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Cooperative Catalysis in the Hydrolytic Kinetic Resolution of Epoxides by Chiral [(salen)Co(III)] Complexes Immobilized on Gold Colloids

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Dedicated to Andreas Pfaltz on the occasion of his 60th birthday.

Supporting information for this article is available on the WWW under http://asc.wiley-vch.de/home/.

Abstract: Chiral salen ligands were incorporated into self-assembled thiolate monolayers (SAMs) on gold colloids. Treatment of the immobilized ligand with $Co(OAc)_2 \cdot 4H_2O$ yielded the corresponding [(salen)Co(II)] complex, and aerobic oxidation in the presence of triflic acid afforded the catalytically active [(salen)Co(III)] complex. Functionalized gold colloids with a diameter of 3.4 nm, coated with a mixed monolayer of *n*-octanethiolates and thiolates with chiral [(salen)Co(III)] end groups were studied as catalysts in the hydrolytic kinetic resolution (HKR) of hexene-1-oxide. Extremely high selectivitiy and significant rate acceleration relative to homogeneous monomeric catalysts were observed. Recovery of the immobilized catalyst was accomplished by simple filtration, and catalyst reoxidation and repeated recycling (seven times) was possible with no loss of reactivity or enantioselectivity.

Keywords: asymmetric catalysis; colloids; immobilization; kinetic resolution; self-assembly

The hydrolytic kinetic resolution (HKR) catalyzed by [(salen)Co(III)] complexes[1] has emerged as a powerful and widely used method for generating enantiopure terminal epoxides as a direct result of its remarkable practical appeal,[2] high selectivity, and broad substrate scope.[3] Detailed mechanistic investigations of the HKR and related epoxide ring-opening reactions using monomeric (salen)metal catalysts have revealed second-order kinetic dependence on catalyst concentration, and point to a cooperative mechanism of catalysis (Figure 1).[4,5] Various strategies have been explored for overcoming the entropic price of bringing two catalyst molecules together in the rate-limiting transition state and thereby enhancing catalytic efficiency in the HKR. Successful approaches identified to date include construction of covalently-linked dimers[6] and oligomers,[7] self-assembly of as well as grafting [(salen)metal] complexes onto dendrimers[8] or polymers.[9] Enhanced reactivity relative to monomeric catalysts has been demonstrated in each case, and highly practical systems have been identified that allow use of very low catalyst loadings.[7c]

Despite these important advances, the discovery of HKR catalysts that display high activity and are easily recovered and recycled remains an important and challenging goal. In this context, we became interested in exploring the immobilization of [(salen)Co(III)] on gold colloids. Alkanethiol-coated gold colloids in the 2–10 nm size range are stable up to 150 °C[10] and maintain many of the practical properties of organic molecules, being amenable to chromatographic purification, dissolution, precipitation, sublimation, crystallization, etc.[11] Characterization techniques that are not normally suitable for the study of solids, such as solution-phase NMR and MS, are applicable to gold colloids. The synthesis of the gold colloids is straightforward, and catalyst immobilization takes place under mild conditions. A single functionalized gold colloid can carry several hundred catalyst moieties on its surface, and the thiolate chains self-assemble to minimize steric interactions, leading to a uniform catalyst distribution on the colloid surface. Finally, the catalyst loading may be varied, depending upon incubation time. In this paper, we describe the successful immobilization of salen ligands on gold surfaces. The colloid-bound catalysts are shown to catalyze the highly enantioselective hydrolytic kinetic resolution with significant rate enhancements relative to monomeric [(salen)Co(III)] complexes.

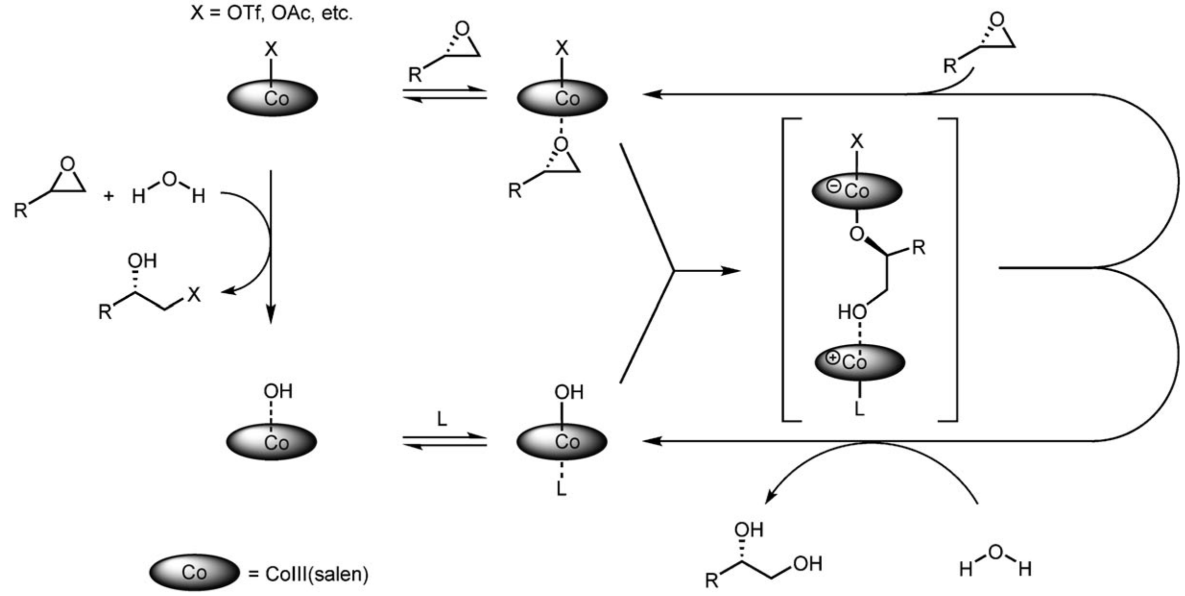
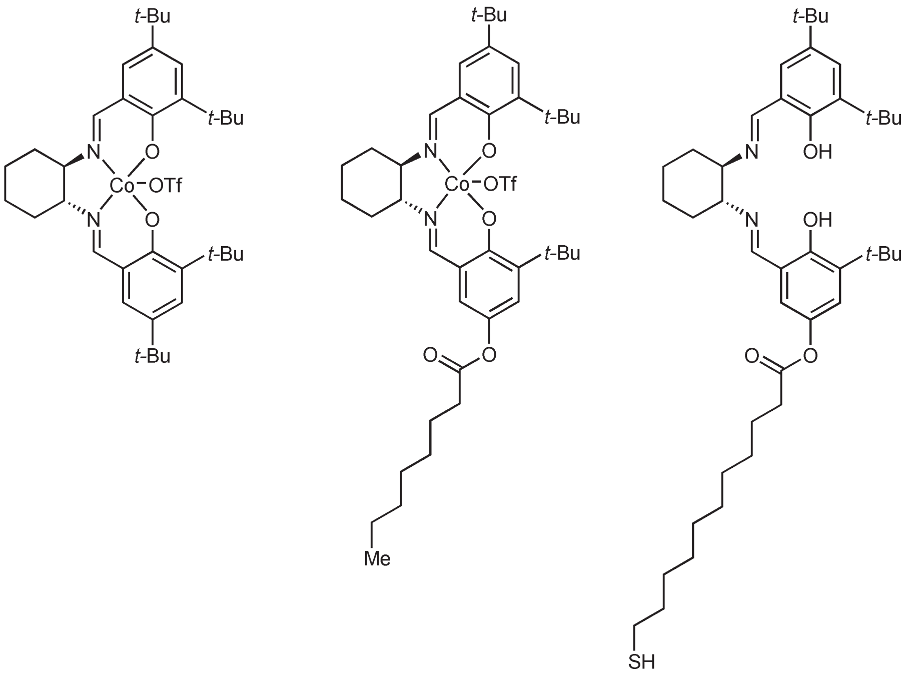


Figure 1. Cooperative bimetallic mechanism of the HKR reaction.

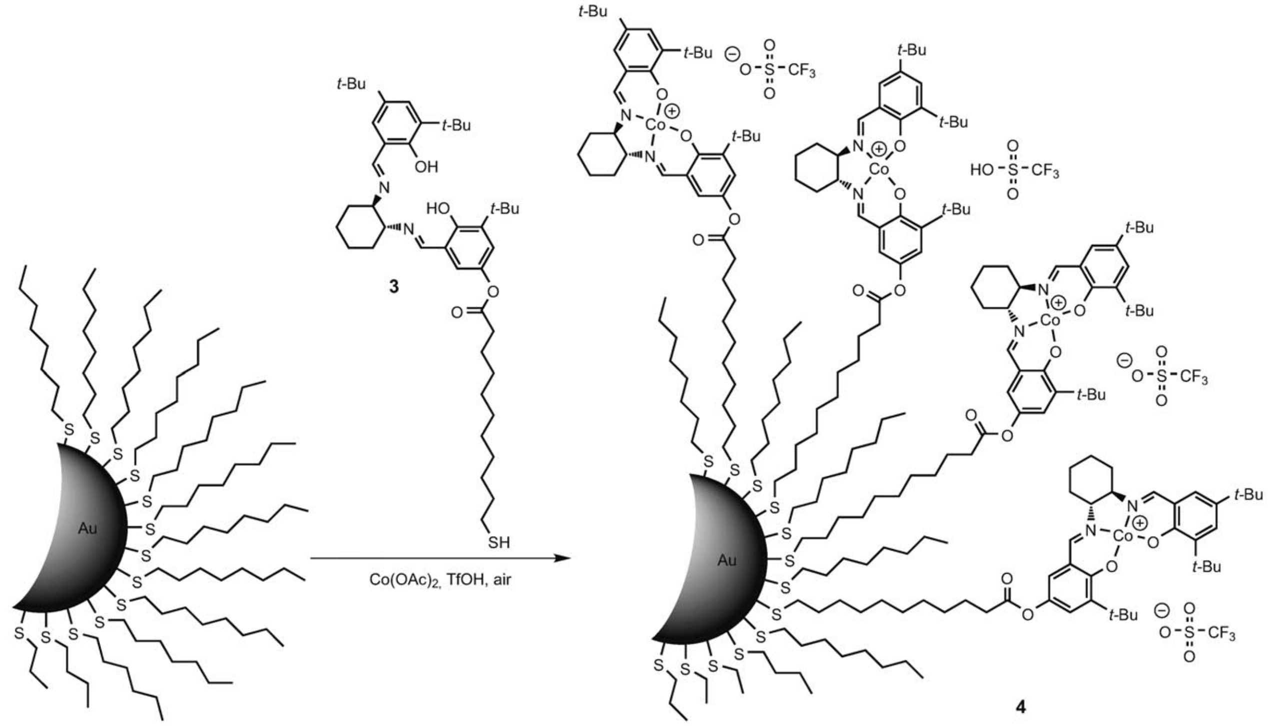
n-Octanethiolate-protected gold colloids were prepared by reduction of gold salts with $NaBH_4$ in toluene in the presence of *n*-octanethiol, as described previously.[12,13] Salen ligand **3**, bearing a long alkyl chain and a terminal thiol functionality (Scheme 1), was prepared from 11-mercaptoundecanoic acid by adaptation of standard protocols.

Incorporation of **3** onto the gold colloids was accomplished *via* an exchange reaction[12,14] in dichloromethane. The resulting functionalized colloids were stable and remained soluble unless precipitation was induced by addition of hexanes. Reaction with $Co(OAc)_2{\cdot}4H_2O$ yielded the [(salen)Co(II)] complex, which was then oxidized in the presence of trifluoromethanesulfonic acid (TfOH) and air to the catalyti-



1 **2** **3**

Scheme 1. Compounds **1–3.**



Scheme 2. Synthesis of catalyst **4**.

cally active [(salen)Co(III)] complex (Scheme 2). The resulting colloid derivative **4** was collected by filtration with a solvent-resistant stirred cell and purified by precipitation from ethanol with hexanes. Characterization was accomplished by transmission electron microscopy (TEM), elemental analysis (EA) and ^{1}H NMR spectroscopy.

The TEM studies revealed that the size of the gold core did not change significantly during the place-exchange reaction (before: $\Delta d = 3.46$ nm, $s_D = 1.16$ nm; after: $\Delta d = 3.41$ nm, $s_D = 1.10$ nm). After an incubation time of 36 h, the ratio of functionalized thiolates **3** to *n*-octanethiolates was 3:1, as determined by EA and ^{1}H NMR spectroscopy. The molecular weight and thiolate surface coverage of the functionalized gold colloids **4** was estimated based on a structural model of the gold core shape. The model employed approximates the gold core as a sphere, covered by a skin of hexagonally close-packed gold atoms.[15] According to this model, colloids **4**, with an average diameter of 3.41 ± 1.10 nm, contain 1221 gold atoms, 191 adsorbed [(salen)Co(III)]-containing thiolates and 64 adsorbed *n*-octanethiolates on the surface. Elemental analysis of **4** was in agreement with the values obtained from this model ($EA_{theor.}$: Au 56.4%, S 3.4%, Co 2.6%, N 1.3%; $EA_{meas.}$: Au 56.7%, S 3.7%, Co 2.7%, N 1.1%).

The [(salen)Co(III)] complexes **1** and **2** and the functionalized gold colloids **4** were compared in the HKR of racemic hexene-1-oxide (Figure 2). Functionalized colloids **4** were highly active, achieving complete kinetic resolution (>99.9% *ee* of recovered epoxide) within 5 h (0.01 mol% catalyst loading), whereas similar results were obtained only after 52 h using complex **2** (Figure 2). Substantially higher loading of complexes **1** or **2** (>0.1 mol%) was necessary to effect complete resolution within 24 h. Both [(salen)Co(III)] complex **2** and the functionalized gold colloids **4** induced the kinetic resolution of 1-hexene oxide with the same high k_{rel} values ($k_{rel} = 180$),[16] whereas [(salen)Co(III)] complex **1** displayed slightly lower selectivity ($k_{rel} = 133$).[17,18]

Upon completion of the HKR reaction, the unreacted epoxide was isolated by vacuum transfer. The colloids could be readily recovered by filtration of the concentrated reaction mixture using centrifugal filter units with a cut-off molecular size of 50 kD. Catalyst **4** reisolated in this manner was reused successfully. Monitoring of the reaction progress over time demonstrated that the enantioselectivity remained constant during seven recycling steps. After the sixth recycling step, the reactivity of the recycled colloids was diminished to half of that observed in the first run. However, reoxidation with TfOH and air resulted in material with identical reactivity as the original batch. After separation of the colloids, analysis of the product solutions by ^{1}H NMR spectroscopy revealed that no leaching of ligand or catalyst had occurred.

To the best of our knowledge, this study represents the first example of cooperative reactivity in catalysts immobilized on gold colloids. The practical advantag-

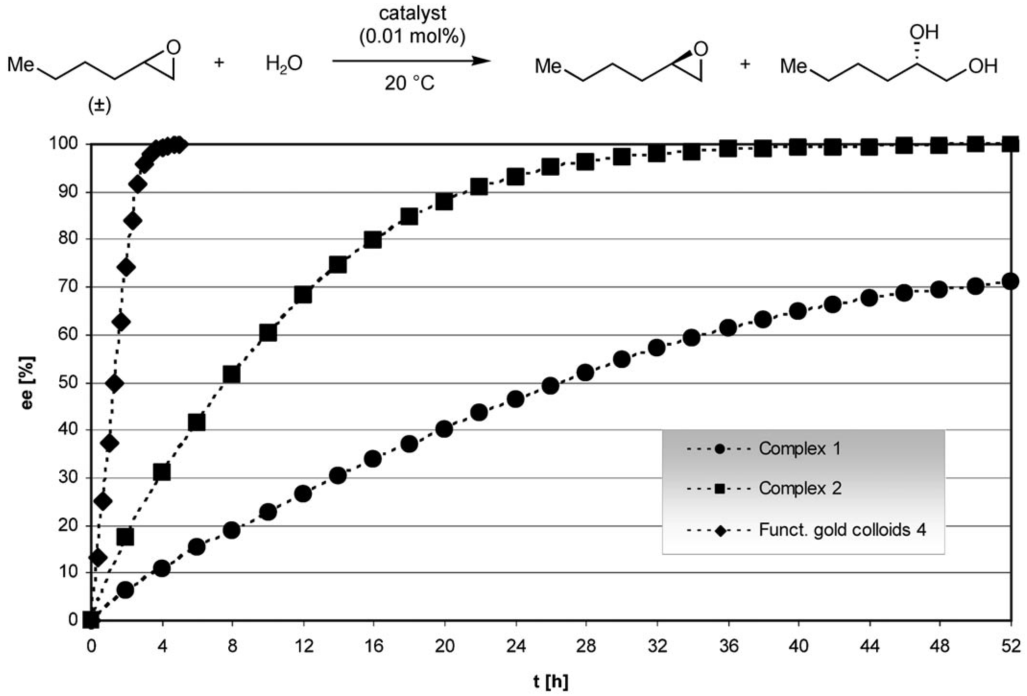


Figure 2. HKR of (±)-hexene-1-oxide with complexes **1**, **2** and functionalized gold colloids **4**.

es of the colloid-bound [(salen)Co(III)] were demonstrated, with high reactivity, selectivity, and facile catalyst recovery and recycling.

Experimental Section

Thiol 3

1-Ethyl-3-(3′-dimethyl-aminopropyl)carbodiimide hydrochloride (0.60 g, 3.13 mmol) and *N*-hydroxybenzotriazole (0.48 g, 3.13 mmol) were added to a solution of 11-mercaptoundecanoic acid (0.60 g, 2.75 mmol) in freshly distilled CH$_2$Cl$_2$ (40 mL) at 0 °C. After five minutes, {(1*R*,2*R*)-2-[(−)-(3,5-di-*tert*-butyl-2-hydroxybenzylideneamino)-cyclohexylimino]methyl}-6-*tert*-butylbenzene-1,4-diol[6] (1.00 g, 1.97 mmol) and triethylamine (0.60 mL, 4.31 mmol) were added and the reaction mixture was stirred for 6 h at 23 °C. The resulting solution was washed with a saturated NH$_4$Cl solution (50 mL) and water (50 mL). The organic phase was dried over MgSO$_4$, filtered and concentrated under reduced pressure. Purification of the crude material by flash chromatography, eluting with 10% diethyl ether in *n*-pentane, gave thiol **3** as a foamy yellow glass; yield: 0.75 g (54%); R_f = 0.63 (*n*-pentane/diethyl ether = 10:1). ^{1}H NMR (400.1 MHz, CD$_2$Cl$_2$, 293 K): δ = 1.31 (s, 9H), 1.36 (m, 9H), 1.44 (s, 11H), 1.47 (s, 9H), 1.52 (m, 4H), 1.65 (quin, J = 7.2 Hz, 2H), 1.76 (m, 4H), 1.92 (m, 2H), 2.10 (m, 2H), 2.54 (m, 4H), 3.40 (m, 2H), 6.83 (d, J = 2.3 Hz, 1H), 6.99 (d, J = 2.3 Hz, 1H), 7.07 (d, J = 2.3 Hz, 1H), 7.37 (d, J = 2.3 Hz, 1H), 8.32 (s, 1H), 8.38 (s, 1H); ^{13}C{^{1}H}-NMR (100.6 MHz, CD$_2$Cl$_2$, 293 K): δ = 24.5, 24.8, 25.2, 28.6, 29.2, 29.3, 29.5, 29.5, 29.7, 29.7, 31.4, 33.3, 33.3, 34.2, 34.4, 34.4, 35.1, 35.1, 72.4, 72.7, 118.1, 118.5, 121.8, 123.1, 126.3, 127.1, 136.4, 138.7, 140.3, 142.0, 158.1, 158.2, 165.1, 166.3, 172.7; IR (NaCl): ν = 2930 (s$_b$), 2858 (s), 1760 (s), 1631 (s), 1596 (m), 1440 (s), 1361 (m), 1315 (m), 1204 (m), 1151 (m$_b$), 1096 cm^{-1} (m); MS (FAB): *m*/*z* (rel int%) = 707 ([M]$^+$, 100), 504 (33), 312 (28), 272 (41), 216 (30).

Functionalized Gold Colloids 4

n-Octanethiolate-protected gold colloids were prepared as previously reported.[13] To a solution of *n*-octanethiol-protected gold colloids (1.70 g, ~1.3 mmol adsorbed *n*-octanethiol, 1 equiv.) in freshly distilled CH$_2$Cl$_2$ (400 mL) was added thiol **3** (3.95 g, 5.60 mmol). The solution was stirred (600 rpm) for 36 h at 23 °C, then concentrated to 50 mL under reduced pressure and treated with Co(OAc)$_2$·4H$_2$O (5.60 g, 22.5 mmol) in methanol (50 mL). The solution was stirred for one hour at 23 °C. The flask was opened to the air and trifluoromethanesulfonic acid (2.00 mL, 22.9 mmol) was added. The mixture was stirred vigorously open to air for 2 h. The solvent was removed. The crude product was dissolved in CH$_2$Cl$_2$ (50 mL) and filtered through Celite to remove excess cobalt. The solution was concentrated to 20 mL under reduced pressure, diluted with ethanol/CH$_2$Cl$_2$/acetone = 3:1:1 (200 mL) and briefly sonicated to ensure complete dissolution of by products. The colloids were collected by filtration with a solvent-resistant stirred cell (Millipore, 47 mm disc filter and an ultrafiltration membrane (regenerated cellulose, PLTK, NMWL: 30000)) and washed with ethanol/dichloromethane/acetone = 3:1:1 (5 · 200 mL). The black solution remaining in the stir cell was concentrated to 20 mL, suspended in hexanes (300 mL) and briefly sonicated to ensure complete dissolution of by-products. The mixture was kept at −60 °C for 48 h to effect complete precipitation. The colloids were collected on a glass filtration frit, and washed twice with hexanes (200 mL). The black material was dried under vacuum for 1 hour to give the functionalized gold nanoparticles **4**; yield: 1.53 g.

Catalyst Recycling

The reaction solution was concentrated under reduced pressure to remove resolved epoxide. The residue was diluted with acetone (8 mL) and transferred to a Millipore Centriplus Centrifugal Filter device with a cut-off molecular size of 50 kD. After centrifugation (3000 rpm) at 23 °C for 40 min, the filtrate containing diol was removed and analyzed by ^{1}H- and ^{19}F NMR to ascertain the amount of catalyst leaching. The remaining colloid solution was diluted with 8 mL acetone and centrifugated again. This procedure was repeated twice in order to remove any remaining product.

The concentrated colloidal solution was transferred to a flask, concentrated to dryness and washed with diethyl ether/*n*-pentane = 1:1. The colloids were then dried under vacuum and reused as catalysts.

Resolution of (±)-1,2-Epoxyhexane

Caution: *HKR of terminal epoxides is an exothermic reaction and care should be taken to ensure adequate heat dissipation.*

Distilled water (0.18 mL, 10.0 mmol) and catalyst were added to (±)-1,2-epoxyhexane (2.00 mL, 16.6 mmol) in a room temperature water bath. Every 20 min, an aliquot was removed, dissolved in diethyl ether, filtered through a silica plug and analyzed by GC. The enantiomeric excess of epoxide was determined by chiral GC analysis [γ-TA, 40 °C, isothermal, t_R (minor) = 4.3 min, t_R (major) = 4.5 min].

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[16] The selectivity factor s or k_{rel} in a kinetic resolution is defined as the relative rate of the two reacting enantiomers of the substrate ($s = k_{rel} = k_{fast}/k_{slow}$). For a discussion of fundamental and practical considerations in kinetic resolution reactions, see: J. M. Keith, J. F. Larrow, E. N. Jacobsen, *Adv. Synth. Catal.* **2001**, *343*, 5–26.

[17] HKR reactions were carried out using 0.20 equiv. of H_2O relative to racemic epoxide. The k_{rel} values were then determined based on the isolated yield and *ee* of pure 1,2-diol, and therefore represent lower limits (see ref.[3]).

[18] Higher selectivity factors have been obtained with ligand **1** with other counterions [k_{rel}(**1**-acetate) = 310]; see ref.[3]