

# Design of a Versatile Bisalen Motif for Cooperative Co-Salen Mediated Epoxide Ring-Opening

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## Introduction

The hydrolytic kinetic resolution (HKR) catalyzed by Co(salen) has emerged as a powerful, simple and widely used method for the generation of terminal epoxides in enantiomerically pure form.<sup>1-2</sup> Mechanistic investigation of the HKR reaction has shown a second-order kinetic dependence on catalyst suggested to arise from the dual activation pathway in the reaction.<sup>1-3</sup> Different approaches have been identified to enhance the activity relative to the monomeric catalyst, including building oligomers,<sup>4,5</sup> dendrimers,<sup>6</sup> polymers,<sup>7</sup> polymer-oxide hybrids<sup>8</sup> and encapsulating complexes in nanocages.<sup>9</sup> A key advantage of the oligomer, dendrimer and macrocyclic oligomeric Co-salen catalysts are the enhanced activities associated with their structures that allow for efficient Co-salen:Co-salen cooperative interactions. A distinct disadvantage, however, is that these catalysts are relatively difficult to recover and reuse, owing to their soluble nature under reaction conditions. Seeking a modular building block for homogeneous and heterogeneous cooperative salen catalysis, here we report a design for a styryl-substituted unsymmetrical "bisalen" and demonstrate its unique versatility in creating highly active, cooperative homogeneous and recyclable heterogeneous catalysts in the hydrolytic kinetic resolution of epoxides.

## Experimental

The styryl substituted unsymmetrical bisalen (**2**) was synthesized by following the one pot protocol developed in collaboration with Weck.<sup>5,7</sup> The formation of the bisalen (**2**) was confirmed by <sup>1</sup>H, <sup>13</sup>C NMR, FAB MS and elemental analysis. Metalation using cobalt acetate tetrahydrate with **2** afforded the Co-bisalen (**3**) in 88% yield. The versatile Co-bisalen (**3**) can act as (i) a soluble small molecule catalyst (vide infra) or it (or **2**) can be employed as a building block in the synthesis of (ii) soluble homogeneous copolymer catalysts (**5a** & **5b**), (iii) insoluble cross-linked polymeric resin catalysts (**6**), or (iv) insoluble silica-supported catalysts (**7**), all of which contain the cooperative bisalen motif (Figure 1).

## Results and Discussion

The active Co(III) catalysts were used at 0.02 mol% Co loading in the HKR of a range of epoxides. At this concentration, the styryl unsymmetrical bisalen was highly active, achieving full resolution (99% ee) in 7 hours, whereas the original monomeric Jacobsen catalyst gave only 13% ee over the same duration (Figure 2). This is a direct consequence of cooperative bimetallic pathway suggested for efficient HKR. Density functional theory (DFT) computations were performed using the Jaguar suite of programs to model the binding of hydroxide to one metal center and the epoxide to the other. We employed the BP86 functional with the LANL2DZ effective core potential for Co and the 6-31G\* basis for other atoms. The resulting DFT structure allowed us to predict that our design can accommodate structures

where two salens are in very close proximity and can cooperate as proposed in the mechanism suggested by Jacobsen.

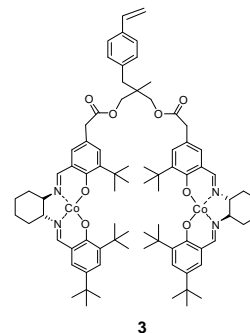


Figure 1. Co-bisalen **3**.

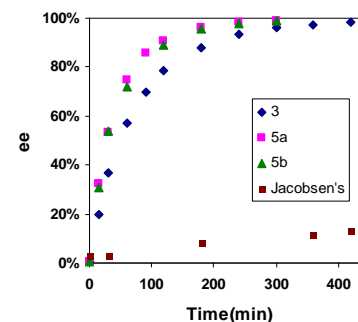


Figure 2. Epichlorohydrin HKR kinetics.

The catalytic performance of the copolymers containing the bisalen monomer is compared in Figure 2. The copolymers **5a**, **5b** are as active as the molecular bisalen **3**. The dilution of bisalen with styrene in the copolymers does not reduce the activity; rather there is a slight increase in the activity, assumed to arise from reduced steric crowding or from the flexibility in the copolymer backbone. The insoluble resin **6** was also tested in the HKR of epichlorohydrin at 0.02 mol % catalyst loading. The results suggest that the resin is also highly active, achieving full conversion in 12 h (99% ee). The recycling of the resin was studied at a 0.04 mol % loading, with the catalyst recovered by filtration after each cycle, then regenerated and reused (Table 1). The selectivity of the recycled catalyst remained the same after three cycles.

## Significance

This is one of the most active supported Co-salen catalysts that can be recycled easily by filtration. A unique advantage of our modular approach is that an array of catalysts with the same bimetallic motif can be prepared, all operating in a cooperative manner with high activity and selectivity.

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