

Simultaneous production of chirally enriched epoxides and 1,2-diols from racemic epoxides via hydrolytic kinetic resolution (HKR)

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Abstract

Hydrolytic kinetic resolution (HKR) of racemic epichlorohydrin, styrene oxide and propene oxide was investigated using dimeric homochiral Co(III) Schiff base complex derived from mono-tartrate salt of (1*R*,2*R*)-(–)-cyclohexane diamine with 3,5-di-*tert*-butyl salicylaldehyde and 5,5-methylene-di-3-*tert*-butyl salicylaldehyde with an objective to get high efficiency and recycling capability of the catalyst. Excellent conversions to enantiomerically pure epoxide and diols along with high chiral induction were obtained in all the cases. With a loading <0.3 mol% of the catalyst, the system works well up to three cycles without any loss in activity and selectivity. © 2002 Elsevier Science B.V. All rights reserved.

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1. Introduction

Kinetic resolution of a racemic compound to give enantiomerically pure compounds is well-documented [1]. For efficient resolution, the reaction rates must be unequal and the reaction must be stopped when only one enantiomer reacts to give a maximum of 50% product leaving behind other enantiomer unreacted. Jacobsen and coworkers, recently demonstrated highly efficient hydrolytic kinetic resolution (HKR) strategy using Co(III) Salen complex as a catalyst and water as the only reagent to produce chirally pure terminal epoxides which were otherwise difficult to prepare till recently [2]. Considering the low cost and easy availability of these racemic epoxides, HKR

seems to hold significant potential for large-scale application. Besides, producing chirally pure epoxides, chirally enriched diols are produced as valuable by-product making the overall process cost effective. Further, chirally pure form of epoxides and 1,2-diols from allyl chloride [3,4], styrene [5] and propene [6] are commercially useful chemicals as these are used as intermediates for the synthesis of chiral drugs, pharmaceuticals and bio-chemicals. Subsequently, this catalyst was immobilised on polystyrene and silica network for its large-scale application in HKR [7]. With an objective to increase the number of active sites on the catalyst for its enhanced reactivity, we report here, the synthesis of homochiral dimeric Co(III) complex 5,5-methylene-di-[(*R,R*)-{*N*-(3-*tert*-butyl salicylidene)-*N'*-(3',5'-di-*tert*-butyl salicylidene)}-1,2-cyclohexanediaminato(2–) cobalt(III) acetate] which carries two catalytically active metal centres. Increase

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in molecular weight due to dimerisations of the complex, results in an advantage of easy recovery of the catalysts from the products. The complex was used as a catalyst in the HKR of racemic epichlorohydrin, styrene oxide and propene oxide in the presence of water. The complex is insoluble in diethyl ether, hence easily separated from the products by extraction method. The recovered catalyst was reactivated with acetic acid while exposed in air and could be reused up to three cycles without any loss of activity and selectivity.

2. Experimental

2.1. Material

Cobalt acetate, sodium acetate, acetic acid from SD fine Chemical, styrene oxide, epichlorohydrin, propene oxide from Aldrich were used as such. The (1*R*,2*R*)-(–)-cyclohexane diamine was resolved from the technical grade mixture of *cis*–*trans*, by the reported procedure [8]. 3,5-Di-*tert*-butyl salicylaldehyde, 5,5-methylene-di-3-*tert*-butyl salicylaldehyde and the dimeric homochiral Schiff base, named as 5,5-methylene-di-[(*R,R*)-{*N*-(3-*tert*-butyl salicylidine)-*N'*-(3',5'-di-*tert*-butyl salicylidene)}-1,2-cyclohexanediamine], were synthesised by reported procedure [9].

2.1.1. Synthesis of 5,5-methylene-di-[(*R,R*)-{*N*-(3-*tert*-butyl salicylidine)-*N'*-(3',5'-di-*tert*-butyl salicylidene)}-1,2-cyclohexanediaminato(2-)*cobalt*(II)] (I)

Hot ethanolic solution of dimeric homochiral Schiff base [9] (0.001 mol) and sodium acetate (0.002 mol) was interacted with cobalt acetate (0.002 mol) in 10 ml of hot degassed water under an inert atmosphere. The orange coloured precipitate appeared immediately, was, however, allowed refluxing for additional 1 h. The desired Co(II) complex was filtered off, washed with absolute ethanol and dried in vacuum. Yield, 0.99 g: 90%, Anal. Calcd. for C₆₅H₈₈N₄O₄Co₂: C, 70.50; H, 8.01; 5.60. Found: C, 70.48; H, 8.00; N, 5.58. IR (KBr) (cm⁻¹): 3433 (br), 2943 (s), 2863 (s), 1612 (s), 1587 (s), 1529 (s), 1438 (sh), 1387 (w), 1318 (w), 1268 (w), 1237 (w), 1203 (m), 1163 (m), 1097 (w), 941 (w), 861 (w), 785 (w), 729 (w), 695

(w), 571 (s), 461 (w). UV–VIS (CH₂Cl₂) λ_{max}(ε) (cm⁻¹): 242 (59176), 262 (59918), 342 (15831), 422 (13798); [α]_D³⁰ = -727 (*c* = 2.75 × 10⁻³, CH₂Cl₂); configuration (*R*); Δ_M (MeOH): 3 Ω⁻¹ cm⁻¹ mol⁻¹.

2.1.2. Hydrolytic kinetic resolution

Before starting the HKR, complex **1** was converted into catalytically active Co(III) form. Thus, complex **1** (0.09 mmol) was taken in 2 ml of toluene, interacted with acetic acid (0.18 mmol, 2 eq.) and was stirred while open to air for 2 h at room temperature. The solvent was completely removed by rotary evaporation and dried in vacuum. The Co(III) complex thus formed was used as catalyst for HKR of racemic epoxides namely styrene oxide, propene oxide and epichlorohydrin. In a typical HKR run, Co(III) complex (0.3 mol%) was added to the pre-cooled racemic epoxide (30.0 mmol) and the temperature of the reaction mixture was maintained at 5 °C with stirring. The addition of water (0.45 eq.) was done slowly so that the temperature should not rise above 5 °C. The reaction was monitored on chiraldex capillary column GTA type. In case of styrene oxide and epichlorohydrin, after completion of reaction, the products was separated by extraction with diethyl ether and purified by reduced pressure distillation; while in case of propene oxide, the epoxide was separated by N₂ draft at reduced temperature till no residual epoxide was left. The reaction mixture then subjected to vacuum distillation while cooling the receiver with ice. The recovered catalyst was regenerated with acetic acid while exposed in air for further use.

2.2. Instrumentation

Microanalysis of the complex was done on Perkin-Elmer Model 1106. Molar conductance was measured at room temperature on Digisun Electronic Conductivity Bridge DI909. The IR spectra were recorded on Perkin-Elmer Spectrum GX spectrophotometer in KBr/nujol mull. Electronic spectra were recorded in dichloromethane on Hewlett-Packard Diode Array spectrophotometer Model 8452A. The optical rotation was measured on Polarimeter Atago, Japan. All the solvents used were purified by known procedure. The purity of the solvent, epoxide and analysis of the product was determined by GLC chiral capillary column GTA type with FID detector.

For styrene oxide and epichlorohydrin, the capillary column temperature was programmed between 60 and 140 °C with the programming rate of 3 °C/min while in case of propene oxide 25 °C isothermal was used. Nitrogen was used as a carrier gas with injection and detector temperatures of 200 °C.

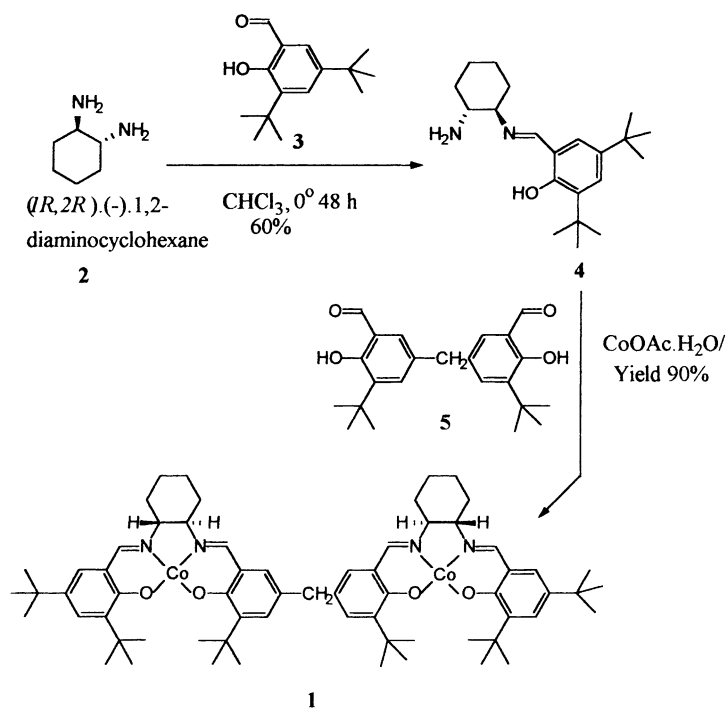
3. Results and discussion

The synthetic strategy for square planar Co(II) homochiral dimeric complex **1** involves the condensation of (1*R*,2*R*)-(-)-cyclohexane diamine (**2**) obtained from its mono tartrate salt with 3,5-di-*tert*-butyl salicylaldehyde (**3**) in 1:2 molar ratio in CHCl₃ at 0 °C to yield complex **4** which was then refluxed with 5,5-methylene-di-3-*tert*-butyl salicylaldehyde (**5**) in CHCl₃ followed by insertion of Co(II) center to give complex **1** as shown in Scheme 1. Complex **1** was characterised by microanalysis, molar conductance, UV–VIS, IR spectroscopy and optical rotation.

Complex **1** was then converted to Co(III) using acetic acid in air and then employed as a catalyst for HKR of racemic styrene oxide, propene oxide and epichlorohydrin in presence of water as resolving agent. The results are summarised in Table 1.

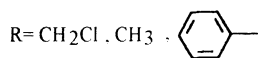
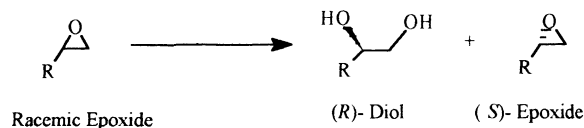
The catalyst gave excellent conversion of (46–52%) enantiomerically pure epoxides with (39–44%) of diols from all racemic epoxide and the reaction completes within 6 h in entries 1 and 2 using 0.09 mmol catalyst and 0.45 eq. of water, while the reaction of styrene oxide **3** was slow (40 h). High enantioselectivity was achieved for epoxide (96–98%) and for diol (92–98%).

The effect of equivalent of water on product distribution in the case of epichlorohydrin was also studied (Figs. 1 and 2). It shows that on increasing the quantity of water, there is an increase in the formation of diol with a decrease in its ee's, concomitantly there is decrease in the yield of epoxide with enhanced ee's. It is therefore possible to fine-tune the yields and ee's of the epoxide or diol by adjusting the amount of water. Further, the



Scheme 1.

Table 1

Data for HKR of racemic terminal alkenes with water catalysed by dimeric homochiral Co(III) Schiff base complex^a

| Entry | Racemic epoxide | Time (h) | Epoxide ^b | | 1,2-Diol ^b | |
|-------|------------------------------|----------|----------------------|----------|-----------------------|----------|
| | | | Yield (%) | Ee's (%) | Yield (%) | Ee's (%) |
| 1 | Epichlorohydrin | 6 | 49 | 97 | 43 | 92 |
| 2 | Propene oxide | 6 | 52 | 96 | 44 | 98 |
| 3 | Styrene oxide | 40 | 46 | 98 | 39 | 99 |
| 4 | Epichlorohydrin ^c | 8 | 45 | 98 | 46 | 88 |
| 5 | Epichlorohydrin ^d | 10 | 42 | 98 | 50 | 86 |

^a Reaction condition—catalyst: 0.09 mmol, 0.3 mol%; racemic epoxide: 30 mmol; water: 0.45 eq., 13.5 mmol.^b Isolated yields.^c Water (0.5 eq.).^d Water (0.55 eq.).

catalyst could be easily separated by extraction process in case of high boiling substrates/products (for example, styrene oxide and epichlorohydrin and their respective diols) or by distillation method in case of highly volatile epoxides (as is the case of propene oxide). The recovered catalyst was regenerated by the treatment of acetic acid in air and could be recycled with no apparent loss in activity and selectivity. The recycling data is given in Table 2.

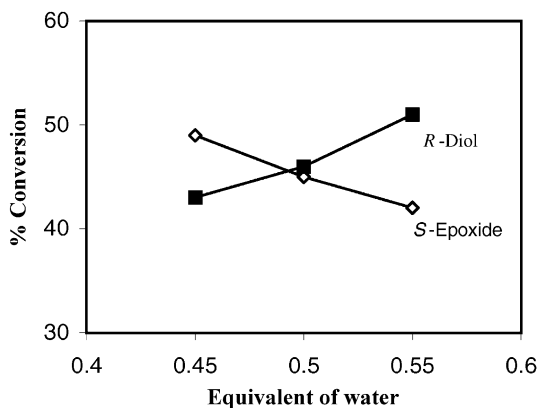


Fig. 1. Effect of equivalent of water on the percentage epichlorohydrin conversion.

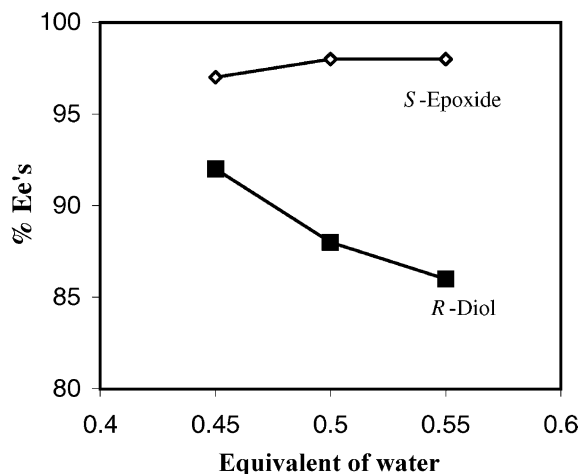


Fig. 2. Effect of equivalent of water on the percentage ee's of the product.

Table 2

Data for recycling of dimeric homochiral Co(III) Schiff base complex for HKR of epichlorohydrin with 0.45 eq. water

| Product | Epoxide | | | Diol | | |
|------------|---------|----|----|------|----|----|
| | 1 | 2 | 3 | 1 | 2 | 3 |
| Run | 1 | 2 | 3 | 1 | 2 | 3 |
| Conversion | 49 | 48 | 49 | 43 | 43 | 42 |
| Ee's | 97 | 97 | 96 | 92 | 92 | 92 |
| Time (h) | 6 | 9 | 12 | 6 | 9 | 12 |

4. Conclusion

In conclusion, the dimeric homochiral Co(III) Schiff base complex worked very well in HKR of racemic epichlorohydrin, propene oxide and styrene oxide. The rate of reaction was faster with epichlorohydrin and propene oxide than styrene oxide while ee's was excellent in all the cases. Further, it is possible to fine-tune the yields and ee's of the epoxide or diol by simple adjusting the amount of water. The activity and selectivity of the recycled catalyst remained unchanged under HKR reaction with retention of ee's up to three cycles.

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