



Tetrahedron: Asymmetry 14 (2003) 3589–3592

TETRAHEDRON: ASYMMETRY

# Commercialization of the hydrolytic kinetic resolution of racemic epoxides: toward the economical large-scale production of enantiopure epichlorohydrin

Jay F. Larrow,<sup>a,\*</sup> Karl E. Hemberger,<sup>a</sup> Serge Jasmin,<sup>a</sup> Hocine Kabir<sup>b</sup> and Phillipe Morel<sup>b</sup>

<sup>a</sup>Rhodia Pharma Solutions, 56 Roland Street, Boston, MA 02129, USA <sup>b</sup>Rhodia Pharma Solutions, Centre de Recherches de Lyon, 85 Avenue des Frères Perret, F-69192 St. Fons Cedex, France

Received 10 June 2003; accepted 2 September 2003

Abstract—The hydrolytic kinetic resolution of racemic terminal epoxides utilizing chiral (salen)Co(III) catalysts provides practical access to enantiopure epoxides and diols. However, general issues surrounding catalyst activation combined with the specific problem of racemization of epichlorohydrin served to make the large-scale production of (R)- or (S)-epichlorohydrin difficult and uneconomical. A process for the large-scale production and isolation of active (salen)Co(III)OAc catalyst and a method of catalyst reduction after reaction using ascorbic acid have been developed to overcome these issues. © 2003 Elsevier Ltd. All rights reserved.

### 1. Introduction

The Jacobsen hydrolytic kinetic resolution (HKR) of racemic terminal epoxides catalyzed by chiral (salen)Co(III) complexes was first reported in 1997, and has since become the standard method for the preparation of enantiopure monosubstituted epoxides and vici-

nal diols (Scheme 1).<sup>1</sup> The technology was rapidly commercialized to provide practical large-scale access to a number of epoxide and diol chiral building blocks derived from inexpensive racemic epoxides such as propylene oxide, methyl glycidate and epichlorohydrin. While the original HKR procedures proved adequate for the commercial preparation of many of these build-



#### Scheme 1.

<sup>\*</sup> Corresponding author. E-mail: jay.larrow@us.rhodia.com

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ing blocks,<sup>2</sup> there were important issues that needed to be addressed in order to enhance the economic practicality of large-scale batchwise practice of the HKR technology. In particular, the HKR of epichlorohydrin was plagued by the presence of racemization/decomposition pathways, which resulted in the formation of side products and made the isolation of epoxide in high enantiomeric excess (ee) difficult at scale.<sup>3</sup> In addition, the overall productivity of the HKR process was limited because the resolution and catalyst preparation reactions were necessarily coupled for reasons discussed below. Combined, these issues served to make the large-scale production of highly enantiomerically enriched epichlorohydrin more cumbersome and costly than expected given the simplicity of the HKR technology.

The oxidation of the inactive (salen)Co(II) complex to the active (salen)Co(III) precatalyst 1 using acetic acid and air (Eq. (1)) was practically and conceptually problematic for all HKR substrates at scale. Conceptually, the isolation of the (salen)Co(II) complex makes little sense because it is inactive in the reaction and constitutes little more than an additional intermediate in the overall synthesis of the active catalyst. From a practical standpoint, the catalyst activation procedure suffered from the following deficiencies: (1) the use of dichloromethane (DCM) as solvent in order to maximize solubility of the Co(II) complex and to avoid the low flashpoints common to most organic solvents during air sparging; (2) the necessity for scrubbing equipment to prevent the release of DCM to the environment; (3) the need for complete removal of DCM prior to the HKR reaction to avoid product contamination, and (4) the inability to isolate complex 1 in solid form due to its high solubility in most solvents. Overcoming these issues would streamline the entire process for preparing the active catalyst, and would effectively decouple the catalyst activation step from the HKR reaction.

(salen)Co(II)+HOAc+
$$\frac{1}{4}O_2 \rightarrow$$
(salen)Co(III)OAc+ $\frac{1}{2}H_2O$ 
(1)

Since the active precatalyst 1 has a high solubility in both polar and non-polar solvents, water was determined to be the only effective anti-solvent to precipitate the complex. Crystalline material could be obtained from methanol by the addition of water to yield a stable, easily filtered solid. Due to its low flashpoint (11°C) however, methanol was not compatible with the air sparging required during the oxidation step after metal insertion into the salen ligand. Because acetic acid is a reactant in the air oxidation step, its use as the bulk solvent for the metal insertion and oxidation was investigated. The flashpoint of acetic acid (40°C) is sufficiently high so that the air sparge can be conducted at room temperature while maintaining a desirable safety margin of more than 15°C between the solvent flashpoint and the vapor temperature. Metal insertion and oxidation were found to occur readily with acetic acid as the only bulk solvent. Isolation of complex 1 from the solution proved difficult, as the addition of water resulted in the formation of a gummy solid unsuitable for scale-up. However, by replacing the bulk of the acetic acid with methanol before precipitation, a highly manageable crystalline solid was obtained.

In the ultimate process, metal insertion and air oxidation were carried out concurrently using 8 volumes of acetic acid as reactant and solvent (Scheme 2). Although ligand 2 was incompletely soluble in this amount of acetic acid, the overall process was determined to be limited by the mass transfer of oxygen into the liquid phase.<sup>4</sup> Optimization of the introduction of air into the reactor via a dip tube enabled metal insertion and oxidation to be complete within 2-3 h. At this point, the reaction mixture was concentrated by reduced pressure (105 mbar) distillation of 75% of the acetic acid (pot temperature 50-55°C) to yield a mobile, homogeneous dark brown solution. The solution was diluted with methanol, and the active Co(III) complex was precipitated from the mixture as a crystalline solid by the addition of water. Seeding the mixture with crystals after 10% of the water addition resulted in larger crystal size and a more easily managed solid product. Excess acetic acid and methanol were removed by water washes, and the product was readily dried under heating and vacuum (40-45°C, 35 mbar).

catalytically By this process, the active (salen)Co(III)OAc complex can be prepared in bulk independently from its use in any HKR reaction. The improved process eliminates the use of dichloromethane, while avoiding the flashpoint issues associated with most other solvents during the air sparge. The solid product is isolated in pure form so that solvent contamination of the HKR product is eliminated, and it can be stored for several months under ambient conditions (closed container). With these improvements and because the Co(II) complex is no longer isolated, the economy of the entire process is significantly enhanced.





# Scheme 3.

With the issues surrounding the preparation and isolation of the active precatalyst 1 successfully addressed, our focus turned to the more specific problem of racemization and decomposition of the epichlorohydrin HKR reaction mixture during isolation. The epihalohydrins (Scheme 3) are unique substrates due to the presence of the halide, the lability of which makes them susceptible to racemization and allows for their possible dynamic kinetic resolution.<sup>3,5</sup> Chiral (salen)Co(III) complexes are known to catalyze the ring closure of chlorohydrins to form epoxides, and this phenomenon is observed during the HKR reaction by the formation of glycidol from 3-chloro-1,2-propanediol.<sup>6</sup> The hydrogen chloride product from this reaction then reacts with epichlorohydrin to form achiral 1,3-dichloro-2-propanol. The reverse reaction provides a low ee pathway to epichlorohydrin that results in the observed racemization in the absence of water.

The primary degradation products glycidol and dichloropropanol constitute approximately 2% of the HKR mixture upon reaching completion (>99% ee) under optimized conditions (0.5 mol% catalyst, 5°C). However, they are formed significantly faster at elevated temperatures and in the absence of water, typical conditions experienced during isolation of the resolved epoxide by distillation. Under these conditions, significant losses can occur during distillation at scale (regardless of racemization). Wiped film evaporation (WFE) can be utilized to minimize these losses, but this introduces additional process constraints and requires capital investment. While the formation of these products could likely not be eliminated during the HKR reaction, we speculated whether the racemization and degradation reactions could be shut down by deactivating the catalyst in some fashion.

Control reactions showed that the (salen)Co(II) complex was also inactive in the racemization/decomposition reactions involving epichlorohydrin and 3-chloro-1,2-propanediol. With this result in hand, convenient chemical reductants were screened for the ability to reduce all Co(III) species present after the HKR reaction to the inactive Co(II) complex. While several reductants were found to be successful, L-ascorbic acid (vitamin C) proved best at stabilizing the reaction mixture and preventing thermal degradation. The use of two equivalents of ascorbic acid relative to the catalyst resulted in the quantitative reduction of the catalyst to the Co(II) species, and allowed for the isolation of the resolved epichlorohydrin by simple vacuum distillation.

The overall yield for the isolated material is typically 40–42%, which is 80–84% of theory and 83–88% of the actual desired enantiomer remaining in the HKR reaction upon reaching completion. An additional 4–5% of material remains in the pot and could be recovered utilizing lower vacuum for the distillation (a maximum pot temperature of 90°C is allowed for safety reasons which allows for the distillation of only about 91% of the epichlorohydrin in the pot at 35 mbar pressure).<sup>4,7</sup> The isolated material shows no loss of enantiomeric excess, and is >99% pure by GC analysis.

With these new process developments, the production of either enantiomer of epichlorohydrin utilizing the Jacobsen hydrolytic kinetic resolution technology has been greatly facilitated and economized. The new process to prepare the active Co(III) precatalyst 1 will also have a positive impact on all processes which utilize this complex, as its synthesis is no longer coupled to the reactions which use it. While these process improvements are aimed primarily at large-scale commercial production with the HKR technology, it is hoped that the procedures presented in this paper will be useful to those utilizing the chemistry in the laboratory as well.

# 2. Experimental

# 2.1. Catalyst preparation

(S,S)-Salen ligand 2 (2.2 kg) was charged to a 70-L reaction vessel equipped with an impeller, thermometer,

and air-sparging dip tube. Cobalt acetate tetrahydrate (1.06 kg) was then added, and the reaction vessel was purged with nitrogen. Acetic acid (18.5 kg) was charged to the reactor over a period of about 0.5 h with stirring at room temperature. While stirring at room temperature, compressed air was bubbled through the dip tube at an approximate rate of 750 L of air/kg of ligand/ hour for 3 h. The effluent air stream was passed through a sodium hydroxide scrubber. The reaction was monitored every 30 min for complete consumption of ligand as determined by TLC analysis ( $R_f = 0.70, 4:1$ hexanes/EtOAc). Upon completion of the reaction, air sparging was discontinued, the vessel was purged with nitrogen, and the pressure within the vessel was slowly reduced to 100-110 mbar. The contents of the vessel were then heated to a pot temperature of 50-55°C (jacket temperature 70°C), and 14 kg of HOAc (75% of the volume used) were distilled over 2-3 h. The vacuum was broken to nitrogen and the contents of the vessel were cooled to room temperature over 1 h. Methanol (10.5 kg) was then charged to the reaction vessel (the quantity of methanol was equivalent to the volume of HOAc removed). Water (11 kg) was continuously added dropwise, with stirring, over 1.5 h to precipitate the catalyst. After 10% addition of the water, the reaction was seeded with crystals (25 g). The resulting slurry was transferred to a filtration still, and the solid was isolated by nitrogen pressure filtration. The isolated solid was washed with water by portion until a clear filtrate solution was obtained (50 kg in total). The final wash filtrate solution had a pH between 3.5 and 4.5. The washed solid was then dried under vacuum (40°C, 35 mbar) to constant weight to yield 2.8 kg of a dark brown solid (95-97% of theory). The dried catalyst was isolated as the methanol adduct, with the solvent molecule occupying the sixth coordination site of the cobalt center. The purity of the product was confirmed by <sup>1</sup>H NMR analysis, and the Co(III)/Co(II) ratio could be determined by cyclic voltammetry.<sup>4</sup> NMR (CD<sub>2</sub>Cl<sub>2</sub>, 600 MHz):  $\delta$  (ppm) 7.46 (d, 1H, J = 3.0Hz), 7.30 (d, 2H, J=2.4 Hz), 7.23 (d, 1H, J=2.4 Hz), 7.19 (d, 1H, J=2.4 Hz), 6.84 (s, 1H), 4.45 (t, 1H, J=10.2 Hz), 3.41 (s, 3H), 3.29 (t, 1H, J=10.2 Hz), 2.77 (dd, 2H, J=2.4, 9.6 Hz), 2.02 (m, 1H), 1.93 (m, 2H), 1.67 (s, 3H), 1.59–1.44 (m, 4H), 1.48 (s, 9H), 1.35 (s, 9H), 1.31 (s, 9H), 1.22 (s, 9H).

### 2.2. HKR of (±)-epichlorohydrin

(±)-Epichlorohydrin (50 kg) was charged to a jacketed 70-L reaction vessel equipped with an impeller and thermometer. The contents were cooled to 5°C under nitrogen, and (*S*,*S*)-catalyst **1** (1.8 kg, 0.5 mol%) was added with stirring. With stirring, water addition (7.3 kg, 0.75 mol equiv.) was begun at a rate of 0.7–0.8 kg/h in order to maintain the reaction temperature at approximately 5°C.<sup>8</sup> After 2.5 h, the water addition rate was increased to 1–2 kg/h. The total time of addition

was 5 h, after which the reaction was maintained at 5°C. The reaction was then monitored every hour for completion (ee >99.0%) as determined by GC analysis. After aging the reaction for 4 h, the completion point was reached and the mixture was treated with L-ascorbic acid (1.0 kg, 2 equiv. to catalyst). The reaction mixture gradually changed from a brown homogeneous solution to a red heterogeneous mixture. At this point, an anti-foaming agent (Rhodorsil 426 R, 20 mL) was added, and the pressure inside the vessel was reduced to 35 mbar. Excess water was removed by azeotropic distillation with continuous recycling of the lower epichlorohydrin layer. Azeotropic drying was continued until water no longer separated in the distillation condensate (8 h, remaining water content <0.25%). At this point, the pure (R)-epichlorohydrin was collected while gradually increasing the pot temperature (47–90°C) to maintain a steady rate of distillation (the vapor temperature was constant at 29°C). The amount of (R)epichlorohydrin isolated was 20.4 kg (40.8% yield, 82% of theory). Analysis of the product by GC indicated enantiomeric excess >99.5% and product purity of 99.1% (area%, glycidol <0.1%, dichloropropanol 0.4%).

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- 7. For further scale-up, more exact hazard evaluation experiments indicated that the pot temperature should not exceed 70°C.
- 8. The rate of water addition (and hence the rate of reaction) is balanced to the rate of heat transfer out of the vessel in order to maintain a reaction temperature of about 5°C. In this experiment, the jacket temperature was maintained near  $-5^{\circ}C$  ( $\Delta T = 10^{\circ}C$ ).