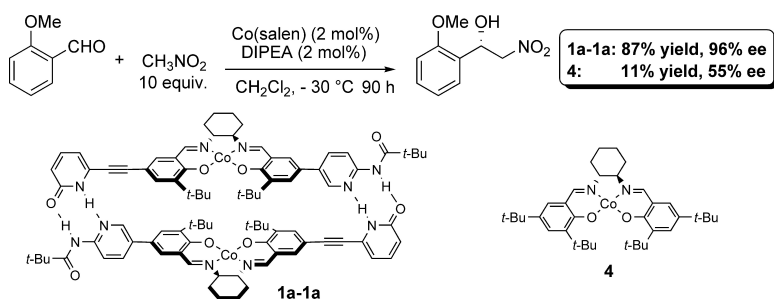


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Self-Assembled Dinuclear Cobalt(II)-Salen Catalyst Through Hydrogen-Bonding and Its Application to Enantioselective Nitro-Aldol (Henry) Reaction

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Cooperative reactivity between multiple metal centers in close proximity is a common phenomenon for enzymatic systems,¹ whereas most synthetic homogeneous transition metal catalysts consist of one metal center. Recently, there have been growing efforts to develop bimetallic catalysts enabling cooperative, simultaneous activation of both an electrophile and a nucleophile in asymmetric catalysis.² For example, chiral metal salen complexes developed by Jacobsen and co-workers are highly efficient catalysts for the asymmetric epoxide opening reactions, wherein two metal centers are involved in the transition state.³ This discovery led to the development of a number of covalently linked macromolecular salen structures⁴ showing improved reactivity as well as enantioselectivity.

The self-assembly or supramolecular approach using reversible noncovalent bonding interactions⁵ such as hydrogen bonding⁶ is a highly attractive strategy which enables rapid construction of multinuclear systems in solution via self-assembly of monomeric units. Herein we wish to report a novel dinuclear Co(II)-salen catalyst self-assembled through complementary hydrogen bonding interactions which results in significant enhancement of reaction rates and enantioselectivity of Henry reactions. Our catalyst design features two 2-pyridone/aminopyridine hydrogen bonding pairs^{6c,f} to create self-assembled dimers in solution (Figure 1). The unsymmetrical (**2a**) and symmetrical (**2b–c**)⁷ salen ligands were prepared by condensation of salicylaldehydes and (*R,R*)-1,2-cyclohexane diamine (Figure 1).⁸ Cobalt (II) complexes **1a–d** were prepared by reacting the corresponding salens with Co(OAc)₂·4H₂O under argon.

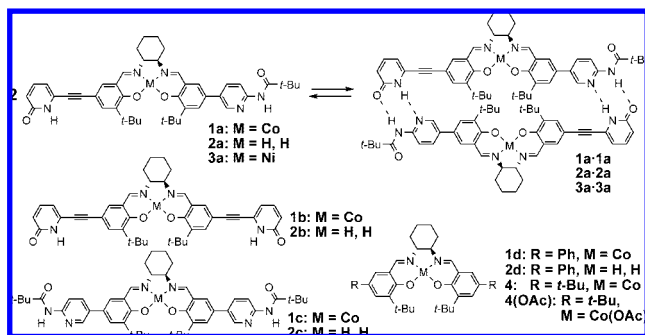


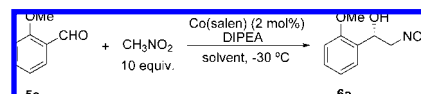
Figure 1. Structure of self-complementary dinuclear Co(salen) complex and symmetrical Co(salen) complexes.

The Henry reaction is an important C–C bond forming reaction, and many excellent asymmetric catalytic systems have been developed.⁹ Recently, the Yamada group^{10a} and the Skarzewski group^{10b} reported that Co(II)- and Cr(III)-salen complexes can catalyze this reaction in the presence of external base. We envisioned that this reaction could serve as an ideal model system to test our new self-assembled catalyst because both aldehydes and

nitronate ions can bind to the metal center and the reaction proceeds in aprotic solvents such as CH₂Cl₂.

Newly prepared Co(salen) catalysts were tested in the reaction of *o*-methoxybenzaldehyde and nitromethane in the presence of 2 mol% of DIPEA (Table 1). We were pleased to find that the unsymmetrical Co(salen) catalyst **1a** afforded the nitroaldol adduct **6a** in 87% yield and 96% ee (entry 1), whereas monomeric Co(II) catalyst **4** and Co(III) catalyst **4(OAc)**¹¹ gave the product in less than 11% yield and 55–64% ee under the same conditions (entries 8–9). Symmetrical Co(salen)s (**1b** and **1c**) gave the product in similarly low yields and slightly improved ee's (entries 5–6). In addition, loss of enantioselectivity was observed when self-assembled catalyst (**1a**) or monomeric catalyst (**4**) was used in MeOH (entries 3 and 10). However, when an equimolar mixture of Co(salen)s **1b** and **1c** was used as a heterodimeric catalyst, 87% ee was obtained, but the yield was low (18%) as they are used alone, suggesting that those two symmetrical salens would form a relatively weak dimeric species (entry 7).¹² When 100 mol% of base were used, the reaction was accelerated with the slight loss of enantioselectivity (entry 2). Interestingly, when free ligand **2a** was added to the reaction mixture, yield was lowered noticeably, suggesting that **2a** might be a competitive inhibitor for the bimetallic species formation (entry 4).

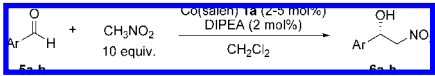
Table 1. Henry Reaction of *o*-Methoxybenzaldehyde^a



entry	Co(salen)	DIPEA (mol%)	solvent	time (h)	yield ^b (%)	ee ^c (%)
1	1a	2	CH ₂ Cl ₂	90	87	96
2	1a	100	CH ₂ Cl ₂	40	91	91
3	1a	2	MeOH	40	89	25
4	1a + 2a ^d	2	CH ₂ Cl ₂	90	59	96
5	1b	2	CH ₂ Cl ₂	90	12	72
6	1c	2	CH ₂ Cl ₂	90	16	69
7	1b + 1c ^e	2	CH ₂ Cl ₂	90	18	87
8	4	2	CH ₂ Cl ₂	90	11	55
9	4(OAc)	2	CH ₂ Cl ₂	90	<10	64
10	4	2	MeOH	40	93	5
11	1d	2	CH ₂ Cl ₂	90	14	70

^a The reaction was carried out at 0.25 mmol scale in CH₂Cl₂ (1.0 mL) or MeOH (1.0 mL) at -30 °C. ^b In cases of low yield, only the unreacted starting material was recovered. ^c Ee was determined by chiral HPLC. ^d Salen ligand **2a** (6 mol%) was used as an additive. ^e **1b** (1 mol%) and **1c** (1 mol%) were used as an equimolar mixture.

The reaction scope was then studied by varying aryl aldehyde substrates using the self-assembled Co(salen) **1a** (Table 2). Slightly more concentrated conditions were used to further reduce the reaction time for less reactive substrates. High enantiomeric excesses (81–96% ee) and good to excellent yields (65–99%) were obtained for various aryl aldehydes.

Table 2. Scope of Aromatic Aldehydes of the Self-Assembled Cobalt(salen) Catalyzed Asymmetric Henry Reaction^a


entry	aldehyde	Co(salen) (mol%)	time (h)	yield (%)	ee ^b (%)
1	<i>o</i> -MeOC ₆ H ₄ (5a)	2	48	89	96
2	<i>o</i> -ClC ₆ H ₄ (5b)	2	14	97	93
3	<i>o</i> -FC ₆ H ₄ (5c)	2	14	97	94
4	<i>p</i> -CF ₃ C ₆ H ₄ (5d)	2	40	99	82
5	<i>p</i> -FC ₆ H ₄ (5e)	2	40	65	90
6	<i>p</i> -MeOC ₆ H ₄ (5f) ^c	5	110	77	81
7	1-naphthyl (5g)	2	40	92	91
8	2-naphthyl (5h)	2	65	88	87

^a The reaction was carried out at 0.25 mmol scale in CH₂Cl₂ (0.25 mL) at -30 °C. ^b Ee was determined by chiral HPLC. ^c 10 mol% of DIPEA were used.

To confirm our hypothesis that the bimetallic activation plays a critical role in the Co(salen) catalyzed Henry reaction, kinetic studies were performed by monitoring initial reaction rates (consumption of *o*-methoxybenzaldehyde) by HPLC. Rate laws were found to be second order in cobalt concentration (Rate = $k_{\text{obs}}[\text{Co-Salen}]^2$) for both monomeric (**4**) and self-assembled Co(salen) complexes (**1a**), indicating that two molecules of **4** and **1a** are involved in the transition state. Rate constant k_{obs} of self-assembled catalyst **1a** is 289 M⁻¹ h⁻¹, which is 48 times larger than that of monomeric cobalt-salen catalyst **4** ($k_{\text{obs}} = 6.02 \text{ M}^{-1} \text{ h}^{-1}$).⁸ The rate acceleration by **1a** can be rationalized by the facile formation of a stable dimer of **1a** through hydrogen bonding in nonpolar media.

The X-ray structure of Ni(Salen) complex **3a** clearly showed self-assembly through hydrogen bonding (Figure 2). The self-assembled dimer adopts the “head-to-tail” conformation where the metal–metal distance is 4.054 Å. To verify the hydrogen-bonding event in solution, ¹H experiments were performed with metal-free salen ligand **2a**.^{8,13} When 25% v/v CD₃NO₂ in CDCl₃ was used as a media which is similar to the actual Henry reaction conditions, the NH proton signal of the pivalamide group and the signals of three protons of the pyridine ring in the ligand **2a** were changed upon variation of concentration (0.14–19.09 mM).¹⁴ The dimerization constant K_{dim} of self-assembled salen ligand **2a** was estimated as $53 \pm 21 \text{ M}^{-1}$ by using nonlinear curve fitting methods.¹⁵ These solution-phase ¹H experiments confirm the hydrogen-bonding interaction in the pyridone-aminopyridine functionalized-salen ligand **2a**.

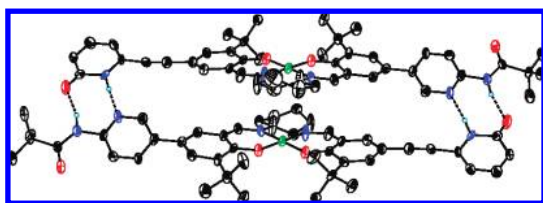


Figure 2. X-ray structure of self-assembled Ni(Salen) complex **3a**•**3a**. The Ni–Ni distance is 4.054(2) Å. The hydrogen-bonding donor–acceptor distances are 2.858(7) for N–H–O and 2.922(7) for N–H–N. Disorders on the cyclohexane rings were removed for clarity.⁸ Thermal ellipsoids are drawn at the 50% probability level.

In conclusion, we have developed a chiral bimetallic Co(II)-salen catalyst self-assembled through hydrogen bonding, which results in significant rate acceleration as well as excellent enantioselectivity in Henry reaction. The self-assembly through hydrogen

bonding was confirmed by the X-ray structure and ¹H experiments. A bimetallic mechanism is suggested by the kinetic experiment (Rate ∝ [catalyst]²). This result proves the validity of novel self-assembly based approaches toward the efficient construction of chiral bimetallic catalyst systems. Further modifications of ligand structure to allow formation of heterobimetallic dimers are in progress.

Acknowledgment. We thank Prof. Ron Castellano for helpful discussions and the University of Florida for financial support.

Supporting Information Available: Experimental details, NMR spectra for new compounds, kinetic data, nonlinear curve-fitting analysis, and HPLC analysis data (pdf), and X-ray crystallographic data for **3a** (cif). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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