Tetrahedron 70 (2014) 4165–4180

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

A broadly applicable and practical oligomeric (salen)Co catalyst for enantioselective epoxide ring-opening reactions

David E. White, Pamela M. Tadross, Zhe Lu, Eric N. Jacobsen *

Department of Chemistry and Chemical Biology, Harvard University, Cambridge, MA 02138, USA

ARTICLE INFO

Article history:
Received 20 February 2014
Received in revised form 7 March 2014
Accepted 12 March 2014
Available online 18 March 2014

Dedicated to Professor Sarah Reisman on the occasion of her receipt of the Tetrahedron Young Investigator Prize

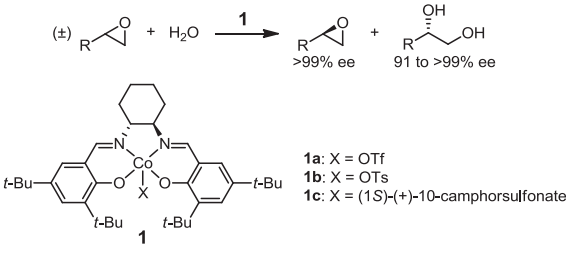
Keywords:
Kinetic resolution
Salen
Desymmetrization
Epoxides
Ring-opening

ABSTRACT

The (salen)Co catalyst (**4a**) can be prepared as a mixture of cyclic oligomers in a short, chromatography-free synthesis from inexpensive, commercially available precursors. This catalyst displays remarkable enhancements in reactivity and enantioselectivity relative to monomeric and other multimeric (salen)Co catalysts in a wide variety of enantioselective epoxide ring-opening reactions. The application of catalyst **4a** is illustrated in the kinetic resolution of terminal epoxides by nucleophilic ring-opening with water, phenols, and primary alcohols; the desymmetrization of meso epoxides by addition of water and carbamates; and the desymmetrization of oxetanes by intramolecular ring opening with alcohols and phenols. The favorable solubility properties of complex **4a** under the catalytic conditions facilitated mechanistic studies, allowing elucidation of the basis for the beneficial effect of oligomerization. Finally, a catalyst selection guide is provided to delineate the specific advantages of oligomeric catalyst **4a** relative to (salen)Co monomer **1** for each reaction class.

1. Introduction

Among the wide assortment of organic transformations catalyzed with high enantioselectivities by chiral (salen)metal complexes,[1] epoxide ring-opening reactions have arguably proven most impactful from a synthetic standpoint in both academic and industrial contexts. In particular, the hydrolytic kinetic resolution (HKR) catalyzed by monomeric (salen)Co complex **1** provides a general approach to the preparation of both enantiopure terminal epoxides and highly enantioenriched 1,2-diols (Scheme 1).[2–5] Monomeric complex **1** has also been applied with more limited success to the phenolytic kinetic resolution (PKR)[6] and the carbamolytic kinetic resolution (CKR)[7] of terminal epoxides to afford enantioenriched α-aryloxy alcohols and *N*-protected 1-amino-2-ols, respectively.[8,9] Other classes of nucleophiles and epoxides have generally remained beyond the scope of this system.[10,11] Moreover, although catalyst loadings required for HKR, PKR, and CKR reactions of most terminal epoxides are low (<5 mol % Co), additional improvements in catalytic reactivity are desirable in order to achieve highly efficient large-scale applications.[12]



Scheme 1. The HKR of terminal epoxides with monomeric (salen)Co complex **1**.

The recognition that the HKR[13] and related[14] epoxide ring-opening reactions proceed via cooperative bimetallic mechanisms, wherein both the epoxide electrophile and nucleophile are activated by separate (salen)Co complexes in the rate-limiting ring-opening event (Fig. 1),[15] has motivated the preparation and study of a wide variety of linked multi-(salen)metal complexes. The goal of these efforts has been to achieve higher catalytic activity by reducing the entropic cost of a second-order bimetallic pathway.[16,17] In several cases, these studies succeeded in uncovering catalyst systems with enhanced reactivity relative to monomer **1**, but that are also far more difficult to prepare and therefore less attractive

* Corresponding author. E-mail address: jacobsen@chemistry.harvard.edu (E.N. Jacobsen).

0040-4020/$ – see front matter © 2014 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tet.2014.03.043

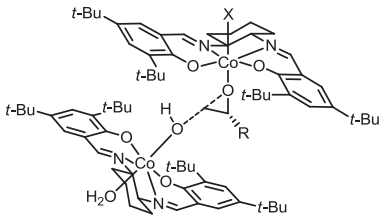


Fig. 1. Proposed rate-limiting transition structure in the hydrolytic kinetic resolution of terminal epoxides catalyzed by monomeric (salen)Co complex **1** (Ref. 15).

from a practical standpoint. This is due in large part to the need to synthesize unsymmetrical salen ligand frameworks to allow dimerization as in Fig. 2A.[18] As an alternative to these catalysts that possess local C_1 symmetry, multimeric (salen)Co complexes have been identified that are straightforward to prepare owing to the fact that they preserve the local C_2 symmetry of each salen unit. As such, they can be synthesized simply by condensation of appropriate linked bis(salicylaldehydes), or by linkage of preformed C_2-symmetric salen units (Fig. 2B).

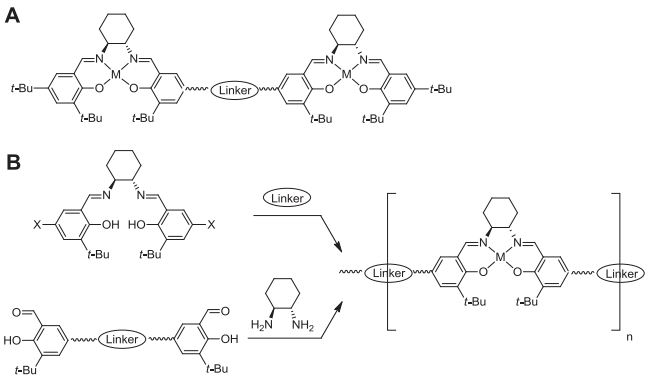
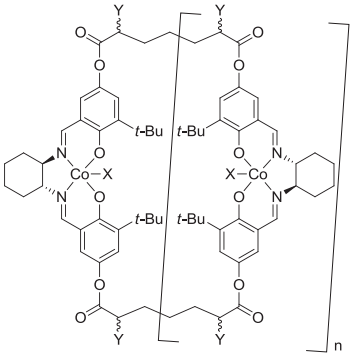


Fig. 2. (A) Linkage of metal salen complexes resulting in local C_1 symmetry in the individual salen units. (B) Strategies for the preparation of linked analogs of **1** with local C_2 symmetry in the individual salen units.

Linked complexes **2**[19] and **3**[20] represented the first reported examples of these more readily accessible catalysts (Fig. 3).[4h,8b,21] These mixtures of cyclic, oligomeric linked (salen)Co units displayed not only dramatic reactivity improvements in the HKR and PKR of terminal epoxides relative to monomer **1**, but also facilitated reactions that were impossible with monomeric catalyst such as the alcoholytic kinetic resolution (AKR) of terminal epoxides as well as the hydrolytic desymmetrization of cyclic meso epoxides. The basis for enhanced reactivity could be traced to cooperative reaction within the linked catalysts, as epoxide ring-opening reactions displayed a first-order kinetic dependence on catalyst concentration.[19]

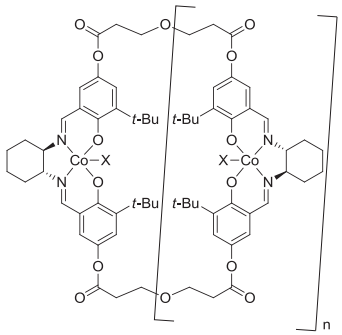


2: X = OTs, Y = Cl, n = 1-5

3a X = (1*S*)-(+)-10-camphorsulfonate, Y = H, n = 1–3
3b X = 3-NO_2-$C_6H_4SO_3$, Y = H, n = 1–3

Fig. 3. First- and second-generation cyclic oligomeric (salen)Co catalysts for epoxide ring-opening reactions.

Despite the very attractive properties of the cyclic oligomeric catalysts **2** and **3**, their practical utility and the ability to study them systematically was limited by their poor solubility. Poor reproducibility both between runs employing the same catalyst batch and between runs employing different catalyst batches was observed in several cases. For example, the conversion in the hydrolysis of *cis*-2-butene oxide using different batches of catalyst **3b** varied from 58 to 94% over 24 h. After systematic evaluation of various structural parameters, we discovered that the relatively minor perturbation of introducing an oxygen atom into the linker chain, as in **4** (Fig. 4), resulted in catalysts with substantially improved physical properties, including solubility in common organic solvents such as CH_2Cl_2 and CH_3CN.[22] Catalyst **4a** (X=OTf) was shown to be highly effective in a variety of HKR reactions, displaying both very high and reproducible activity and stereoselectivity with representative terminal epoxides. Tosylate derivative **4b** was found to be less reactive, but most effective for highly reactive terminal epoxides such as styrene oxide.[22,23] Catalyst **4a** has found application in several advanced synthetic applications[24] and new enantioselective ring-opening reactions.[25]



4a X = OTf
4b X = OTs

Fig. 4. Third-generation cyclic oligomeric (salen)Co catalysts for epoxide ring-opening reactions.

We provide here a full account of the scope of catalyst **4a** in enantioselective epoxide ring-opening reactions, thereby establishing **4a** as the most general and effective system for such reactions identified to date. We describe a practical, chromatography-free synthesis of catalyst **4a**, and document the application of this catalyst in the kinetic resolution of terminal epoxides by nucleophilic ring-opening with water, phenols, and primary alcohols, as well as the desymmetrization of meso epoxides by addition of water and carbamates, and the desymmetrization of oxetanes by intramolecular ring opening with alcohols and phenols. The favorable solubility properties of complex **4a** under the catalytic conditions were exploited in mechanistic studies, allowing elucidation of the basis for the beneficial effect of oligomerization. Finally, we provide a catalyst selection guide to delineate the specific advantages of oligomeric catalyst **4a** relative to (salen)Co monomer **1** for each reaction class.