%). ^d A 0.7 equiv amount of H₂O used relative to racemic epoxide; 72 h reaction time. ^e *i*-PrOH used as solvent (1:1 (v/v) relative to epoxide).

The HKR of Boc protected 2,3-epoxy-1-aminopropane (entry 3) required relatively higher catalyst loading (2 mol % **1**·OAc) and longer reaction time (48 h) to produce the epoxide in >99% ee. The resolution of methyl glycidate (entry 4) also required 2.0 mol % catalyst, with the enantioenriched epoxide recovered in 43% yield.²⁴

Epoxy ketones proved to be among the most problematic substrates for the HKR. Under standard HKR conditions, substrates such as 3,4-epoxy-2-butanone (Table 4, entry 5) underwent only partial resolution, with the reduced, inactive Co(II) complex **1** precipitating from the reaction mixture within a few hours. A stoichiometric Baeyer–Villiger-like pathway is presumably responsible for reduction of the catalyst, although no tractable byproducts could be identified. To maintain the catalyst in the requisite Co(III) oxidation state, the HKR of ketone-containing epoxides was carried out under an atmosphere of O₂. In the presence of 2 mol % AcOH and 0.7 equiv of H₂O and with 2 mol % **1**·OAc, 3,4-epoxy-2-butanone was recovered in >99% ee and 40% isolated yield after 48 h.²⁹ The HKR of 1,2-epoxy-3-pentanone (entry 6) was effected under similar conditions to yield recovered epoxide in >99% ee and 41% yield.

(d) Aryl, Vinyl, and Alkynyl Epoxides. Styrene oxide derivatives are among the most useful terminal epoxides from a synthetic standpoint and are therefore particularly important candidates for the HKR reaction. In principle, HKR of these substrates might be plagued by conflicting steric and electronic factors influencing regioselectivity in the epoxide ring opening. It was gratifying, therefore, to observe that resolution of epoxides derived from various types of conjugated terminal olefins (styrene, diene, and enyne derivatives) was possible with catalyst **1**·OAc using water-miscible solvents such as THF (Table 5). The HKR of (±)-styrene oxide was effected using 0.8 mol % catalyst and 0.55 equiv of H₂O, affording the recovered epoxide in 87% yield and >99% ee after 72 h (entry 1). Under similar conditions, both 3- and 4-chlorostyrene oxide were obtained in >99% ee and 77 and 80% yield, respectively (entries 2 and 3).³⁰ Other 3-substituted styrene oxide derivatives

(29) This reaction was applied as a key step in the total synthesis of the natural product fostriecin: Chavez, D. E.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2001**, *40*, 3667.

(30) For an account of the application of epoxidation/HKR protocols to the preparation of 3-chlorostyrene oxide, see: Brandes, B. D.; Jacobsen, E. N. *Tetrahedron: Asymmetry* **1997**, *8*, 3927.

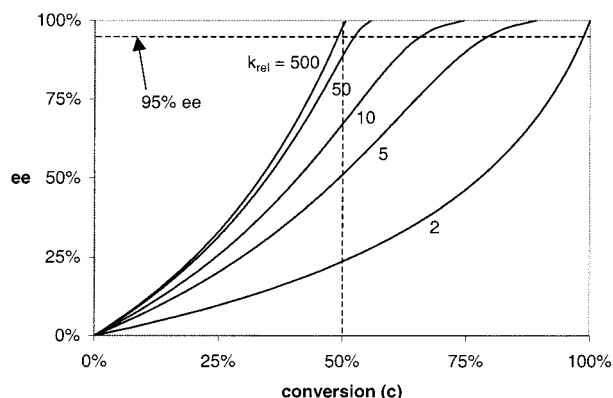


Figure 1. Plot of enantiomeric excess of recovered substrate as a function of conversion for representative k_{rel} values as calculated using the equation $k_{rel} = \ln[(1 - c)(1 - ee_{SM})]/\ln[(1 - c)(1 + ee_{SM})]$.³⁴

displayed similar reactivity in the HKR (entries 4 and 5). In contrast, the resolution of 2-chlorostyrene oxide require increased catalyst loading (1.5 mol % **1**·OAc) in order to attain >99% ee (entry 6).

The Eastman process for the low-cost aerobic epoxidation of butadiene³¹ has rendered butadiene monoepoxide a practically useful building block for organic synthesis and an appealing target for the HKR.³² The resolution of this substrate proceeded in 72 h with 1.5 mol % **1**·OAc and 0.7 equiv of H₂O to yield recovered epoxide in 99% ee and 36% yield (Table 5, entry 7). Alkynyl epoxides also appear to be good substrates for the HKR, as evidenced by the successful resolution of the protected 1,2-epoxybutyne derivative in entry 8 using 0.8 mol % catalyst and *i*-PrOH as solvent.

(III) Preparation of Enantioenriched 1,2-Diols via the HKR. As noted in the Introduction, one of the most attractive features of kinetic resolution processes is the fact that ee of recovered starting substrate increases with conversion, and overresolution (i.e. reactions taken to >50% conversion) allows production of very highly enantioenriched material even if the resolution itself is only moderately selective. This is represented graphically in Figure 1, which depicts the familiar correlation between conversion and ee as a function of the selectivity factor ($k_{rel} = k_{fast}/k_{slow}$). As such, a kinetic resolution with a k_{rel} value as low as 10 can provide recovered substrate in 95% ee and 34% yield. The situation with respect to product formation is substantially different, however, since the ee of kinetic resolution product decreases with conversion. As reflected in the graph in Figure 2, very high selectivity factors are required in order to generate kinetic resolution products in high ee (e.g. >95%) and yields approaching 50%. For example, to obtain product with the same criteria outlined above (95% ee and 34% yield), a selectivity factor of 63 would be required. For this reason, it comes as no surprise that the vast majority of kinetic resolutions involving synthetic catalysts has involved reactions targeting substrate recovery.³³

The fact that the HKR of terminal epoxides was observed to proceed with apparently very high selectivity for a broad range

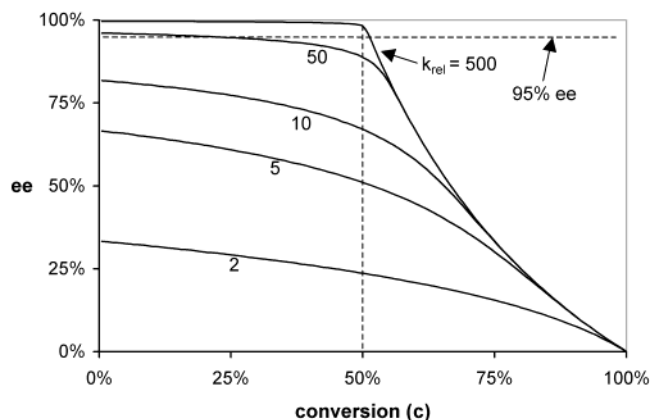


Figure 2. Plot of enantiomeric excess of product as a function of conversion for representative k_{rel} values as calculated using the equation $k_{rel} = \ln[1 - c(1 + ee_P)]/\ln[1 - c(1 - ee_P)]$.³⁴

of substrates suggested the possibility that this reaction might be applicable to product generation with synthetically useful ee's. We therefore undertook an investigation of the HKR of terminal epoxides under conditions designed to allow isolation of 1,2-diol products with an optimal compromise of ee and yield. In general, satisfactory results were obtained in reactions employing 0.45 equiv of H₂O relative to racemic epoxide. Reactions were usually complete within 12 h using the same catalyst loadings that had been identified in HKR's in which epoxide recovery was targeted (Table 6).

Outstanding results were obtained in the preparation of unhindered aliphatic 1,2-diols by the HKR procedure, with products isolated in 99% ee and >40% yield. The observation of such high product ee's reflects selectivity factors in excess of 300 for the HKR of these substrates (vide infra). Terminal, unhindered olefins are among the poorest substrates for Os-catalyzed asymmetric dihydroxylation reactions,³⁵ so the HKR methodology constitutes an especially interesting alternative for the preparation of these important building blocks. While vinyl cyclohexane oxide underwent HKR with similar success (entry 6), other, relatively hindered terminal aliphatic epoxides underwent hydrolysis with somewhat lower selectivity. Thus, 3-phenyl-1,2-propanediol was isolated in 95% ee and 40% yield, as was the 1,2-diol derived from *tert*-butyloxirane (entries 5 and 7).

The HKR also provided practical access to a series of enantioenriched 1-halo-2,3-propane diol derivatives.^{16b} Epichlorohydrin underwent ring opening to afford 1-chloro-2,3-propanediol in 95% ee and 40% yield (Table 6, entry 8). However, direct distillation of the product from the reaction mixture resulted in deterioration of the ee of the product by as much as 5%. An alternative isolation procedure was developed, wherein unreacted epoxide was removed by vacuum transfer, the reaction residue was partitioned between hexanes/EtOAc (95:5) and H₂O,

(31) Monnier, J. R. In *3rd World Congress on Oxidation Catalysis*, 1997; Grasselli, R. K., Oyama, S. T., Gaffney, A. M., Lyons, J. E., Eds.; Elsevier: New York, 1997; pp 135–149.

(32) An effective dynamic kinetic resolution of butadiene monoepoxide with inorganic carbonates has been developed: Trost, B. M.; McEachern, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 8649. While this method does not allow isolation of recovered epoxide in the enantioenriched form, it provides an attractive approach to the corresponding diol.

(33) Exceptions include: (a) Sharpless kinetic resolution: Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765. (b) Kinetic resolution of terminal epoxides with azide: Reference 17c. Kinetic resolution of terminal epoxides with phenols: Ready, J. M.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1999**, *121*, 6086. (c) Dynamic kinetic resolution processes (reviews): Noyori, R.; Tokunaga, M.; Kitamura, M. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 36. Strauss, U. T.; Felfer, U. *Tetrahedron Asymmetry* **1999**, *10*, 107. El Gihani, M. T.; Williams, J. M. *J. Curr. Opin. Chem. Biol.* **1999**, *3*, 11.

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

(35) See: Reference 22. Vanhessche, K. P. M.; Sharpless, K. B. *Chem. Eur. J.* **1997**, *3*, 517.

Table 6. Synthesis of Enantioenriched 1,2-Diols via the HKR of Terminal Epoxides^a

entry	epoxide substituent	cat. loading ^b (mol %)	cat. oxidation method	solvent ^c	diol ee (%)	isolated yield ^d (%)
Aliphatic Epoxides						
1	CH ₃	0.2	A		99	45
2	(CH ₂) ₃ CH ₃	0.5	B		99	44
3	(CH ₂) ₁₁ CH ₃	0.5	A	TBME	99	40
4	(CH ₂) ₂ CH=CH ₂	0.5	B	THF	99	44
5	CH ₂ Ph	0.5	B	THF	95	40
6	<i>c</i> -C ₆ H ₁₁	0.5	B	THF	99	41
7	<i>t</i> -C ₄ H ₉	2.0	A	<i>i</i> -PrOH	95	40
Halogenated Epoxides						
8	CH ₂ Cl	0.5	A	THF	95	40
9 ^e	CH ₂ Br	0.5	A	THF	96	90
10	CH ₂ F	0.5	A		97	38
11	CF ₃	0.5	A		>99	42
Epoxides Bearing Ether and Carbonyl Functionality						
12	CH ₂ OBn	0.5	B	THF	95	40
13	CH ₂ O(TBS)	0.5	B	THF	98	42
14	CH ₂ OPh	0.5	B	THF	95	41
15	CH ₂ O(1-naphthyl)	0.5	B	THF	97	42
16	CH ₂ CH ₂ OBn	0.5	B	THF	95	42
17 ^f	oxiranyl ^g	1.0	A	THF	96	36
18	CH ₂ OCOn-C ₃ H ₇	0.5	B	THF	43	45
19	CH ₂ CO ₂ Et	0.5	B	THF	95	41
20	CH ₂ NHBoc	2.0	A	THF	78	36
21	CO ₂ CH ₃	2.0	A	THF	97	37
22 ^h	COCH ₃	2.0	A	THF	97	40
23 ^h	COCH ₂ CH ₃	2.0	A	THF	96	33
Aryl, Vinyl, and Alkynyl Epoxides						
24	C ₆ H ₅	0.8	A	THF	98	42
25	4-ClC ₆ H ₄	0.8	A	THF	94	37
26	3-ClC ₆ H ₄	0.8	A	THF	91	44
27	3-(CH ₃ O)C ₆ H ₄	0.8	A	THF	95	41
28	3-(NO ₂)C ₆ H ₄	0.8	A	THF	99	44
29	2-ClC ₆ H ₄	1.5	A	THF	94	42
30	CH=CH ₂	0.5	A	THF	97	38
31	C≡C(TBS)	0.8	A	THF	99	41

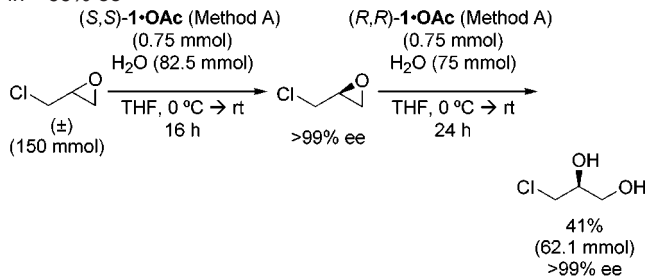
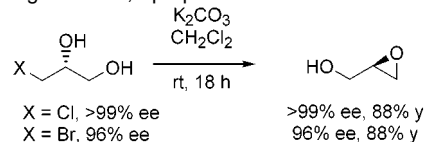
^a Unless noted otherwise, reactions were carried out for 12–14 h with 0.45 equiv of H₂O relative to racemic epoxide. Water was added dropwise to a solution of catalyst and epoxide at 0 °C, and the reaction mixture was allowed to warm to room temperature and stir for the indicated time.

^b Catalyst loading based on racemic epoxide. ^c In those cases where solvent was included, 1:1 (v/v) ratio was used relative to racemic epoxide. ^d Isolated yield of diol based on racemic material (theoretical maximum = 45%). ^e A 1.5 equiv amount of H₂O used relative to racemic epoxide. The theoretical yield in this dynamic kinetic resolution reaction is 100%. ^f A 0.4 equiv amount of H₂O used relative to racemic epoxide. ^g The substrate was D,L-butadiene diepoxide. ^h A 5 h reaction time.

and the mixture filtered to break up the emulsion. The organic layer was separated and extracted further with H₂O, and the combined aqueous extracts were concentrated to yield pure 1-chloro-2,3-propanediol with no deterioration of ee. The HKR of epifluorohydrin and trifluoropropylene oxide proceeded effectively to yield the corresponding diols in 97% ee (38% yield) and >99% ee (42% yield), respectively.

In cases where 1,2-diol of very high enantiomeric excess is required, it is a straightforward matter to effect a “double resolution” wherein highly enantioenriched epoxide is obtained by methods outlined in part II and then subjected to a second HKR with the opposite enantiomer of catalyst. This approach is illustrated in Scheme 3 in the context of the preparation of 1-chloro-2,3-propanediol of >99% ee.

The HKR of epibromohydrin proved particularly interesting. As noted in section IIb, this was the only substrate examined that failed to undergo resolution to provide recovered epoxide

Scheme 3. Double Resolution Route to 1-Chloro-2,3-propanediol in >99% ee**Scheme 4.** Preparation of Enantioenriched Glycidol from the Corresponding 1-Halo-2,3-propanediols

in high ee (Table 2, entry 2). However, with 0.45 equiv of H₂O, diol was obtained in 96% ee. These results suggested that epibromohydrin might be undergoing racemization with adventitious bromide ion under the conditions of the HKR, raising the possibility that dynamic kinetic resolution may be possible.³⁶ Indeed, this turned out to be the case: the dynamic kinetic resolution was accomplished using 2 mol % (*R,R*)-1-OAc (method A), 1.5 equiv of H₂O in THF (5.0 M) at 0 °C to yield (*R*)-1-bromo-2,3-propanediol in 96% ee and 90% yield. Both 1-bromo- and 1-chloro-2,3-propanediol are useful intermediates for the preparation of glycidol and its derivatives (Scheme 4).³⁷

As summarized in Table 6, the HKR of nearly all terminal epoxides examined proceeded effectively under standard conditions to afford 1,2-diol products in 94–99% ee and in good yield. Among the exceptions, the HKR of (±)-glycidyl butyrate yielded the corresponding 1,2-diol in only 43% ee upon isolation (entry 18). Given the fact that under similar conditions epoxide can be recovered in >99% ee (Table 4, entry 1), it appears likely that the diol is undergoing racemization during the HKR by a transesterification pathway. The HKR of the Boc protected 3-amino-1,2-epoxypropane (entry 20) afforded the diol in 36% yield and only 78% ee. This particular substrate appears to be one of the poorest for this resolution process of those examined.

(IV) Determination of *k*_{rel} Values. Because the ee's of starting material and product change as a function of conversion, it is often most useful to characterize kinetic resolution reactions not in terms of the ee obtained but rather in terms of the relative reaction rates of the two enantiomeric substrates (*k*_{rel} = *k*_{fast}/*k*_{slow}). Assuming a first-order kinetic dependence on these substrates,³⁸ the relationship between the conversion, *c*, of the reaction and the ee of the of the unreacted substrate and of the product formed is straightforward and depicted graphically in Figures 1 and 2, respectively. The practical matter of determining accurate *k*_{rel} values is clearly dependent on accurate

(36) For a review, see: Noyori, R.; Tokunaga, M.; Kitamura, M. *Bull. Chem. Soc. Jpn.* **1995**, 68, 36.

(37) The HKR of glycidol itself provided resolved epoxide in low (<20%) yield as a result of the participation of undesired oligomerization pathways. It is interesting to note, however, that epoxide ring opening has not been observed in any cases with the 1,2-diol products of the HKR.

(38) Different ee vs conversion curves are obtained in kinetic resolutions with kinetic dependencies on substrate other than 1. See: Luukas, T. O.; Girard, C.; Fenwick, D. R.; Kagan, H. B. *J. Am. Chem. Soc.* **1999**, 121, 9299. Johnson, D. W., Jr.; Singleton, D. A. *J. Am. Chem. Soc.* **1999**, 121, 1, 9307.

measurement of both ee and conversion, and for highly selective processes (e.g. $k_{\text{rel}} > 50$) even small errors in these measurements can translate to large errors in the calculation of the selectivity factor.³⁹

It became clear with experimentation that highly reproducible measurements of ee ($\pm 0.1\%$) could be obtained by capillary GC analysis of epoxide or diol products, but substantially greater variability was observed in measurements of conversion. Analysis of Figures 1 and 2 reveals that, in highly selective kinetic resolutions, lowest sensitivity to errors in the measurement in conversion is attained with evaluation of product at low conversions. For consistency, we carried out all measurements by effecting HKR reactions using 0.20 equiv of H₂O relative to racemic epoxide. The conversions were then determined by measuring the isolated yield of pure 1,2-diol. As a result, the values for conversion c listed in Table 7 represent lower limits, as do the values calculated for k_{rel} .

The precision of such high k_{rel} values was evaluated by carrying out reproducibility studies on vinylcyclohexane oxide (entry 6), one of the best substrates for the HKR. It was found that the yield varied $\pm 2\%$ and the ee varied by $\pm 0.1\%$ in seven resolutions carried out under identical conditions. These variations result in calculated k_{rel} values ranging from 490 to 840. Thus, while the relative magnitudes of the values in Table 7 provide useful guidelines for evaluation of the HKR, the absolute magnitudes for the best substrates are certainly lacking precision.

Nevertheless, the data in Table 7 highlight one of the principal features of the HKR: all practical issues notwithstanding, this reaction is one of the most selective asymmetric catalytic reactions discovered to date. The observation of k_{rel} values in excess of 100 for a broad range of substrates is remarkable, and the extraordinary ($k_{\text{rel}} > 500$) selectivities seen in certain cases point to a nearly perfect chiral recognition mechanism for particular substrates.

(V) Catalyst Recycling. The possibility of recycling a catalyst has obvious practical appeal, particularly in cases where the catalyst is precious due to cost or limited availability. Catalyst **1** is prepared in bulk from low-cost components, and as a result it is quite inexpensive relative to most chiral catalysts. On the other hand, the HKR employs reactants (racemic epoxide, water, minimal if any solvent) that impact the cost of the overall process to an almost negligible extent in many cases, and as a result the catalyst is a significant contributor to the material costs. Accordingly, efforts were directed toward identifying practical methods for effecting catalyst recovery and recycling.

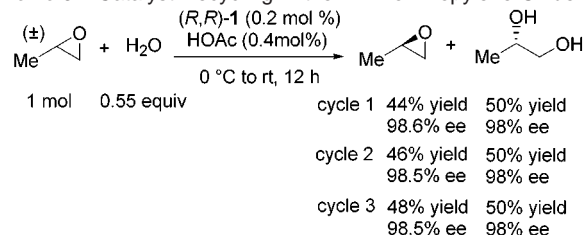
The HKR reaction of propylene oxide presents an especially straightforward scenario with respect to catalyst recovery because both the epoxide and the diol are relatively volatile and can be removed by distillation. The solid residue remaining in the reaction vessel after product separation was found to have the characteristic red-brick color of the reduced (salen)Co^{II} complex **1**. Reoxidation to **1**·OAc with air and AcOH (method B) led to catalyst with undiminished levels of reactivity and selectivity (Scheme 5).⁴⁰

Table 7. Determination of k_{rel} Values in the HKR of Terminal Epoxides^a

entry	epoxide substituent	conversion ^b (%)	diol ee (%)	k_{rel} ^c
Aliphatic Epoxides				
1	CH ₃	19	99.5	500
2	(CH ₂) ₃ CH ₃	19	99.2	310
3	(CH ₂) ₁₁ CH ₃	18	99.5	490
4	(CH ₂) ₂ CH=CH ₂	20	99.4	420
5	CH ₂ Ph	20	97.4	96
6	<i>c</i> -C ₆ H ₁₁	19	99.6	630
7	<i>t</i> -C ₄ H ₉	16	97.0	79
Halogenated Epoxides				
8	CH ₂ Cl	20	98.7	190
9	CH ₂ Br	20	96	49
10	CH ₂ F	17	98	120
11	CF ₃	18	99.6	620
Epoxides Bearing Ether and Carbonyl Functionality				
12	CH ₂ OBn	20	97	83
13	CH ₂ O(TBS)	18	99	250
14	CH ₂ OPh	18	98	120
15	CH ₂ O(1-naphthyl)	20	99	250
16	CH ₂ CH ₂ OBn	19	97	82
17	oxiranyl ^d	20	98	130
18 ^e	CH ₂ OCO _n -C ₃ H ₇	54	99.4	68
19	CH ₂ CO ₂ Et	20	98	130
20	CH ₂ NHBoc	18	74	7.8
21	CO ₂ CH ₃	19	98	120
22	COCH ₃	18	97	81
23	COCH ₂ CH ₃	18	96	60
Aryl, Vinyl, and Alkynyl Epoxides				
24	C ₆ H ₅	20	98	130
25	4-ClC ₆ H ₄	18	97	81
26	3-ClC ₆ H ₄	17	98	120
27	3-(CH ₃ O)C ₆ H ₄	19	98	120
28	3-(NO ₂)C ₆ H ₄	19	99	280
29	2-ClC ₆ H ₄	18	98	120
30	CH=CH ₂	18	98	120
31	C≡C(TBS)	19	99.4	420

^a Unless noted otherwise, reactions were carried out with 0.2 equiv of H₂O relative to racemic epoxide. Water was added dropwise to a solution of catalyst **1**·OAc (prepared by method B) and epoxide at 0 °C, and the reaction mixture was allowed to warm to room temperature and stir for 12 h. Catalyst loadings and solvents were identical to those used in Table 6 for the same substrates. ^b Isolated yield of 1,2-diol. ^c Calculated using the equation $k_{\text{rel}} = \ln[1 - c(1 + \text{ee}_p)] / \ln[1 - c(1 - \text{ee}_p)]$. ^d The substrate was D,L-butadiene diepoxide. ^e Because the diol product from this reaction was susceptible to racemization, determination of k_{rel} was made by evaluating unreacted epoxide using standard preparative conditions and applying the equation $k_{\text{rel}} = \ln[(1 - c)(1 - \text{ee}_{\text{SM}})] / \ln[(1 - c)(1 + \text{ee}_{\text{SM}})]$.

Scheme 5. Catalyst Recycling in the HKR of Propylene Oxide



A more ambitious test of the recyclability of the HKR catalyst was undertaken wherein each subsequent cycle was carried out with a different substrate (Table 8). Starting with 400 μmol of (*R,R*)-**1** (242 mg), six HKR reactions were carried out sequentially, with epoxide isolated by vacuum transfer, and diol isolated either by vacuum distillation or by trituration.⁴¹ Recovered catalyst was reactivated with air and HOAc as a common

(39) For a lucid analysis of kinetic resolutions with either enantiopure or enantioimpure catalysts and of the obstacles to obtaining accurate measurements of k_{rel} , see: Blackmond, D. G. *J. Am. Chem. Soc.* **2001**, *123*, 545.

(40) In the description of this result in the initial report on the HKR (ref 16a, Scheme 2), the absolute stereochemistries of the epoxide and diol products were accidentally reversed. The stereochemistries indicated here in Scheme 5 are correct.

(41) Complete experimental details of the recycling experiments are provided in the Supporting Information Experimental Section.

Table 8. HKR with Catalyst Recycling^a

cycle	epoxide substituent	cat. loading ^b (mol %)	cat. oxidation method	solvent ^c	epoxide yield ^d (%)
1	CH ₂ Cl	0.5	A	THF	40
2	CH ₃	0.2	A		44
3	Ph	0.8	A	THF	41
4	CO ₂ Me	2.0	A	THF	40
5	CH ₂ OPh	0.5	B	THF	43
6	(CH ₂) ₃ CH ₃	0.5	B		41

^a Reactions were carried out with 0.55 equiv of H₂O relative to racemic epoxide. Water was added dropwise to a solution of catalyst and epoxide at 0 °C, and the reaction mixture was allowed to warm to room temperature with continuous stirring for 16–72 h. ^b Catalyst loading based on racemic epoxide. The entire batch of catalyst (400 μmol) was used in each experiment, with the amount of other reagents adjusted accordingly. ^c In those cases where solvent was included, 1:1 (v/v) ratio was used relative to epoxide. ^d Isolated yield of >99% ee epoxide based on racemic material (theoretical maximum = 50%).

intermediate step. Again, no loss of catalytic activity or enantioselectivity was observed. At the end of the sixth cycle, the catalyst was isolated by filtration to yield (*R,R*)-**1** in 88% recovery (212 mg, 351 μmol).

Conclusions and Outlook

The extraordinarily high levels of selectivity observed in the HKR raise interesting questions about the mechanism of catalysis. While a full investigation will be the topic of an upcoming, separate paper, it is clear from preliminary kinetic studies that the reaction follows a second-order dependence on catalyst concentration.^{16a} This is consistent with observations made in (salen)Cr-catalyzed reactions of epoxides with azide⁴² and suggests a cooperative, bimetallic mechanism for the selectivity-determining epoxide ring-opening event.⁴³ This insight has led to the design and development of multimetric (salen)Co catalysts with dramatically enhanced reactivity—and in some cases improved enantioselectivity—in epoxide ring-opening reactions.⁴⁴ These new generation catalysts are interesting both on a fundamental and a practical level with regard to the future elucidation and development of the HKR and related reactions. On the other hand, the monomeric catalyst **1** displays broad effectiveness for the selective hydrolysis of racemic, terminal epoxides, and it holds special appeal due to its simplicity and ready availability at low cost. Thus, it is likely that catalyst **1** will remain the system of choice for HKR reactions, on a laboratory scale in particular.

The HKR provides a straightforward method for the preparation of a wide assortment of terminal epoxides in highly enantioenriched form.⁴⁵ Given that in many cases there exist no practical alternatives for accessing the valuable chiral building blocks, it is hoped that the HKR will have a beneficial and enabling effect on the field of organic synthesis.

Experimental Section

Complete experimental procedures for all substrates are provided as Supporting Information.

[(*R,R*)-*N,N'*-Bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminato(2-)]cobalt(II) ((*R,R*)-1**).** A solution of cobalt(II) acetate tetrahydrate (5.98 g, 24.0 mmol) in MeOH (80 mL) was added to a solution of ligand [(*R,R*)-*N,N'*-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediamine]⁴⁶ (10.9 g, 20.0 mmol) in CH₂Cl₂ (80 mL) via cannula under an atmosphere of N₂ with careful exclusion of air. A brick-red solid began to precipitate before addition was complete. The sides of the reaction flask were rinsed with MeOH (20 mL), and the mixture was allowed to stir for 15 min at room temperature and then 30 min at 0 °C. Precipitated solids were isolated by vacuum filtration and rinsed with cold (0 °C) MeOH (2 × 75 mL). The red solid was collected and dried in vacuo to yield [(*R,R*)-*N,N'*-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminato(2-)]cobalt(II) ((*R,R*)-**1**) (11.6 g, 19.2 mmol, 96%).

Representative Procedures for the HKR of Terminal Epoxides.

(a) Method A. (*S,S*)-Propylene Oxide. A 100 mL flask equipped with a stir bar was charged with (*S,S*)-**1** (242 mg, 400 μmol, 0.002 equiv). The catalyst was dissolved in 5 mL of PhMe and treated with AcOH (240 μL, 4.2 mmol). The solution was allowed to stir at room temperature open to air for 30 min over which time the color changed from orange-red to a dark brown. The solution was concentrated in vacuo to leave a crude brown solid. The resulting catalyst residue was dissolved in propylene oxide (14.0 mL, 11.6 g, 200 mmol) at room temperature, the reaction flask was cooled to 0 °C, and H₂O (1.98 mL, 110 mmol, 0.55 equiv) was added dropwise over 5 min. The reaction was allowed to warm to room temperature and stir 14 h at which time (*S,S*)-propylene oxide (5.35 g, 92.1 mmol, 46%) was isolated by distillation from the reaction mixture at atmospheric pressure and 36 °C. Propylene diol was removed by vacuum distillation (65 °C, 0.25 Torr). The catalyst was recovered by suspension in MeOH and collection by vacuum filtration. The ee of the propylene oxide was determined to be 99.7% by chiral GC analysis of the 1-azido-2-trimethylsiloxypropane derivative obtained by opening the epoxide with TMSN₃ (Cyclodex-B, 55 °C, isothermal, *t*_R(minor) = 12.29 min, *t*_R(major) = 12.57 min). [α]_D²⁵ -11.6° (neat).

(b) Method B. (*R*)-1,2-Epoxy-5-hexene. A 100 mL flask equipped with a stir bar was charged with (*R,R*)-**1** (302 mg, 500 μmol, 0.005 equiv). The catalyst was treated with (±)-1,2-epoxy-5-hexene (11.3 mL, 9.81 g, 100 mmol), AcOH (120 μL, 2.1 mmol, 0.02 equiv), and 1 mL of THF. The reaction flask was cooled to 0 °C, and H₂O (1.0 mL, 55 mmol, 0.55 equiv) was added in one portion. The reaction was allowed to warm to room temperature and stir 16 h at which time the volatile materials were isolated by vacuum transfer at 0.25 Torr into a cooled (-78 °C) receiving flask. The recovered epoxide was filtered through a silica plug to remove residual water, and the THF was removed by rotary evaporation to yield (*R*)-1,2-epoxy-5-hexene (4.23 g, 43.1 mmol). The diol was distilled under reduced pressure (56 °C, 0.25 Torr). The catalyst was recovered by suspension in MeOH and vacuum filtration. The ee of the recovered epoxide was determined to be 99.5% by chiral GC analysis of the 1-azido-2-trimethylsiloxy-5-hexene derivative obtained by opening the epoxide with TMSN₃ (Cyclodex-B, 70 °C, isothermal, *t*_R(minor) = 38.00 min, *t*_R(major) = 39.06 min). [α]_D²⁵ +9.36° (neat).

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Supporting Information Available: Complete experimental procedures and characterization data (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>. JA016737L

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