SELF-ASSEMBLED DINUCLEAR CATALYSTS THROUGH HYDROGEN-BONDS FOR ASYMMETRIC REACTIONS

By

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To my family
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Self-assembled dinuclear catalysts through hydrogen-bonds for asymmetric reactions

By

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Chair: Sukwon Hong
Major: Chemistry

Recently, there have been growing efforts to develop multinuclear catalysts enabling cooperative, simultaneous activation of both an electrophile and a nucleophile in asymmetric catalysis. To construct multi-metallic catalysts, the use of covalent bond linkage has been a general strategy. As an alternative way, a self-assembly approach toward bimetallic catalyst using hydrogen bonds has been devised.

Based on this idea, we have developed a novel dinuclear (salen)Co(II) catalyst self-assembled through two complementary H-bonding interactions for asymmetric Henry reaction. Our catalyst design features two 2-pyridone/aminopyridine hydrogen bonding pairs to create a self-assembled dimer in solution. The self-assembled dinuclear (salen)Co(II) catalyst results in significant rate acceleration (48 times faster) as well as high enantioselectivity in the Henry reaction compared to the corresponding non-functionalized (salen)Co(II) catalyst. Rate laws were found to be second order in cobalt concentration for both self-assembled (salen)Co and monomeric complexes, suggesting a bimetallic mechanism is operating. The self-assembly through hydrogen-bonding was confirmed by the X-ray structure and by the $^1$H NMR experiments.
Bis-urea functionalized (salen)Co catalysts have been also devised for the hydrolytic kinetic resolution of epoxides. This new design features urea hydrogen bonding as a self-assembling motif and is expected to benefit from simple catalyst synthesis and desired metal-metal distance for dual activation. Those bis-urea (salen)Co(III) catalysts showed significant rate acceleration (4.2 to 13.7 times) compared to the unfunctionalized (salen)Co(III) catalyst in the HKR of epichlorohydrin in THF. The rate acceleration was caused by self-assembly of catalytic units, which was verified by control experiments, IR and NMR experiments, X-ray analysis and MM2 calculations.

As an extension of this promising strategy, we also developed novel bis-urea spacing dimeric (salen)Co catalysts. In this ligand design, two salen units are linked by a bis-urea spacer. The resulting complexes have been found to efficiently catalyze asymmetric hydrolysis reaction of meso-epoxides which is known to be very challenging with the monomeric (salen)Co catalyst. Those results demonstrate the novel self-assembled approach can provide a powerful tool for the generation of bimetallic catalysts.
CHAPTER 1
INTRODUCTION

Cooperative Activation in Asymmetric Catalysis

Catalytic asymmetric reactions have been one of the most powerful and economical methods to prepare a variety of enantioenriched compounds. In order to achieve the reactivity and selectivity in asymmetric catalysis, the single activation strategy has been utilized over the past four decades. In this context, a number of chiral Lewis acid and Lewis base catalysts have been devised to activate electrophiles or nucleophiles by coordination. The resulting electrophile/Lewis acid complex (or nucleophile/Lewis base complex) reacts with a nucleophile (or electrophile) in an enantioselective manner to afford enantioenriched products. While remarkable advances have been achieved with this approach over the years, there are still a number of important asymmetric transformations that lack efficient catalytic methods.

Synergistic, cooperative activation through multiple reaction centers in close proximity is a general strategy in biological system. Positioning two reaction partners in optimal geometry through coordination or non-covalent interactions allows for high efficiency and selectivity under mild reaction conditions. This cooperative activation makes the reaction occur in an intramolecular fashion, which generally gives superior reactivity and selectivity compared to the reaction in an intermolecular fashion with single activation catalysts. Inspired by this remarkable efficiency of biocatalysts, there has been much interest in designing and developing highly efficient catalysts to explore the concept of cooperative activation over the past decade. In this catalyst design, two catalytic moieties that can activate both reaction partners, are integrated into one molecule, resulting in high reactivity and selectivity.
Two general approaches toward efficient dual activation systems have been currently utilized in asymmetric catalysis. In one approach, carefully designed chiral dinucleating ligands are used to host two metallic or functional moieties in one molecule. This type of catalysts includes bimetallic catalysts, Lewis acid/base and organocatalytic bifunctional catalysts (Figure 1-1). Among those catalysts, bimetallic catalysts will be described in detail in the next section.

![Figure 1-1. Schematic illustration of bifunctional catalytic systems](image)

In another approach, two catalyst entities are often linked together by covalent tethers for the reaction displaying a second-order rate dependence on catalysts (Figure 1-2). This linking approach allows for the development of much more efficient catalysts than the monomeric catalyst. This attempt will be described in detail later in Chapter 1.

![Figure 1-2. Schematic illustration of tethering strategy for bimetallic catalysts](image)
Bimetallic Catalysts in Asymmetric Synthesis

Catalytic systems involving two metal centers are ubiquitously found in enzymes such as methane monooxygenase, aminopeptidase, urease, and phosphoesterases.\(^3\)

The catalytic system utilizing two metal centers has been proved highly effective for many types of transformations. In this context, there have been growing efforts to develop bimetallic catalysts enabling cooperative and simultaneous activation of two reaction partners in asymmetric catalysis.\(^4\)

As an early attempt, Kumada and co-workers reported new chiral ligand 1-2 for the asymmetric palladium-catalyzed allylic alkylation, which has a chelation-control motif (Scheme 1-1).\(^5\) By employing those additional control groups, moderate selectivity was achieved (52% ee). When they tested the ligand lacking the ester functional group (1-3), selectivity was significantly decreased (15% ee). Thus, the chelation of a nucleophile through the alkali metal cation was a crucial factor to achieve the improved stereoselection (Figure 1-3).

![Scheme 1-1](image)

Scheme 1-1. Enantioselective allylic alkylation
From this initial experiment, more improved ligands bearing other directing group have been reported. Ito and co-workers devised aza-crown ether bearing bisphosphine ligand 1-5, which showed improved enantioselectivity (72%) in the allylic alkylation of β-diketone (Figure 1-4). The other related ligand 1-6 has been also successfully expanded to asymmetric allylic alkylation of α-nitroesters in the presence of RbF and RbClO₄, wherein good ee (80%) was achieved.

In 1992, Shibasaki and co-workers reported lanthanide-based heterobimetallic systems that contain one rare earth metal, three alkali metals and three 1,1′-bi-2-naphthols (BINOL) for asymmetric nitroaldol reaction (Figure 1-5). The reaction is promoted by the combination of the Brønsted basicity of the alkali metal portion (generation of nucleophiles) and the Lewis acidic lanthanide center (activation of electrophiles), and high selectivity (90% ee) was obtained. This rare earth-alkali metal-BINOL (REMB) complex 1-7 has been successfully extended to other asymmetric
transformations such as cyanoethoxycarbonylation,\textsuperscript{9} conjugate addition,\textsuperscript{10} hydrophosphonylation,\textsuperscript{11} Tishchenko-aldol\textsuperscript{12} and direct aldol reaction.\textsuperscript{13}

![Structure of 1-7 and the enantioselective Henry reaction](image)

Figure 1-5. Structure of 1-7 and the enantioselective Henry reaction

A few years later, the same group also developed a BINOL-derived aluminum/alkali metal bimetallic system (Scheme 1-2).\textsuperscript{14} The alkali metal heterobimetallic catalyst was found to be efficient for the conjugate addition of malonates, wherein the aluminum center played as a Lewis acid and alkali-metal alkoxide behaved as a Brønsted base (Figure 1-6).

![Scheme 1-2. Enantioselective conjugate addition](image)
Kozlowski and co-workers reported a salen-based bimetallic complex that incorporates two chiral binol moieties. This Ni/Cs bimetallic complex was an effective catalyst for the enantioselective Michael addition of benzyl malonate to cyclohex-2-enone (Scheme 1-3). Similarly, the Lewis acid/alkali metal cooperative effects are crucial for the high enantioselectivity (90% ee) observed in this catalytic system.

In addition to transition metal/alkali metal bimetallic systems, there is another type of bimetallic catalysts, in which two transition metals are involved. The TMSCN addition reactions to carbonyl compounds via bimetallic activation were reported by Belokon, North and co-workers (Scheme 1-4). It was found that the bridged bimetallic μ-oxo titanium species 1-16 is the actual precatalyst, which simultaneously activates both the electrophile and the nucleophile (Figure 1-7). This bimetallic μ-oxo titanium species 1-16 is in equilibrium to monometallic species 1-15, which is catalytically inactive, relying on concentration. This catalyst has been proven to be highly efficient for the synthesis of...
optically active cyanohydrins derivatives because good to excellent enantiomeric excesses (52-92%) can be achieved using as low as 0.1 mol% of catalyst.

Scheme 1-4. Asymmetric trimethylsilylcyanation of aldehydes

Figure 1-7. Proposed transition state of cyanohydrin reaction

Jacobsen and co-workers reported the first example of asymmetric catalysis in the conjugate addition reactions of cyanide (Scheme 1-5). In this reaction, chiral (salen)AlCl complex 1-20 was used as a catalyst, and high yields and enantioselectivity
were observed with α,β-unsaturated imides. Preliminary kinetic study shows that a bimetallic, dual-activation mechanism is involved.

\[
\begin{align*}
\text{Ph} & \quad \text{O} \quad \text{N} \quad \text{C} \quad \text{R} \\
&& \quad \downarrow \quad \text{1-20 (10 mol\%)} \\
&& \quad \text{TMS CN, } \text{t-PrOH,} \\
&& \quad \text{tol u e n e, 45°C} \\
\text{Ph} & \quad \text{O} \quad \text{N} \quad \text{C} \quad \text{R} \\
&& \quad \downarrow \quad \text{70-96\% yield} \\
&& \quad \text{87-98\% ee} \\
\end{align*}
\]

Scheme 1-5. Conjugate addition of TMSCN to unsaturated imides catalyzed by (salen)AlCl complex

The use of two different chiral metal catalysts is beneficial for dual activation in some cases. Jacobsen and co-workers reported that the combination of μ-oxo dimeric (salen)Al complex 1-22 and (pybox)ErCl₃ complex 1-23 improved catalytic efficiency further in the same cyanide conjugate addition (Scheme 1-6).\(^{18}\) In contrast to (salen)AlCl complex 1-20, μ-oxo analogue 1-22 was found to be inactive owing to the lack of the cyanide activation. They found that the addition of (pybox)ErCl₃ complex 1-23 in the presence of 1-22 efficiently promotes this reaction through the dual activation of the cyanide nucleophile by 1-23 and the imide by 1-22. Compared to the (salen)AlCl system, total catalyst loadings in the dual catalysis system were decreased from 10 mol\% to 5 mol\% without any loss of enantioselectivity.

The cyanide addition to imine electrophiles is also a very useful reaction because the resulting compounds can be transformed into various compounds. Shibasaki and co-workers have reported gadolinium complex 1-25-Gd for the asymmetric Strecker reaction of ketimines (Scheme 1-7).\(^{19}\) This chiral Gd complex was prepared from Gd(OiPr)₃ and α-glucose-derived ligand 1-25 in a 1:2 ratio, and the resulting complex
showed high enantioselectivity in the asymmetric TMSCN addition to a wide range of \(N\)-diphenylphosphinoyl ketimines. This glucose-based gadolinium catalyst was very useful for other various reactions, including the cyanosilylation of ketones,\(^{20}\) the conjugate addition of TMSCN to \(\alpha,\beta\)-unsaturated \(N\)-acyl pyrroles,\(^{21}\) and ring-opening reactions of meso-aziridines with TMSCN and TMSN\(_3\).\(^{22}\)

![Scheme 1-6. Conjugate addition of TMSCN to unsaturated imides](image1)

The results of mechanistic and ESI-MS studies indicated that the active catalyst is a self-assembled Gd/1-25 = 2:3 complex. Thus, the mechanism involving bimetallic activation was proposed as a working model (Figure 1-8).\(^{23}\) In this cooperative system, one gadolinium metal activates the electrophile, and the cyanide nucleophile is activated by the other gadolinium metal ions rather than by the phosphane oxide moiety.
To gain structural information, they attempted to obtain the crystal structure of the actual catalytic species (Gd/1-25 = 2:3 complex). However, the single crystal obtained from the 1-25-Gd complex (Gd(OiPr₃)/1-25 = 2:3) in propionitrile/hexane solution was a 4:5 complex (Gd/1-25 = 4:5) with a μ-oxo atom (Scheme 1-8, 1-27).²⁴ Interestingly, ESI-MS study of 1-27 indicates that this tetranuclear structure is maintained in a solution state. Unexpectedly, when higher-order aggregated crystal 1-27 was employed to the same Strecker reaction of N-diphenylphosphinoyl ketimines, much slower reaction and opposite enantioinduction were observed. Thus, they concluded that the assembly mode is the determining factor for the function of asymmetric induction in polymetallic catalysis, not the structure of each chiral ligand module.

Trost and co-workers developed a dinuclear zinc catalyst that was successfully applied to enantioselective direct aldol reactions (Scheme 1-9).²⁵ This chiral semicrown/Zn catalyst promotes the reaction of acetophenone and bulky aldehydes with high enantioselectivity, wherein one zinc metal acts as a Lewis acid and the other zinc metal acts as a Brønsted base. The use of this dinuclear zinc catalyst has been successfully applied to desymmetrization of meso-diol,²⁶ enantioselective Henry,²⁷ aza-Henry,²⁸ alkynylation,²⁹ Friedel-Crafts,³⁰ Mannich,³¹ and conjugate addition reactions.³²
Scheme 1-8. Enantioselective Strecker reaction of ketimines catalyzed by 1-27

\[
\begin{align*}
\text{1-24} & \xrightarrow{1-26 (7 \text{ mol\%})} \text{1-26} (7 \text{ mol\%}) \\
\text{1-26} & \xrightarrow{T\text{MSCN (1.5 eq)}} \text{NC} \xrightarrow{\text{CH}_3\text{CH}_2\text{CN, } -40^\circ\text{C}} \text{NC} \\
\text{(R)-1-26} & \xrightarrow{82-98\% \text{ ee}} \\
\end{align*}
\]

Scheme 1-9. Chiral dinuclear zinc catalyst for asymmetric aldol reactions

\[
\begin{align*}
\text{1-29} & \xrightarrow{(5 \text{ mol\%})} \text{1-29} (5 \text{ mol\%}) \\
\text{1-29} & \xrightarrow{\text{Et}2\text{Zn (10 mol\%)} \quad \text{Ph}_3\text{P=S (15 mol\%)} \quad \text{MS 4 \AA, 5\%}} \\
\text{1-30} & \xrightarrow{24-79\% \text{ yield}} \quad \text{56-99\% ee} \\
\end{align*}
\]
Recently, Shibasaki and co-workers reported salen-based heterobimetallic catalysts (Scheme 1-10). They showed that this heterobimetallic Cu-Sm-Schiff base complex 1-33 efficiently catalyze nitro-Mannich reactions with high syn diastereoselectivity and enantioselectivity. The cooperative activation of the imine and the nitroalkane by two different metals is the key to achieving such high selectivities. The interesting feature of this Schiff base ligand system is that a smaller transition metal can be selectively installed into the inner N$_2$O$_2$ cavity and an oxophilic rare earth metal with a large ionic radius into the outer O$_2$O$_2$ cavity.

![Diagram](image)

Scheme 1-10. Shibasaki’s Cu-Sm-Schiff base system

The same group successfully expanded this dinucleating Schiff base ligand system to other catalytic asymmetric reactions. The bench-stable homodinuclear Ni$_2$-Schiff base complex (1-36) works well for the anti-diastereoselective formation of α-tetrasubstituted anti-α,β-diamino acid surrogates with high enantioselectivity (Scheme 1-11). The introduction of 1,1'-binaphthyl-2,2'-diamine backbone in 1-36 allows for the incorporation of metals with a smaller ionic radius into the O$_2$O$_2$ outer cavity in contrast to 1-33. This dinucleating Schiff base system proved to be highly efficient for a variety of different asymmetric reactions, and often different combinations of inner and outer metals were used.
Scheme 1-11. Diastereoselective nitro-Mannich reaction catalyzed by 1-36

A highly efficient heterogeneous bimetallic catalyst has been introduced by Shibasaki and co-workers. The amide-based ligand bearing a m-oriented phenolic hydroxyl group was utilized as a platform to form a heterobimetallic complex with a rare-earth metal and an alkali metal (Scheme 1-12). This heterogeneous Nd/Na heterobimetallic catalytic system demonstrates excellent anti-selectivity and enantioselectivity in nitroaldol reaction for a broad range of aldehydes and nitroalkanes.

Scheme 1-12. Heterogeneous bimetallic system for anti-selective nitroaldol reactions

Recently, Peters and Jautze reported bispalladacycle complex 1-42 for the enantioselective Michael addition of α-aryl-substituted α-cyanoacetates to vinyl ketones
This soft bimetallic complex is capable of simultaneously activating both substrates in a highly stereocontrolled manner, resulting in the formation of a quaternary stereocenter with high enantiomeric excess. As shown in Figure 1-9, the enone electrophile can be activated by the carbophilic Pd center, and the α-cyanoacetate nucleophile can be activated by the other Pd center. The use of this bispalladacycle catalyst has been successfully applied to tandem azlactone formation-Michael addition reaction.

Scheme 1-13. Bispalladacycle-catalyzed asymmetric Michael addition

Enhancement of Cooperative Bimetallic Activation

As described in the previous section, there have been growing efforts to construct more efficient catalytic systems using dual activation concept. Mechanistic and kinetic
studies have disclosed that certain types of metal-catalyzed reactions involve a bimetallic reaction pathway between individual catalytic units. However, this intermolecular bimetallic activation often led to low efficiency and selectivity at low catalyst loading or at the late stage of reactions. To overcome this limitation, the covalently-linking or merging strategy has been utilized, in which two or multiple catalytic units are linked through an appropriate linker or merging within a single framework. In this section, those attempts will be discussed.

The asymmetric ring opening (ARO) of epoxides has emerged as a powerful method for the preparation of synthetically useful aminoalcohols, diols, and related compounds in an optically active form. The asymmetric ring opening of meso-epoxides with TMSN₃ catalyzed by (salen)Cr(III) complexes was reported by Jacobsen and co-workers in 1995, which affords 1,2-azido silylethers with good to excellent enantioselectivity (Scheme 1-14).

![Scheme 1-14. Asymmetric ring opening of meso-epoxide with TMSN₃](image)

It was found that catalyst 1-45a was a precatalyst, and the actual catalytic species was 1-45b. The kinetic studies revealed the second-order rate dependence on catalyst, and significant non-linear effects were observed in the (salen)Cr(III) catalyzed ARO of epoxides with TMSN₃. Those studies show that a bimetallic mechanism is operating,
wherein simultaneous activation of the nucleophile and the electrophile by distinct catalyst molecules occurs (Figure 1-10).

Figure 1-10. Bimetallic mechanism for ARO of epoxides with TMSN$_3$

The aforementioned mechanistic studies led to design of new catalysts that could enforce bimetallic cooperative activation. Covalent tethering has been employed to construct dimeric salen systems for the purpose of increasing bimetallic environment. In this regard, Jacobsen and co-workers devised dinuclear salen complexes using flexible tethers (Figure 1-11).$^{40}$ This bimetallic complex enforced cooperativity between catalysts. It was also shown that the length of tether significantly impact the reactivity, where the dimeric catalyst with medium tether ($n = 5$) displayed a maximum value of $k_{\text{intra}}$ and enantioselectivity.

Figure 1-11. Dimeric (salen)Cr catalyst for ARO of epoxides
As with the ARO of epoxides with TMSN₃, the hydrolytic kinetic resolution (HKR) of terminal epoxides using (salen)Co(III) complexes follows similar bimetallic mechanism. Due to its importance of HKR, a great deal of effort has been made to develop more efficient catalytic system. The achievement of HKR of epoxide will be described in more detail in Chapter 3.

In the previous section, the chiral (salen)Al catalyzed conjugate cyanation was described as an example of bimetallic cooperative catalysis. To enforce bimetallic activation, the similar strategy has been taken. Jacobsen and Mazet reported tethered dinuclear (salen)AlCl complex 1-48 for the conjugate cyanation of α,β-unsaturated imides (Scheme 1-15).⁴¹ Compared to the monomeric Al-Cl complex, this covalently-linked dinuclear catalyst 1-48 showed superior efficiency in terms of reactivity without loss of enantioselectivity. Kinetic studies of this reaction proved that an intramolecular pathway is two orders of magnitude greater than the second-order component of the reaction catalyzed by 1-48.

![Scheme 1-15. Covalently tethered dinuclear (salen)Al catalyst for conjugate addition](image_url)

91-99% yield
84-96% ee
Coates and co-workers reported a highly efficient bimetallic catalyst for the enantioselective polymerization of epoxides (Scheme 1-16).\(^4^2\) The bimetallic catalyst 1-50 featuring a chiral binaphthol linker proved to be highly active and selective for the preparation of stereoregular polyethers. By X-ray analysis, Co-Co separations are found to be 5.963 and 5.215 Å, which are very close to the ideal metal-metal separation of 6 Å for epoxide opening reactions they suggest.

![Scheme 1-16. Enantioselective polymerization of epoxides](image)

Very recently, Ding and co-workers reported highly efficient dimeric titanium complex 1-52 for the cyanohydrin synthesis, in which two salen units were connected through a covalent tether (Scheme 1-17).\(^4^3\) As described in Scheme 1-4, the catalytically active $\mu$-oxo titanium(salen) species is in equilibrium to the inactive oxo species. To minimize the catalytically unfavorable dissociation of $\mu$-oxo species, the cis-5-norbornene-endo-2,3-dicarboxylate bridge was employed between two salen units. The resulting dimeric catalyst showed excellent reactivity and enantioselectivity in the asymmetric cyanohydrins synthesis even at as low as 0.0005 mol% of catalyst loading. This remarkable catalytic efficiency can be attributed to the reinforcement of cooperative dual activation by reducing the dissociation of catalytic species.
Scheme 1-17. Bridged bimetallic titanium complex for enantioselective cyanohydrin synthesis

Optically pure binaphthol (BINOL) and its derivatives constitute the core structure of many highly effective chiral ligands for a wide range of asymmetric catalysis\(^\text{44}\) as well as biaryl natural products.\(^\text{45}\) The catalytic oxidative coupling of 2-naphthols has drawn much attention lately as an atom-efficient, mild, and direct synthetic route to enantiomerically pure BINOL.\(^\text{46}\) Several metal-based catalysts involving copper, iron, cobalt, and vanadium have been developed for this reaction, where either monometallic or bimetallic mechanism has been proposed depending on the catalytic system.\(^\text{45,46}\)

Martell and co-workers reported dinuclear Cu complex \textbf{1-54} for the enantioselective oxidative coupling (Scheme 1-18).\(^\text{47}\) In this catalyst design, two Cu metals are bound to two N\(_2\)O\(_2\) cavities in the fused macrocyclic Schiff base ligand. This bimetallic Cu complex efficiently catalyzes the oxidative coupling to afford BINOL products with high enantioselectivity. A homolytic coupling of two radical species that were generated through one-electron transfer from substrate to the Cu(II) center, was suggested as a plausible mechanism.
Scheme 1-18. Dinuclear Cu catalyst for the enantioselective oxidative coupling

The chiral vanadium complexes have been also employed to asymmetric oxidative coupling of 2-naphthols. Chen and Uang independently reported the chiral vanadium complexes derived from naphthyl backbone, which can catalyze the oxidative coupling of 2-naphthol and its derivatives (Figure 1-12). However, moderate ee values (51-87%) were obtained for the 2-naphthol substrates lacking an ester functionality at the C-3 position.

Figure 1-12. Chiral vanadium complexes for oxidative coupling

To improve the catalytic efficiency, dinuclear vanadium complexes have been devised. Gong and co-workers reported dinuclear bis-vanadium complex 1-60 for the highly enantioselective oxidative coupling of 2-naphthol (Scheme 1-19). The structural feature of this catalyst is the V-O-V linkage. Their kinetic and mechanistic studies suggest that the catalytic oxidative coupling reaction occurs through intramolecular
radical-radical coupling pathways involving two vanadium metals. Sasai and co-workers also developed similar chiral dinuclear vanadium catalyst 1-61. With the dinuclear catalyst, up to 91% ee was achieved for the formation of (S)-BINOL. From kinetic analysis, they found that the coupling reaction rate using dinuclear catalyst is 48 times faster than that of the mononuclear catalyst. Interestingly, the catalyst of which the absolute configuration is same as that of Gong’s catalyst gave the opposite enantiomer as a major product. Although the reason for the reversed enantioselectivity is not clear at this point, the authors suggest that the generation of oligomeric dinuclear complexes could be involved.

Scheme 1-19. Dinuclear vanadium catalyzed oxidative coupling of 2-naphthols
Supramolecular Catalysis

Supramolecular chemistry has grown into an important area in organic and inorganic chemistry over the last three decades. Large and complex structures can be obtained through the self-assembly of relatively simple subunits without using covalent bonds. These subunits are programmed to form the supramolecular structure by the utilization of weak and reversible interactions such as metal-coordination, hydrogen-bonds, π-π interactions, and van der Waals interactions between the components. Indeed, nature largely utilizes those weak interactions for recognition of substrates as well as organization of catalytic systems. Therefore, the application of supramolecular chemistry to catalysis has drawn much attention to develop more efficient and selective catalysts. However, despite the recent progress in supramolecular catalysis, successful examples of supramolecular catalysis are still rare compared to the conventional catalysis. The reason is that the prediction and control of weak interactions is still challenging, and those interactions can affect and often inhibit the catalytic site. However, if it is possible to control and predict those interactions in supramolecular catalysis, this approach could provide a lot of opportunities to develop powerful and selective catalytic systems.

In general, two main approaches are considered in the field of supramolecular catalysis. First, the reversible non-covalent interactions have been utilized to recognize substrates. Second, more sophisticated catalysts can be constructed via self-assembly of relatively simple units through non-covalent interactions. Both approaches have offered a great opportunity to find the efficient catalytic system for challenging reactions or even to enable completely unknown chemical transformations. This section will focus on the second approach and recent examples will be described in detail.
Coordination-Driven Supramolecular Catalysts

The metal-coordination has been utilized to build supramolecular catalytic systems. In 2002, Lin and co-workers developed a chiral organometallic triangle for the dialkylzinc addition to aldehydes (Scheme 1-20). \(^{52}\) This macrocyclic ligand features three platinum metals at the vertices of the triangle formed by the three BINOL “edges”. The macrocyclic triangle ligand 1-62 gave high ee (91%) for the addition of diethylzinc to 1-naphthaldehyde, whereas monomeric ligand 1-63 showed a slightly lower ee (80%).

![Scheme 1-20. Asymmetric dialkylzinc addition to aldehyde](image)

An interesting feature of the metal-coordination based supramolecular catalysts is that the allosteric regulation is possible owing to its reversible nature. Mirkin and co-workers reported the salen based dinuclear Cr catalyst in which two Rh metals were used as the allosteric, structural motifs (Figure 1-13). \(^{53}\) In the closed dimeric form 1-65, the Rh metal site is chelated by both phosphine and sulfur atoms, and the two catalytic metal (CrCl) sites are in close proximity (~5.2 Å separation). This coordination-driven supramolecular catalyst 1-65 reveals the significant 20-fold rate enhancement in the
asymmetric ring opening of cyclohexene oxide with TMSN₃, as compared to a corresponding monomeric (salen)Cr(III) analogue. In addition, the observed enantiomeric excess is much higher under the same reaction conditions (68% vs 12% for monomer). By addition of the external ligands Cl⁻ and CO to the closed form, the cooperative activity between catalytic metal (CrCl) sites can be regulated. Because the thioether sulfur atoms are relatively poor donors, the ligand exchange readily occurs to give the open dimeric form 1-66. The open macrocyclic catalyst exhibits two-fold rate increase for the same epoxide opening reaction, compared to the closed dimeric catalyst. This remarkable result demonstrates that the reactivity and selectivity of the supramolecular catalysts can be modulated by the addition of controllers such as Cl⁻ or CO.

Figure 1-13. Mirkin’s supramolecular allosteric catalyst
The utilization of metal-coordination or hydrogen-bonds in the formation of supramolecular bidentate ligands is highly attractive, because large libraries can be easily accessed and rapid screening is possible by simply varying components. Two general methods have been recently developed: template mediate assembly and direct assembly (Figure 1-14). Three components are required in the template mediated assembly to make rather complicated systems. Nevertheless, large ligand libraries are easily accessible by this approach (10 x 10 x 10 = 1000 members based on 30 components). In contrast, the direct assembly provides a simpler system because it requires only two components. However, to achieve large ligand libraries, more building blocks are required in this approach (30 x 30 = 900 members based on 60 components).

Figure 1-14. Schematic illustration of supramolecular bidentate ligands

In this regard, Reek and co-workers developed template-mediated bidentate ligands for the rhodium-catalyzed hydroformylations for the first time (Scheme 1-21).\textsuperscript{54} In this ligand assembly, bis-(porphyrin)Zn complex was employed as a template and Zn-pyridine coordinations were utilized. Although this supramolecular catalyst did not give
good enantioselection (33% ee), it displayed unusually high regioselectivity for the branched product in hydroformylation (branched:linear = >100:1).

Scheme 1-21. Asymmetric hydroformylation using supramolecular rhodium catalyst

Based on the direct ligand assembly approach through metal coordination, Reek and co-workers developed zinc porphyrin/pyridine based ligands for rhodium-catalyzed asymmetric hydrogenation reactions (Scheme 1-22). The optimal combination of components (1-72) was chosen after rapid screening of a library of 64 ligands, which was readily accessible with this strategy.

Based on a similar strategy, Takacs and co-workers developed self-assembled chiral bidentate bis-phosphite ligands for the asymmetric Pd-catalyzed allylic amination (Scheme 1-23). Treating two monophosphite ligands bearing a pendant bisoxazoline with Zn(OAc)$_2$ led to the preferential formation of the heteroleptic (box)$_2$Zn complex, in which the Zn metal served as a structural element. Like other supramolecular bidentate
ligands, this modular and combinatorial approach allowed for rapid screening of 50 different combinations of spacers and backbones to find optimal catalytic efficiency. As a consequence, Pd complex 1-75 was found to be the optimal combination which efficiently catalyzed the allylic amination with high enantioselectivity.

Scheme 1-22. Asymmetric hydrogenation using supramolecular rhodium catalyst

Scheme 1-23. Self-assembled chiral diphosphite-palladium catalyzed asymmetric allylic aminations

Another interesting use of metal coordination in supramolecular chemistry is the building of cage-like macromolecules, which can accommodate small molecules inside the cavity. The resulting molecular cages can function as a nanoreactor by providing a confined reaction environment. In 1995, Fujita and co-workers reported the formation
of M₆L₄-assembling encapsulated cage by mixing tridentate 4-pyridyl ligands and Pd precursors in aqueous solution (Figure 1-15). The resulting supramolecular cage is thermodynamically stable and is able to accommodate guest molecules such as adamantyl carboxylate ion. In addition, the well-defined, hydrophobic cavity of this coordination-driven cage can provide a microenvironment that promotes reactions such as trimerization of trialkoxysilanes, alkane oxidations, and Diels-Alder reactions. Quite impressively, the unusual reactivity and selectivity inside the cavity led to discover new transformations which were otherwise inaccessible.

![Diagram of Fujita’s M₆L₄ supramolecular assembly](image)

Figure 1-15. Fujita’s M₆L₄ supramolecular assembly

In 2002, the same group showed that this cage could be a good encapsulated catalyst for photocatalyzed [2+2] cycloaddition of sterically demanding olefins. This cage can nicely accommodate reactants inside the cavity in the head-to-tail syn configuration through aromatic interactions (Scheme 1-24). After irradiation of 1-77a•1-78 complex, as a result, the head-to-tail syn isomer 1-79 was obtained in excellent yield
without any other regio- and stereoisomers. Without the cage, no photoaddition products were observed even at a very high concentration.

Scheme 1-24. [2+2] Photocycloaddition within encapsulated catalyst

Very recently, the enantioselective catalysis with this cage catalyst has been accomplished. In 2008, Fujita and co-workers utilized their chiral M₆L₄ cage catalyst 1-77b for enantioselective [2+2] cross photocycloaddition reactions of fluoranthrene with a maleimide (Scheme 1-25).⁶³ To build a chiral cage, (1R,2R)-N,N-diethyl-1,2-diaminocyclohexane ligands were used. Good asymmetric induction (50% ee) and regioselection were observed considering the remote location of the chiral ligand.

Scheme 1-25. Asymmetric [2+2] photocycloaddition within a cage
Raymond and co-workers reported $M_4L_6$ self-assembled system ($M = \text{Ga}^{3+}, \text{Al}^{3+}, \text{Fe}^{3+}, \text{Ge}^{4+}, \text{Ti}^{4+}$, $L = 1,5\text{-bis}(2',3''\text{-dihydroxybenzamido})\text{naphthalene}$) with metal coordination bond (Figure 1-16). This cavity-containing metal-assembly provides well-defined, polyanionic and hydrophobic cavity, which allows for encapsulation of cationic species. The self-assembled cage 1-83 has been used as a nanoreactor for the C-H activation, acidic hydrolysis of orthoformates and isomerization of allylic alcohols.

![Figure 1-16. Raymond’s $M_4L_6$ supramolecular assembly](image)

In this context, Raymond and co-workers also showed that self-assembled cage 1-83 can catalyze the unimolecular [3,3] aza-cope rearrangement of allyl enammonium salts (Figure 1-17). This host assembly accelerates the rates for rearrangement by up to 3 orders of magnitude, and independence of rates with solvents support this reaction occurring inside the cavity.

Although the building blocks for this $[\text{Ga}_4\text{L}_6]^{12-}$ assembly are achiral, 1-83 is chiral as a result of the three bidentate catecholates binding to each gallium centers. Those two enantiomeric forms $\Delta\Delta\Delta\Delta$-1-83 and $\Lambda\Lambda\Lambda\Lambda$-1-83 were successfully separated by addition of (-)-$N'$-methylnicotinium iodide (Scheme 1-26). After treating with ion exchange chromatography, both enantiomers were obtained as the tetramethyl-
ammonium salts. With this chiral capsule, they performed the enantioselective version of the aza-Cope rearrangement, which afforded the resulting rearranging product with high enantioselectivity (78%). This ee value is the highest ee by synthetic supramolecular hosts to date.

Figure 1-17. Aza-Cope rearrangement within a self-assembled cavity

Scheme 1-26. Enantioselective aza-Cope rearrangement by a chiral supramolecular assembly
Hydrogen-Bonding Mediated Supramolecular Catalysts

Hydrogen-bonding interaction represents probably the most important non-covalent interaction used in the supramolecular chemistry owing to their pronounced directionality and relatively high strength. Although hydrogen bond itself is a much weaker bond compared to the covalent bond, it can be utilized to build strongly assembled structures by combining multiple hydrogen bonds. In this context, hydrogen bonding interactions have been recognized as one of the main forces to construct supramolecular structures and recognize specific guest molecules. However, the successful application of this interaction for supramolecular catalysis has been rarely developed so far.

As an early example, Yano and co-workers developed a self-assembled catalytic system by the use of hydrogen bonds and electrostatic interactions. The 2,6-diaminopyridine moiety has been known as a thymine receptor through three hydrogen bonds. Based on this idea, they devised a supramolecular system in which thymine bearing thiazolium ion 1-89 and 2,6-diaminopyridine derivative 1-88 are self-assembled via hydrogen bonds (Figure 1-18). The pyruvate anion can be attracted via ionic interactions to the alkali metal cation bound into the crown ether moiety of 1-88, rendering the reaction intramolecular in nature. This catalytic system exhibited rate acceleration up to 160 times for the thiazolium-catalyzed oxidative decarboxylation of pyruvate.

Like metal-coordination driven capsules, properly oriented multiple hydrogen bonding interactions can be utilized to construct the molecular capsule having a well-defined cavity. In contrast to metal-coordination cages, those hydrogen-bonds mediated
cages are generally not stable in polar or aqueous media due to the nature of hydrogen bonds. Rebek and co-workers reported molecule 1-90 which can self-assemble through multiple hydrogen bonds to form a molecular capsule in nonpolar solvent (Figure 1-19).\(^7\) The dimerization constant of 1-90 is very large (>\(10^6\) M\(^{-1}\)) in benzene and the resulting self-assembled capsule possess an interior volume of \(\sim 300\) Å\(^3\). This self-assembled capsule provides a well-defined hydrophobic cavity that can accommodate more than one small guest molecule, and certain type of intermolecular reactions can be accelerated inside the cavity. Indeed, this encapsulated catalyst displays 200 times rate acceleration for Diels-Alder reaction compared to non-catalyzed reaction.

A few years later, Rebek and Chen also reported a self-assembled cylindrical cavity for 1,3-dipolar cycloaddition reactions (Figure 1-20).\(^7\) The resorcinarene based molecule (1-94) can dimerize through twelve hydrogen bonds. The cavity size of the self-assembled capsule is calculated as \(\sim 450\) Å\(^3\), which is larger than that of previous self-assembled systems. In the presence of this molecular capsule, the rate acceleration was observed in the 1,3-dipolar cycloaddition between phenyl azide 1-95 and phenylacetylene 1-96. In addition, a single regioisomer (1-97) was formed.
exclusively in this system. However, due to the product inhibition, substoichiometric catalysis was not accomplished.

Figure 1-19. Self-assembled molecular capsule for Diels-Alder reaction

Figure 1-20. Self-assembled cylindrical capsule for cycloaddition reaction
Aida and co-workers utilized hydrogen bonds to assemble dimeric bifunctional catalyst (Figure 1-21). In this catalyst design, 2-ureidoisocytosine motif was employed to assemble two catalytic units in close proximity through quadruple hydrogen bonds. This interesting catalyst showed rate acceleration up to 4.7 fold in the epoxide opening reaction with thiol.

![Figure 1-21. Supramolecular catalyst via multiple hydrogen bonds](image)

Another example of supramolecular organocatalyst has been reported by Clarke and Fuentes. The feature of this system is that a chiral precatalyst and an achiral additive are self-assembled through complementary hydrogen bonds, in which achiral additives would alter the steric environment around the catalytic site (Scheme 1-27). This modular approach allows the enantioselectivity to be fine-tuned easily by simply changing achiral additives. In this report, aminonaphthyridine-derived proline was used as a chiral catalyst unit, and a library of achiral pyridinone compounds was used as an achiral additive. As a consequence, the optimal combination (1-100) enhanced the reaction rate as well as diastereo- and enantioselectivity compared to a simple proline catalyst in the asymmetric conjugate addition of cyclic ketones to nitroalkenes.

Ionic interactions are generally stronger than hydrogen bonding interactions, thus they have been used for supramolecular assembly. Recently, Ooi and co-workers reported a unique ion pair catalyst which is assembled through hydrogen-bonding
Scheme 1-27. Self-assembled organocatalyst for asymmetric conjugate addition networks for asymmetric conjugate addition (Scheme 1-28). Supramolecular ion pair catalyst 1-104•(OPh)3H2 was prepared by ion exchange of tetraaminophosphonium chloride 1-104•Cl with hydroxide, and subsequent neutralization with phenol. The self-assembled structure of 1-104•(OPh)3H2 was confirmed by a single crystal X-ray analysis. The authors proposed that enolate 1-102’ could replace the phenoxide anion of 1-104•(OPh)3H2, maintaining similar hydrogen-bonding networks. When the modified self-assembled catalyst 1-104•(3,5-Cl2-C6H3O)3H2 was employed in the asymmetric conjugate addition of azlactone 1-102, the desired adduct 1-105 was obtained in excellent yield with high dr and ee. The same reaction with 1-104•Cl gave much lower enantioselectivity (34% ee), indicating that all components are necessary for high selectivity.

Zhao and Mandal reported modularly designed organocatalytic assemblies through ionic interactions (Scheme 1-29). They utilized quinidine thiourea and proline as components to build self-assembled catalysts. This multicomponent catalyst was very efficient for direct nitro-Michael addition reactions of ketones to nitroalkenes.
Ionic interactions also can be used for the construction of main-chain functionalized polymers. Recently, Itsuno and co-workers developed main-chain chiral polymer 1-109 containing a quaternary ammonium sulfonate as a repeating unit (Scheme 1-30). This chiral polymer can function as a chiral organocatalyst, displaying good efficiency and enantioselectivity in the asymmetric benzylolation of N-diphenylmethylidene glycine ester in biphasic conditions. In addition, owing to its
insoluble nature, the catalyst could be easily separated from the reaction mixture and recycled.

Scheme 1-30. Main-chain ionic polymer catalyst

Transition metal catalysts have been a key player for numerous asymmetric transformations. Therefore, it would be interesting to construct supramolecular transition metal catalysts using hydrogen bonds. However, the control of H-bonds in metal-catalytic systems is difficult, because hydrogen bond donors/acceptors are also generally good ligands for the metals. Nevertheless, some pioneering research has been reported with this approach.

Among those attempts, supramolecular bidentate ligands through hydrogen bonding interactions have been successfully developed. Like coordination-driven approach, this strategy allows an easy access to various combinations of ligand libraries. In some cases, hydrogen-bonded bidentate ligands showed comparable or even better performance compared to those of covalently bonded diphosphine ligands. Breit and Seiche realized the self-assembled bidentate ligand system through hydrogen bondings for the first time. They utilized the 2-pyridone/2-hydroxypyridine tautomers to
construct self-assembled bidentate phosphine ligands, which can form a bidentate chelate with a transition metal (Scheme 1-31). The resulting supramolecular rhodium(I) catalyst 1-114 proved to be efficient and highly regioselective for the hydroformylation of terminal alkenes.

Scheme 1-31. Supramolecular bidentate catalyst for hydroformylation

As mentioned earlier, hydrogen bonds can be utilized to generate supramolecular bidentate ligand libraries. Based on this concept, the Breit group developed a heterodimeric bidentate ligand system, in which the 2-aminopyridine/isoquinolone H-bonding pair was utilized as an A-T base pair analogue (Figure 1-22).\textsuperscript{82} Owing to its array of H-bonding donor/acceptor, the formation of homodimeric species would be suppressed. This supramolecular heterobidentate system allowed for facile generation of a 4 x 4 library. From the screening of this library for the rhodium-catalyzed hydroformylation of terminal alkenes, the optimal catalyst combinations were successfully identified.

Figure 1-22. Self-assembled heterobidentate ligand
This highly modular approach has been extended to asymmetric catalysis by employing chiral ligands. The same group reported chiral heterobidentate ligands for rhodium-catalyzed asymmetric hydrogenation reaction, where the same 2-aminopyridine/isoquinolone H-bonding motif was incorporated into chiral phosphonite ligands (Scheme 1-32). The most efficient catalyst combination (1-118) displayed excellent performance in the asymmetric hydrogenation of acetamidoacrylates with up to 99% enantiomeric excess.

Scheme 1-32. Self-assembled heterobidentate catalyst for asymmetric hydrogenation

Ding and co-workers reported supramolecular phosphoramidite ligand for the rhodium catalyzed asymmetric hydrogenation of (Z) and (E)-acrylates and itaconate derivatives (Scheme 1-33). In this report, monodentate phosphoramidite ligands bearing an N-H bond was found to be very reactive and selective. Theoretical calculations and NMR studies reveal that the intermolecular H-bonds between adjacent mono-phosphoramidite ligands around the Rh metal center could reduce the inter-ligand bite angle for the exceptional reactivity.

Based on a similar concept, Reek and co-workers recently developed a series of supramolecular bidentate ligand systems using hydrogen bonds for the asymmetric hydrogenation reactions. In one example, they reported supramolecular bidentate
Scheme 1-33. Asymmetric hydrogenation catalyzed by 1-121 phosphine ligands (UREAphos), by the use of intermolecular urea-urea hydrogen bonding interaction (Scheme 1-34). The resulting UREAphos-rhodium complex showed impressive efficiency for asymmetric hydrogenation of acetamidoacrylates.

Scheme 1-34. Supramolecular bidentate ligand for asymmetric hydrogenation

The same group also utilized a single hydrogen bond between the NH group of the phosphoramidite and the urea carbonyl group of a functionalized phosphine to build supramolecular heterobidentate system (Scheme 1-35). The resulting rhodium complex 1-125 exhibited very high enantioselectivity (>99% ee) for the asymmetric hydrogenation of methyl 3-hydroxy-2-methylpropionate 1-124 (Roche ester).

An interesting supramolecular bidentate system based on ligand tautomerism was also developed by Reek and co-workers. The authors disclosed that sulfonamide derived phosphine compound 1-127a has a stable tautomer 1-127b in CDCl₃ (Scheme
Scheme 1-35. Supramolecular Rh catalyst for asymmetric hydrogenation
1-36). These two tautomers can form hydrogen bonded bis-ligated metal complex 1-128. Solution IR and NMR studies revealed that the hydrogen-bonding interaction exists between the NH group of coordinated 1-127a and the S-O group of 1-127b. The chiral version of the adaptive supramolecular catalyst 1-129 showed excellent enantioselectivity (99% ee) in the asymmetric hydrogenation of methylacrylamide 1-117 (MAA).

Scheme 1-36. Adaptive supramolecular catalyst for asymmetric hydrogenation
Recently, Gennari and co-workers reported novel chiral supramolecular ligands, PhthalaPhos, which were utilized for enantioselective rhodium-catalyzed hydrogenation reactions (Scheme 1-37). The PhthalaPhos ligand was self-assembled through amide hydrogen bonds, and the resulting rhodium complex 1-131 showed excellent efficiency for the enantioselective hydrogenation of challenging cyclic enamides 1-130.

Scheme 1-37. Asymmetric hydrogenation catalyzed by PhthalaPhos-Rh complex

Immobilization of catalyst on organic or inorganic solid supports has been an important area, because separation and recycling of precious catalysts is highly desirable. Traditionally, the catalysts were anchored on the support through covalent linker. Although the covalent-linking approach enabled the catalyst recycling, the preparation of such immobilized catalysts generally required long synthetic steps and time-consuming purifications. Thus, as an alternative, non-covalent anchoring approach has emerged. The non-covalent approach could offer facile modulation of catalytic sites and reuse of catalysts. Bianchini and co-workers reported tripodal polyphosphine rhodium catalysts immobilized on silica via hydrogen bonding (Figure 1-23). The authors found that the immobilized Rh catalyst is more chemo-selective in the hydrogenation and hydroformylation reactions and more easily recyclable than the unsupported analogue.
Figure 1-23. Supported hydrogen-bonded catalysts

Reek, Meijer and co-workers utilized hydrogen bonds and ionic interactions to anchor phosphine ligands on a soluble poly(propylene imine) dendrimer backbone (Figure 1-24). The binding studies revealed that the acid containing phosphine ligand was tightly bound to the periphery of the dendrimer through the combination of H-bonds and ionic interaction. The resulting supramolecular Pd complex showed similar activity and selectivity in the allylic amination reaction of crotyl acetate and piperidine to that of the monomeric complex. In addition, this large supramolecular catalyst can be easily separated from the reaction mixture using nanofiltration techniques.

Figure 1-24. Supramolecular anchoring of catalysts on dendrimer

As an extension of this approach to heterogeneous catalysis, Ding and co-workers reported immobilized Rh catalyst by orthogonal self-assembly through hydrogen bonding and ligand-to-metal coordination interactions (Scheme 1-38). They integrated MonoPhos ligand and 6-methyl-2-ureido-4[1H]pyrimidone (UP) group into one molecule. This UP moiety has been known to form very strong dimer ($K_a = 6 \times 10^7$ M$^{-1}$ in CHCl$_3$).
through complementary, quadruple H-bonding interactions. By addition of [Rh(cod)$_2$]BF$_4$ to the resulting ligand, the orthogonal self-assembled polymer 1-133 can be formed, which is thermally stable and insoluble in less polar organic solvents such as toluene. The resulting heterogeneous, polymeric Rh(I) catalyst displayed excellent asymmetric induction in the catalytic hydrogenation of dehydro-$\alpha$-amino acid and enamide derivatives. In addition, an efficient recovery and reuse of catalyst was achieved.

Scheme 1-38. Self-supported Rh complex through hydrogen bonds

Recently, Wärnmark and co-workers reported a dynamic supramolecular heterobimetallic (salen)Mn-(porphyrin)Zn system, where multiple hydrogen-bond interactions were introduced to assemble two units (Scheme 1-39). In this catalyst design, complementary pyridone/isoquinolone hydrogen-bonds are used to assemble (salen)Mn complex 1-138 and (porphyrin)Zn complex 1-139. This catalytic system was designed to give substrate selectivity in the catalytic epoxidation reaction of olefin, as the (porphyrin)Zn could bind pyridine containing substrates preferentially. However, the observed selectivity between pyridine containing substrate 1-136 and phenyl derived...
substrate 1-137 was not high but noticeable in competing experiment (1.55:1). Although the observed selectivities are not high, this approach showed that weak, kinetically labile hydrogen bonding interactions can be applied to build supramolecular dinuclear catalysts containing transition metals.

Scheme 1-39. Catalytic epoxidation by supramolecular catalytic system

**Supramolecular Bioconjugate Systems**

Nature offers a great deal of chiral environment, generating chiral molecules with high selectivity in biotransformation. The combination of metal-catalysis and biocatalysis could be a highly attractive strategy toward efficient asymmetric catalysis. Covalent attachment of metal-catalyst to biopolymers such as antibody and protein has been achieved by several groups, however this approach gave very limited success with respect to efficiency and stereoselectivity. Alternatively, one can conceive a supramolecular anchoring strategy, where multiple weak interactions such as hydrogen bonds, ionic interaction, and stacking interactions are utilized in lieu of covalent bonds. The supramolecular strategy can be advantageous because many different
combinations can be easily tested like other supramolecular catalysis, and the chemical conversion with biomolecules which is sometimes troublesome, can be avoided.

As early as 1978, Wilson and Whitesides reported an achiral rhodium-avidin hybrid catalyst for enantioselective hydrogenation (Scheme 1-40).\textsuperscript{97} The biotin-avidin non-covalent interactions is very strong in biological systems ($K_a = 10^{15} \text{ M}^{-1}$).\textsuperscript{98} Although the enantioselection was moderate (39% ee), this research demonstrated that the chiral environment of biomolecules could be utilized for asymmetric reactions catalyzed by achiral metal-complex. Recently, Ward and co-workers have improved the enantioselectivity of this catalytic system up to 96% ee by changing avidin to streptavidin, which is known to possess a deeper binding pocket.\textsuperscript{99}

![Scheme 1-40. Enantioselective hydrogenation catalyzed by biotin/avidin hybrid Rh complex](image)

Ward and co-workers expanded this approach to other enantioselective reactions. They reported ruthenium complex/streptavidin hybrid for the enantioselective reduction of acetophenone to 1-phenylethanol by transfer hydrogenation (Scheme 1-41).\textsuperscript{100} To obtain the best catalytic efficiency, a combined structural variation of both chemical and
biological components was utilized. As such, the artificial metalloenzyme substantially improved the performance of metal-complex/protein hybrids. After screening, they found the combination of $\eta^6$-$p$-cymene capping arene and the mutant Pro64Gly gave the desired product in the highest conversion (92%) and ee (94%).

Scheme 1-41. Ruthenium complex/streptavidin hybrid catalyzed asymmetric reduction

Reetz and Jiao reported copper-phthalocyanine conjugates of bovine serum albumins for the Diels-Alder cyclization (Scheme 1-42). In this hybrid system, polysulfonic acid mediated ionic interaction was employed to anchor Cu-phthalocyanine 1-148 into the protein. The resulting protein conjugate catalyzed Diels-Alder reactions with high enantioselectivity up to 93% ee.

Scheme 1-42. Albumin-conjugated copper complex for Diels-Alder reactions
The use of double-helix DNAs has recently emerged as a new area of bioconjugate catalyst. As a pioneering work, Feringa and Roefles demonstrated hybrid DNAzymes in asymmetric catalysis for the first time (Scheme 1-43). An acridine moiety was utilized as an intercalator, and was responsible for supramolecular assembly with the right-handed double-helix DNA. The resulting 1-152-Cu/DNA hybrid catalyst showed good endo stereoselectivity for Diels-Alder cyclization of cyclopentadiene with pyridine containing dienophiles.

![DNA-Cu hybrid catalyst](image)

Scheme 1-43. DNA-based hybrid catalysts for the stereoselective Diels-Alder cyclization

In the last decade, we have witnessed advances in the design and application of supramolecular catalysts. Since the non-covalent bonds have an inherent dynamic character, the supramolecular approach provides new opportunities in catalysis. Particularly, this concept has been effectively applied for the generation of ligand libraries, recyclable catalysts, and nanoreactors. However, it is still very challenging to
rationally design efficient catalytic system using a supramolecular strategy due to the lack of understanding of catalytic mechanism and non-covalent interactions. Nonetheless, by considering the apparent advantage such as easy access to large libraries, the supramolecular approach could find more applications in catalysis.
CHAPTER 2
SELF-ASSEMBLED DINUCLER CATALYST THROUGH HYDROGEN BONDS FOR ASYMMETRIC HENRY REACTIONS

Ligand Design and Synthesis

Inspired by previous research on cooperative activation and supramolecular catalysis, we devised a new bimetallic system in which hydrogen bonds were utilized to connect two chiral metal catalyst units. By introducing hydrogen bonding motifs to chiral metal framework with an appropriate linker, chiral bimetallic catalyst could be readily formed in solution via self-assembly (Figure 2-1).\textsuperscript{103}

![Figure 2-1. Design of self-assembled dinuclear catalyst via H-bonding interactions](image)

The apparent advantage of this approach is that various homodimeric, heterodimeric, or even heterobimetallic catalysts can be obtained by mixing monomeric units in solution (Figure 2-2). If we can access various bimetallic catalysts without having to synthesize individual ligands, it would dramatically increase chances of finding new bimetallic catalysts and new synthetic methodologies which are not currently available. In addition, we can modulate the metal-metal distance and the strength of association of catalytic units by varying hydrogen bonding motif and linker parts.
Figure 2-2. Homodimeric, heterodimeric, and heterobimetallic catalysts mediated by hydrogen bonding interactions

In 1994, Wuest and Ducharme reported that the self-aggregation behavior of dipyridone scaffolds. According to this report, unsymmetrical dipyridone compound 2-1 discretely forms dimeric structure through two complementary hydrogen-bonding interactions in both dilute CHCl₃ solution (-ΔG° > 6.5 kcal/mol) and in the solid state (Figure 2-3a). In contrast, symmetrical dipyridone compound 2-2 prefers the formation of linear oligomeric aggregated structures (Figure 2-3b). Inspired by the pioneering work of Wuest and co-workers, we initially decided to utilize this complementary 2-pyridone/2-pyridone hydrogen bonding pair for novel self-assembled catalyst.

(a)

$$2 \quad \rightleftharpoons \quad 2-1 \quad -\Delta G^\circ > 6.5 \text{ kcal/mol in CHCl}_3 \quad \text{2-1-2-1}$$

(b)

$$n \quad \rightleftharpoons \quad 2-2 \quad (2-2)_n$$

Figure 2-3. Self-complementary dipyridone system
The chiral salen (tetradentate Schiff base) framework has been recognized as a privileged class of ligands in asymmetric catalysis.\textsuperscript{105} The metal-salen complexes have exhibited excellent efficiency in a wide range of asymmetric transformation such as epoxidation, kinetic resolution of epoxides, sulfoxidations, cycloadditions, conjugate additions, and Mannich reactions with good to excellent levels of asymmetric induction.\textsuperscript{106} The metal-salen complexes preferentially adopt a planar geometry. It has been known that the metal-salen complex also can have α-cis or β-cis conformation depending on the type of backbone and metal.\textsuperscript{107} However, the metal-salen complexes with diaminocyclohexane backbone generally exhibit a square-planar geometry, where one of the apical positions is available for substrate binding. Another advantage of salen catalysts is their accessibility. Salen ligands are generally obtained by condensation of chiral diamine backbone and salicylaldehydes in nearly quantitatively yield. Subsequent metalation allows a variety of metal-salen complexes from first and second row transition metals as well as main group metals. In this regard, we decided to use salen as a chiral framework to develop self-assembled catalysts.

In the initial catalyst design, two symmetrical salens were devised to form a heterodimeric structure. In symmetrical salen 2-3, 2-pyridone ring is connected to the salen core through an acetylene linker on 6-position of pyridone ring. The other symmetrical salen 2-4 has the connection on 3-position of the pyridone ring (Figure 2-4a). Owing to their H-bonding array, two symmetrical salen compounds cannot form homodimeric structures; instead, the heterodimeric structures are expected to form when they are employed together. In contrast, unsymmetrical salen 2-5 is expected to
form a homodimeric structure through two complementary hydrogen bonding
interactions (Figure 2-4b).

![Diagram 1](image1.png)

![Diagram 2](image2.png)

Figure 2-4. Design of pyridone/pyridone H-bonding self-assembled salen catalysts

The synthesis of symmetrical (salen)Co complex 2-3 began with the reaction of 2-8 and trimethylsilylacetylene under typical Sonogashira coupling conditions (Scheme 2-1). After removal of trimethylsilyl group using K₂CO₃, the resulting compound (2-9) was reacted under Sonogashira coupling conditions with iodosalicylaldehyde 2-7 which was prepared using a known method. After removal of the benzyl group with TMSI, the resulting salicylaldehyde (2-11) was condensed with (R,R)-1,2-diaminocyclohexane to furnish symmetrical salen ligand 2-12. The salen ligand was then reacted with
Co(OAc)$_2$•4H$_2$O in MeOH at room temperature under argon to give 2-pyridone incorporated (salen)Co complex 2-3 in 78% yield.

Scheme 2-1. Synthesis of symmetrical (salen)Co complex 2-3

To prepare another symmetrical salen complex 2-4, a similar synthetic strategy was applied (Scheme 2-2). 3-Bromo-2-hydroxypyridine 2-13 was selectively benzylated on O-position using Ag$_2$CO$_3$ in hexane to afford 2-14 in 74% yield. The resulting product (2-14) was coupled with trimethylsilylacetylene under Sonogashira coupling conditions, followed by the removal of TMS group with KOH in aqueous MeOH. The resulting compound (2-15) was then coupled with iodosalicylaldehyde 2-7 under Sonogashira coupling conditions to give 2-16 in 71% yield. To afford deprotected pyridone
intermediate 2-17, iodotrimethylsilane was used in CH$_2$Cl$_2$. Although 2-17 was isolated in 57% yield, this compound was unstable in solution and in the solid state. According to the literature, this array of pyridone-acetylene functional groups is prone to cyclize to form fused furan ring as described in Figure 2-5. Therefore, (salen)Co complexes 2-4 and 2-5 might not be suitable for catalysis, because of the instability.

Scheme 2-2. Synthesis of intermediate 2-17

Figure 2-5. Plausible intramolecular cyclization of intermediate 2-17

The replacement of hydrogen-bonding motif was necessary to address the stability issue with our initial design. Adenine/thymine (AT) hydrogen bonding motif was found ubiquitously in nature. In addition, as described in Chapter 2, Breit and co-workers successfully utilized pyridone/aminopyridine hydrogen bonding motif as an AT base pair mimic for the supramolecular bidentate ligands (Figure 2-6a). Inspired by those examples, we designed new symmetrical salen complex 2-18 that can form a heterodimeric structure with another symmetrical salen 2-3 (Figure 2-6b). In addition, unsymmetrical (salen)Co complex 2-19 was newly designed. In both cases, the 2-
aminopyridine motif was introduced as a suitable hydrogen bonding partner with the 2-pyridone motif.

(a)

(b)

Figure 2-6. New catalyst design using a pyridone/aminopyridine H-bonding pair

The synthesis of symmetrical salen complex 2-18 began by reacting commercial 2-aminopyridine 5-boronic ester 2-20 with pivaloyl chloride (Scheme 2-3). The resulting compound was transformed into salicylaldehyde 2-21 using Suzuki coupling reaction protocols. The desired symmetrical (salen)Co complex (2-18) was easily prepared using similar metalation conditions from symmetrical salen ligand 2-22.

For the synthesis of unsymmetrical salen ligand 2-23, two different salicylaldehydes were reacted with \((R,R)\)-1,2-diaminocyclohexane in the direct condensation protocol (Scheme 2-4). Interestingly, the yield of this reaction (53-78%) was more than the statistical maximum (50%). Usually, such direct condensation protocols gave the unsymmetrical salen products in less than 50% yields.\textsuperscript{110} This result
could be rationalized by a template effect through hydrogen bonding interactions (Figure 2-7). Finally, the desired unsymmetrical (salen)Co complex (2-19) was obtained by metalation of 2-23.

Scheme 2-3. Synthesis of symmetrical (salen)Co complex 2-18

Scheme 2-4. Synthesis of unsymmetrical (salen)Co complex 2-19

Figure 2-7. Template effect in the synthesis of 2-23
To gain insights about the structure and the mode of self-assembly of these (salen)Co complexes, we tried to obtain single crystals of self-assembled (salen)Co complex 2-19 for X-ray analysis. However, many attempts to grow a single crystal of cobalt complex 2-19 were unsuccessful. Thus, other metal-salen complexes such as Ni and Zn were prepared (Scheme 2-5).

Scheme 2-5. Synthesis of (salen)Ni and (salen)Zn complexes

Among them, an orange-colored, single crystal of (salen)Ni complex 2-24 suitable for X-ray analysis was finally obtained by slow diffusion of hexane to CH$_2$Cl$_2$ solution. The ORTEP view of Ni complex 2-24 is shown in Figure 2-8. The Ni metal is coordinated in a N$_2$O$_2$-coordination compartment and adopts a near square-planar geometry.

The X-ray packing structure of the (salen)Ni complex 2-24 clearly indicated the proposed self-assembly through complementary hydrogen bonding (Figure 2-9). The self-assembled dimer 2-24-2-24 adopts the “head-to-tail” conformation where the metal-metal distance is determined as 4.054(2) Å. This result suggests that the geometry and
place of hydrogen bonding motifs was nicely arranged to form a strong dimeric structure, as we anticipated.

Figure 2-8. ORTEP view of the crystal structure of 2-24 with the thermal ellipsoids drawn at 50% probability

Figure 2-9. X-ray structure of self-assembled dimeric (salen)Ni complex 2-24•2-24

Catalytic Enantioselective Henry (Nitro-Aldol) Reaction

The asymmetric Henry (nitro-aldol) reaction represents a powerful C-C bond forming reaction to provide chiral β-nitro alcohols which are highly valuable building blocks in asymmetric synthesis. In addition, the nitro alcohols can be further transformed into amino alcohols and α-hydroxy acids. In 1992, Shibasaki and co-
workers reported the first asymmetric Henry reactions using the heterobimetallic catalyst as described in Chapter 1. Since then, a number of excellent catalysts including metal complexes, phase-transfer catalysts, and organocatalysts, have been employed for this reaction. It is important to note that both aldehydes and nitronates can coordinate to the metal centers, which might enable dual activation for this reaction.

Chiral (salen)metal complexes have been also applied to asymmetric Henry reactions. In 2004, Yamada and co-workers reported (salen)Co(II) catalyzed Henry reactions for the first time (Scheme 2-6). However, only ortho-halogenated benzaldehydes gave nitroaldol adducts with good enantioselectivity. A few years later, Skarżewski and co-workers showed that (salen)Cr(III) complex can catalyze asymmetric Henry reactions with moderate enantioselectivity (Scheme 2-6). Although both (salen)metal complexes can catalyze Henry reaction smoothly, those catalysts suffer from low reactivity and moderate enantioselectivity.

Scheme 2-6. (Salen)metal catalyzed asymmetric Henry reaction

Interestingly, the introduction of sterically demanding groups at the 5,5'-positions of salen ligands has a beneficial effect on enantioselectivity as well as reactivity.
Skarżewski and co-workers recently reported sterically modified (salen)Cr(III) complex 2-29 which showed improved reactivity and enantioselectivity compared to the t-butyl substituted (salen)Cr(III) complex (Scheme 2-7).

Scheme 2-7. Sterically modified (salen)Cr complex for asymmetric Henry reactions

Very recently, Shibasaki and co-workers reported heterobimetallic Pd/La/Schiff base complexes for anti-selective asymmetric nitroaldol reactions. This dinucleating Schiff base complex displayed high anti diastereoselectivity, which was very challenging with conventional methods. Using this catalyst, (-)-ritodrine (2-31) and β-adrenoreceptor agonist (2-32) were synthesized in a short reaction sequence (Scheme 2-8).

Scheme 2-8. The anti-selective catalytic asymmetric nitroaldol reactions promoted by a Pd/La heterobimetallic catalyst
Although no mechanistic proof was provided at the outset of this research, it was conceivable that metal-salen catalyzed Henry reactions could proceed via a bimetallic mechanism. Therefore, we decided to evaluate our self-assembled catalysts for the asymmetric Henry reactions.

**Self-Assembled Dinuclear (Salen)Co(II) Catalyzed Henry Reaction**

To determine the catalytic efficiency, newly prepared symmetrical and unsymmetrical (salen)Co complexes were tested in the reaction of o-methoxy-benzaldehyde and nitromethane in the presence of 2 mol% of DIPEA in CH$_2$Cl$_2$ at -30°C (Table 2-1). While unsymmetrical (salen)Co(II) catalyst 2-19 afforded nitroaldol adduct 2-33a in 87% yield with 96% ee (entry 1), monomeric (salen)Co(II) catalyst 2-26 provided the product in 11% yield with 55% ee under the same reaction conditions (entry 8). To see the effect of the metal oxidation state on reactivity, monomeric Co(III) acetate 2-26(OAc) was prepared by a known method.$^{116}$ In this test, Co(III) catalyst 2-26(OAc) gave the product in less than 10% yield with 64% ee (entry 9). Two symmetrical (salen)Co complexes (2-3 and 2-18) gave the product in low yields (12 and 16%) and ee's that were similar to those of monomeric Co catalyst (entries 5-6). As described in the previous section, both symmetrical (salen)Co complexes are expected to form oligomeric or polymeric aggregates owing to their arrays of hydrogen-bonding donors and acceptors. When MeOH was used as a solvent, a loss of enantioselectivity was observed and shorter reaction times (40 h) were required (entries 3 and 10). Interestingly, when an equimolar mixture of (salen)Co complexes 2-3 and 2-18 was used as a heterodimeric catalyst, the product was obtained with good ee (87%), but the yield was low (18%) as when they are used alone (entry 7). This result suggests that those two symmetrical salen complexes would form a relatively weak heterodimeric
species. When 100 mol% of base were used, the reaction was accelerated with the slight loss of enantioselectivity (entry 2).

Scheme 2-9. (Salen)Co catalyzed asymmetric Henry reaction

Table 2-1. Henry reaction of o-methoxybenzaldehyde

<table>
<thead>
<tr>
<th>entry</th>
<th>(salen)Co</th>
<th>DIPEA (mol%)</th>
<th>solvent</th>
<th>time (h)</th>
<th>yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2-19</td>
<td>2</td>
<td>CH₂Cl₂</td>
<td>90</td>
<td>87</td>
<td>96</td>
</tr>
<tr>
<td>2</td>
<td>2-19</td>
<td>100</td>
<td>CH₂Cl₂</td>
<td>40</td>
<td>91</td>
<td>91</td>
</tr>
<tr>
<td>3</td>
<td>2-19</td>
<td>2</td>
<td>MeOH</td>
<td>40</td>
<td>89</td>
<td>25</td>
</tr>
<tr>
<td>4</td>
<td>2-19 + 2-23 (6 mol%)</td>
<td>2</td>
<td>CH₂Cl₂</td>
<td>90</td>
<td>59</td>
<td>96</td>
</tr>
<tr>
<td>5</td>
<td>2-3</td>
<td>2</td>
<td>CH₂Cl₂</td>
<td>90</td>
<td>12</td>
<td>72</td>
</tr>
<tr>
<td>6</td>
<td>2-18</td>
<td>2</td>
<td>CH₂Cl₂</td>
<td>90</td>
<td>16</td>
<td>69</td>
</tr>
<tr>
<td>7</td>
<td>2-3 + 2-18</td>
<td>2</td>
<td>CH₂Cl₂</td>
<td>90</td>
<td>18</td>
<td>87</td>
</tr>
<tr>
<td>8</td>
<td>2-26</td>
<td>2</td>
<td>CH₂Cl₂</td>
<td>90</td>
<td>11</td>
<td>55</td>
</tr>
<tr>
<td>9</td>
<td>2-26(OAc)</td>
<td>2</td>
<td>CH₂Cl₂</td>
<td>90</td>
<td>&lt;10</td>
<td>64</td>
</tr>
<tr>
<td>10</td>
<td>2-26</td>
<td>2</td>
<td>MeOH</td>
<td>40</td>
<td>93</td>
<td>5</td>
</tr>
<tr>
<td>11</td>
<td>2-34</td>
<td>2</td>
<td>CH₂Cl₂</td>
<td>90</td>
<td>14</td>
<td>70</td>
</tr>
</tbody>
</table>

Interestingly, when free ligand 2-23 (6 mol%) was added to the reaction mixture in the presence of 2-19 (2 mol%), yield was lowered noticeably without loss of enantioselectivity (Table 2-1, entry 4). This result suggests that free ligand 2-23 might play a role as a competitive inhibitor for the bimetallic species formation (Figure 2-10).
The substrate scope was then examined with 2 mol% of (salen)Co 2-19 (Scheme 2-10). The results are shown in Table 2-2. To reduce the reaction time further, slightly more concentrated conditions were used. ortho-Substituted benzaldehydes were found to be more reactive and selective in general (entry 1-3). Although more catalyst loading (5 mol%) and longer reaction time (110 h) was required, electron-rich p-methoxybenzaldehyde was smoothly converted to the nitroaldol adduct in 77% yield and 81% ee (entry 6). Overall, various aryl aldehydes afforded high enantiomeric excesses (81-96% ee) and good to excellent yield (65-99%).

<table>
<thead>
<tr>
<th>entry</th>
<th>aldehyde</th>
<th>(salen)Co (mol%)</th>
<th>time (h)</th>
<th>yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>o-MeOC₆H₄ (1-17a)</td>
<td>2</td>
<td>48</td>
<td>89</td>
<td>96</td>
</tr>
<tr>
<td>2</td>
<td>o-ClC₆H₄ (1-17b)</td>
<td>2</td>
<td>14</td>
<td>97</td>
<td>93</td>
</tr>
<tr>
<td>3</td>
<td>p-FC₆H₄ (1-17c)</td>
<td>2</td>
<td>14</td>
<td>97</td>
<td>94</td>
</tr>
<tr>
<td>4</td>
<td>p-CF₃C₆H₄ (1-17d)</td>
<td>2</td>
<td>40</td>
<td>99</td>
<td>82</td>
</tr>
<tr>
<td>5</td>
<td>p-FC₆H₄ (1-17e)</td>
<td>2</td>
<td>40</td>
<td>65</td>
<td>90</td>
</tr>
<tr>
<td>6</td>
<td>p-MeOC₆H₄ (1-17f)</td>
<td>5</td>
<td>110</td>
<td>77</td>
<td>81</td>
</tr>
<tr>
<td>7</td>
<td>1-naphthyl (1-17g)</td>
<td>2</td>
<td>40</td>
<td>92</td>
<td>91</td>
</tr>
<tr>
<td>8</td>
<td>2-naphthyl (1-17h)</td>
<td>2</td>
<td>65</td>
<td>88</td>
<td>87</td>
</tr>
</tbody>
</table>
Kinetic Study

To verify our hypothesis of bimetallic activation, kinetic studies of the Henry reaction catalyzed by 2-19 were conducted by monitoring initial reaction rates (consumption of o-methoxybenzaldehyde). Mesitylene was used as an internal standard. The reaction progress was monitored by the removal of 20 μL aliquots from the reaction mixture and HPLC analysis for the first 15-45% of the reaction. The slopes of the least square lines for the plots of ([SM]₀-[SM]) versus time were determined (Figure 2-11). Same kinetic experiments were also performed with the monomeric (salen)Co catalyst 2-26 for comparison (Figure 2-12).

![Graph showing initial rates of the asymmetric Henry reaction with 2-19](image)

Figure 2-11. Initial rates of the asymmetric Henry reaction with 2-19

In these experiments, reaction rates were determined over a 5-10 fold range of catalyst concentrations. A linear correlation between rates vs [catalyst]² was obtained in both cases (Figure 2-13), indicating a second-order dependence on catalyst. This result supports that two (salen)Co(II) catalysts are involved in the rate-determining transition state. The measured rate constant $k_{obs}$ with self-assembled catalyst 2-19 is found to be
Figure 2-12. Initial rates of the asymmetric Henry reaction with 2-26
289 M$^{-1}$h$^{-1}$ which is 48 times larger than that with monomeric catalyst 2-26 ($k_{obs} = 6.02$ M$^{-1}$h$^{-1}$). The rate acceleration by 2-19 can be attributed to the facile formation of bimetallic species through two complementary hydrogen bonds in non-polar media.

Figure 2-13. Rate dependence on catalyst concentration

However, after the careful inspection of rate laws, we found that the catalyst order in the reaction can change depending on the self-association strength of catalyst and its concentration. Thus, further kinetic and mechanistic studies might be needed to obtain
more precise reaction model of this self-assembled catalyst. More detailed discussion will be provided in Chapter 3.

Self-Assembly Study

NMR spectroscopy is particularly useful in the study of self-assembly in solution. It would be desirable to perform NMR experiments with (salen)Co(II) complex 2-19, but the (salen)Co(II) complex exhibited broad signals due to the paramagnetism of Co(II). Although the Co(III) complexes are diamagnetic, the signal of corresponding Co(III)(OAc) complex was still broad. For this reason, we decided to use metal-free ligand 2-23 as a model compound to estimate self-association strength. First, we tried to determine the dimerization constant of 2-23 in CDCl₃ at room temperature. However, no obvious chemical shift change (< 0.02 ppm) was observed for the pivalamide NH proton at the three representative concentrations (0.15, 1.5, and 10 mM), as shown in Figure 2-14. Assuming more than 90% dimer formation at the lowest concentration measured.

![Figure 2-14. Stacked ¹H NMR (300 MHz) spectra of aromatic region of salen ligand 2-23 at the concentration of 0.15, 1.5, and 10 mM in CDCl₃ at 25°C](image-url)
(0.15 mM), the dimerization constant $K_{\text{dim}}$ can be estimated as exceeding $3.0 \times 10^5 \text{ M}^{-1}$ in CDCl$_3$ at 25°C.

Aforementioned $^1$H NMR experiment in CDCl$_3$ indicates the strong hydrogen-bonding interactions in the 2-pyridone/aminopyridine functionalized salen ligand. To obtain more precise information on the strength of self-assembly in this system, more polar medium was chosen. When 25% v/v CD$_3$NO$_2$ in CDCl$_3$ was used as a medium which is similar to the actual Henry reaction conditions, the NH signal of the pivalamide group and the signals of three protons of the pyridine ring in the free ligand were changed upon variation of concentration (0.14-19.09 mM). As depicted in Figure 2-15, downfield shifts of those signals were observed upon increasing concentration.

![Figure 2-15](image-url)

Figure 2-15. Stacked $^1$H NMR (300 MHz) spectra of aromatic region of diluted samples (0.14-19.1 mM) of 2-23 in 25% v/v CD$_3$NO$_2$ in CDCl$_3$ at 25°C
Table 2-3. Measured chemical shifts of pivalamide NH, H_a, H_b, and H_c using 25% v/v CD_3NO_2 in CDCl_3 at 25°C

<table>
<thead>
<tr>
<th>Concentrations</th>
<th>δ(NH)</th>
<th>δ(H_a)</th>
<th>δ(H_b)</th>
<th>δ(H_c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.14 mM</td>
<td>8.311</td>
<td>8.216</td>
<td>8.050</td>
<td>7.619</td>
</tr>
<tr>
<td>0.26 mM</td>
<td>8.311</td>
<td>8.217</td>
<td>8.050</td>
<td>7.620</td>
</tr>
<tr>
<td>0.40 mM</td>
<td>8.314</td>
<td>8.218</td>
<td>8.051</td>
<td>7.621</td>
</tr>
<tr>
<td>0.66 mM</td>
<td>8.318</td>
<td>8.219</td>
<td>8.052</td>
<td>7.622</td>
</tr>
<tr>
<td>0.93 mM</td>
<td>8.320</td>
<td>8.220</td>
<td>8.053</td>
<td>7.623</td>
</tr>
<tr>
<td>1.58 mM</td>
<td>8.327</td>
<td>8.221</td>
<td>8.055</td>
<td>7.625</td>
</tr>
<tr>
<td>2.22 mM</td>
<td>8.335</td>
<td>8.223</td>
<td>8.056</td>
<td>7.627</td>
</tr>
<tr>
<td>2.85 mM</td>
<td>8.343</td>
<td>8.225</td>
<td>8.058</td>
<td>7.629</td>
</tr>
<tr>
<td>3.48 mM</td>
<td>8.349</td>
<td>8.226</td>
<td>8.059</td>
<td>7.631</td>
</tr>
<tr>
<td>4.70 mM</td>
<td>8.359</td>
<td>8.228</td>
<td>8.061</td>
<td>7.633</td>
</tr>
<tr>
<td>5.90 mM</td>
<td>8.373</td>
<td>8.230</td>
<td>8.063</td>
<td>7.635</td>
</tr>
<tr>
<td>8.20 mM</td>
<td>8.392</td>
<td>8.234</td>
<td>8.066</td>
<td>7.638</td>
</tr>
<tr>
<td>10.39 mM</td>
<td>8.408</td>
<td>8.237</td>
<td>8.067</td>
<td>7.641</td>
</tr>
<tr>
<td>12.49 mM</td>
<td>8.415</td>
<td>8.238</td>
<td>8.069</td>
<td>7.642</td>
</tr>
<tr>
<td>14.48 mM</td>
<td>8.426</td>
<td>8.240</td>
<td>8.071</td>
<td>7.644</td>
</tr>
<tr>
<td>19.09 mM</td>
<td>8.457</td>
<td>8.244</td>
<td>8.073</td>
<td>7.647</td>
</tr>
</tbody>
</table>

Assuming a fast exchange condition in this system, the resulting data were fitted using a nonlinear curve-fitting method to find three parameters (K_{dim}, δ_{mono}, and δ_{dim}) in the following equation, where the standard deviation (Σ(δ_{obs} – δ_{cal})^2) shows a minimum value.

\[
[\text{mono}] = [\text{dim}] + \left\{ \left[ 1 - (8K_{\text{dim}}[\text{mono}]_0 + 1)^{1/2} \right] / 4 K_{\text{dim}} [\text{mono}]_0 \right\} / (δ_{\text{dim}} – δ_{\text{mono}})
\]

The dimerization constant (K_{dim}) of the self-assembled salen ligand 2-23 was estimated as 53 ± 21 M\(^{-1}\) by using non-linear curve fitting methods. The calculation result was shown in Figure 2-16.

After our report, Wärnmark and co-workers reported dynamic supramolecular (salen)CrCl catalysts for epoxide ring opening reactions with trimethylsilyl azide based on similar concept (Figure 2-17). In this research, they utilized self-complementary 2-
Figure 2-16. Complexation-induced chemical shift changes of proton signals in metal-free salen ligand 2-23 in 25% v/v CD$_3$NO$_2$ in CDCl$_3$ at 25°C

Figure 2-17. Self-assembled (salen)CrCl catalyst for epoxide opening reactions pyridone containing isoquinone/quinolinone motif to assemble two (salen)Cr catalysts, and a 6-fold rate acceleration was observed in the asymmetric ring opening of epoxides
with azide nucleophile. However, the enantioselectivity observed was generally less than 10% ee.

Summary

In summary, we developed a novel chiral dinuclear (salen)Co catalyst self-assembled through hydrogen bonds, and this catalyst successfully mediated the enantioselective Henry reaction. The self-assembled dinuclear (salen)Co(II) catalyst results in significant rate acceleration (48 times faster) as well as high enantioselectivity compared to the non-functionalized (salen)Co(II) catalyst. The observed rate acceleration can be rationalized by the facile formation of dimeric catalyst through H-bonds. To the best of our knowledge, this is the first example of chiral bimetallic system using hydrogen bonds. In addition, we also suggest that bimetallic mechanism is operating in (salen)Co(II) catalyzed Henry reaction.

Experimental

General Remarks

All reactions were conducted in flame-dried glassware under an inert atmosphere of dry argon. THF, CH₂Cl₂, Et₂O and toluene were purified under positive pressure of dry nitrogen by Meyer Solvent Dispensing System prior to use. All the chemicals used were purchased from Sigma-Aldrich Co., Acros Organics, TCI America, and Strem Chemical Incs. and were used as received without further purification. NMR spectra were recorded using a Mercury 300 FT-NMR, operating at 300 MHz for ¹H NMR and at 75.4 MHz for ¹³C NMR. All chemical shifts for ¹H and ¹³C NMR spectroscopy were referenced to residual signals from CDCl₃ (¹H) 7.26 ppm and (¹³C) 77.23 ppm. High resolution mass spectra were recorded on a GC/MS spectrometer or a TOF-LC/Ms spectrometer. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter.
Enantiomeric ratios were determined by chiral HPLC analysis (Shimadzu) using Chiralpak IA and IB columns.

**Catalyst Preparation**

![Chemical Structure]

**3-tert-Butyl-2-hydroxy-5-iodobenzaldehyde (2-7).** 3-tert-Butoxy-2-hydroxy-benzaldehyde 2-6 (2.50 g, 14.03 mmol) was dissolved in glacial acetic acid (15 mL), and then iodine monochloride (3.18 g, 19.59 mmol) in glacial acetic acid (15 mL) was added to the resulting solution at room temperature. The mixture was heated to reflux for 3 h, and then cooled to room temperature. This solution was poured into water (100 mL), and then extracted into CH₂Cl₂ (2 x 50 mL). After extraction, the organic layer was washed with aqueous sodium thiosulfate solution, dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The resulting crude product was purified by column chromatography on silica-gel (10% ethyl acetate in n-hexane) to give 2-7 (4.25 g, 100%) as a yellow solid. ¹H NMR (300 MHz, CDCl₃) δ 11.74 (s, 1 H), 9.80 (s, 1 H), 7.72 (d, J = 2.3 Hz, 1 H), 7.69 (d, J = 2.3 Hz, 1 H), 1.41 (s, 9 H); ¹³C NMR (75 MHz, CDCl₃) δ 196.1, 161.1, 142.8, 141.6, 140.2, 122.7, 80.8, 35.3, 29.2; HRMS (DIP-CI-MS) calcd for C₁₁H₁₃IO₂ [M⁺]: 303.9960, found: 303.9939.

![Chemical Structure]

**2-(Benzyloxy)-6-((trimethylsilyl)ethynyl)pyridine (2-35).** A stirred mixture of 2-bromo-6-benzyloxy pyridine 2-8 (2.02 g, 7.65 mmol), Cul (58 mg, 0.30 mmol), PdCl₂(PPh₃)₂ (63 mg, 0.15 mmol), (trimethylsilyl)acetylene (1.3 mL, 9.14 mmol), and
triethylamine (5 mL, 35.87 mmol) in THF (5 mL) was heated at reflux under argon for 12 h. The mixture was cooled to room temperature, diluted with Et₂O (100 mL), and washed with H₂O, and then dried over anhydrous Na₂SO₄. Volatiles were removed by evaporation under reduced pressure, the residue was then purified by column chromatography on silica-gel (10% ethyl acetate in n-hexane) to give 2-35 (2.12 g, 98%) as a pale yellow liquid. ¹H NMR (300 MHz, CDCl₃) δ 7.44-7.58 (m, 3 H), 7.31-7.44 (m, 3 H), 7.11 (d, J = 7.4 Hz, 1 H), 6.77 (d, J = 9.1 Hz, 1 H), 5.42 (s, 2 H), 0.31 (s, 9 H); ¹³C NMR (75 MHz, CDCl₃) δ 163.5, 140.1, 138.8, 137.4, 128.7, 128.5, 128.1, 121.6, 111.9, 104.2, 94.3, 68.2, 0.1; HRMS (APCI-TOF) calcd for C₁₇H₂₀NOSi [M+H]⁺: 282.1309, found: 282.1314.

2-(Benzyloxy)-6-ethynylpyridine (2-9). A mixture of 2-35 (2.12 g, 7.53 mmol), TBAF•3H₂O (2.85 g, 9.03 mmol), and 1N HCl (7.6 mL) in THF (20 mL) was stirred overnight at room temperature. The resulting mixture was diluted with ethyl acetate (100 mL), washed with H₂O (2 x 100 mL), and dried over anhydrous Na₂SO₄. Volatiles were removed by evaporation under reduced pressure, the residue was then purified by column chromatography on silica-gel (10% ethyl acetate in n-hexane) to give 2-9 (1.53 g, 97%) as a pale yellow liquid. ¹H NMR (300 MHz, CDCl₃) δ 7.44-7.61 (m, 3 H), 7.29-7.43 (m, 3 H), 7.13 (d, J = 6.5 Hz, 1 H), 6.81 (d, J = 8.5 Hz, 1 H), 5.40 (s, 2 H), 3.14 (s, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 163.6, 139.3, 138.9, 137.2, 128.7, 128.4, 128.1, 121.4, 112.4, 83.2, 76.7, 68.2; HRMS (APCI-TOF) calcd for C₁₄H₁₂NO [M+H]⁺: 210.0913, found: 210.0914.
5-((6-(Benzyloxy)pyridin-2-yl)ethyl)-3-tert-butyl-2-hydroxybenzaldehyde (2-10). A stirred mixture of 2-9 (1.53 g, 7.31 mmol), Cul (56 mg, 0.29 mmol), PdCl$_2$(PPh$_3$)$_2$ (60 mg, 0.15 mmol), 3-tert-butyl-2-hydroxy-5-iodobenzaldehyde 2-7 (2.22 g, 7.32 mmol), and triethylamine (5 mL, 35.87 mmol) in THF (10 mL) was heated at reflux under argon for 12 h. The mixture was cooled to room temperature, diluted with ethyl acetate (100 mL), and washed with H$_2$O, and then dried over anhydrous Na$_2$SO$_4$. Volatiles were removed by evaporation under reduced pressure, the residue was then purified by column chromatography on silica-gel (10% ethyl acetate in n-hexane). The combined fractions were then triturated with ethyl acetate to give 2-10 (1.70 g, 60%) as a pale yellow solid.  $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 11.98 (s, 1 H), 9.88 (s, 1 H), 7.74 (d, $J = 2.0$ Hz, 1 H), 7.70 (d, $J = 2.3$ Hz, 1 H), 7.58 (dd, $J = 8.5$, 7.4 Hz, 1 H), 7.44-7.52 (m, 2 H), 7.31-7.44 (m, 3 H), 7.17 (d, $J = 7.1$ Hz, 1 H), 6.79 (d, $J = 8.2$ Hz, 1 H), 5.44 (s, 2 H), 1.44 (s, 9 H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 196.8, 163.7, 161.9, 140.4, 139.3, 138.9, 137.6, 137.3, 135.9, 128.7, 128.4, 128.1, 121.1, 120.7, 113.7, 111.6, 88.1, 87.9, 68.2, 35.3, 29.3; HRMS (APCI-TOF) calcd for C$_{25}$H$_{24}$NO$_3$ [M+H]$^+$: 386.1751, found: 386.1750.

3-tert-Butyl-2-hydroxy-5-((6-oxo-1,6-dihydropyridin-2-yl)ethynyl)-benzaldehyde (2-11). TMSI (0.29 mL, 2.03 mmol) was added to a solution of 2-10 (600 mg, 1.56 mmol) in CH$_2$Cl$_2$ (10 mL), and allowed to stir overnight at room temperature
under argon. After the addition of MeOH (5 mL) to the reaction mixture, and then volatiles were removed by evaporation under reduced pressure. The residue was purified by column chromatography on silica-gel (10% ethyl acetate in n-hexane, then pure ethyl acetate), and then the combining fraction was triturated with ethyl acetate to give 2-11 (379 mg, 82%) as a pale yellow solid. $^1$H NMR (300 MHz, CDCl$_3$) δ 12.45 (br s, 1 H), 12.04 (s, 1 H), 9.89 (s, 1 H), 7.73 (d, $J$ = 2.1 Hz, 1 H), 7.71 (d, $J$ = 2.1 Hz, 1 H), 7.39 (dd, $J$ = 9.2, 6.9 Hz, 1 H), 6.59 (d, $J$ = 9.3 Hz, 1 H), 6.47 (d, $J$ = 6.8 Hz, 1 H), 1.47 (s, 9 H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 196.8, 164.9, 162.4, 141.1, 139.5, 137.5, 136.2, 129.8, 121.1, 120.7, 112.5, 111.2, 94.0, 81.7, 35.3, 29.3; HRMS (APCI-TOF) calcd for C$_{18}$H$_{18}$NO$_3$ [M+H]$^+$: 296.1281, found: 296.1284.

2-12. To a solution of (1$R$,2$R$)-cyclohexane-1,2-diamine (55 mg, 0.48 mmol) in THF (8 mL), 2-11 (298 mg, 1.01 mmol) was added at room temperature, and then allowed to stir for 3 h. The solution was concentrated under reduced pressure, and the residue was purified by column chromatography on silica-gel (ethyl acetate) to give 2-12 (321 mg, 100%) as a yellow solid. $^1$H NMR (300 MHz, DMSO-d$_6$) δ 14.80 (br s, 2 H), 11.86 (br s, 2 NH), 8.53 (s, 2 H), 7.33-7.46 (m, 6 H), 6.43 (d, $J$ = 6.8 Hz, 2 H), 6.36 (d, $J$ = 9.1 Hz, 2 H), 3.42-3.64 (m, 2 H), 1.98 (d, $J$ = 5.9 Hz, 2 H), 1.75-1.87 (m, 2 H), 1.56-1.75 (m, 2 H), 1.40–1.54 (m, 2 H), 1.31 (s, 9 H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 165.5, 164.8, 162.6, 141.0, 138.5, 133.8, 133.7, 130.7, 119.9, 118.5, 111.4, 110.5, 95.3, 81.2,
72.4, 35.1, 32.8, 29.4, 24.4; HRMS (ESI-TOF) calcd for C_{42}H_{45}N_{4}O_{4}\ [M+H]^+: 669.3435, found: 669.3504; [\alpha]_{D}^{21} +80.0 (c 0.54, CH_{2}Cl_{2}).

![Chemical Structure](image)

**2-3.** To a solution of 2-12 (140 mg, 0.21 mmol) in MeOH (5 mL), Co(OAc)$_2$$\cdot$4H$_2$O (52 mg, 0.21 mmol) in MeOH (3 mL) was added, and allowed to stir at room temperature for 1 h under argon. Precipitate was collected by filtration, and then dried under vacuum for 24 h to give 2-3 (123 mg, 81%) as a reddish brown solid. HRMS (ESI-TOF) calcd for C$_{42}$H$_{42}$CoN$_4$O$_4$ [M]$^+$: 725.2538, found: 725.2533.

![Chemical Structure](image)

**N-(5-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)pivalamide (2-36).** Pivaloyl chloride (0.30 mL, 2.44 mmol) was added to a solution of 2-aminopyridine-5-boronic acid pinacol ester 2-20 (446 mg, 2.03 mmol), and triethylamine (0.37 mL, 2.63 mmol) in CH$_2$Cl$_2$ (3 mL) at 0°C, the resulting mixture was allowed to warm to room temperature, and then allowed to stir overnight. The reaction mixture was concentrated under reduced pressure, and the residue was diluted with Et$_2$O (30 mL), and then washed with water, 1N HCl (5 mL), and water. The combined aqueous fractions were back-extracted with CH$_2$Cl$_2$ (4 x 20 mL). The combined organic layers were dried over anhydrous Na$_2$SO$_4$, and then concentrated under reduced pressure to give 2-36 (599 mg, 87%) as a white solid. This crude product was used for next step without further purification. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 9.73 (br s, 1 H), 8.52 (d, J = 1.1 Hz, 1 H), 8.44
\((d, J = 8.5 \text{ Hz}, 1 \text{ H}), 8.21 \ (dd, J = 8.8, 1.7 \text{ Hz}, 1 \text{ H}), 1.34 \ (s, 9 \text{ H}), 1.23 \ (s, 12 \text{ H})\). \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 178.3, 152.7, 149.8, 147.7, 114.6, 84.8, 75.3, 40.6, 27.4, 25.1; HRMS ((-)-ESI-TOF) calcd for \(\text{C}_{16}\text{H}_{24}\text{BN}_{2}\text{O}_{3} [\text{M-HCl}]^+\): 303.1889, found: 303.1878.

\(N\)-(5-(3-\text{tert-Butyl}-5-formyl-4-hydroxyphenyl)pyridin-2-yl)pivalamide (2-21). A stirred mixture of 2-20 (303 mg, 0.89 mmol), 3-\text{tert-Butyl-2-hydroxy-5-iodobenzaldehyde} 2-7 (302 mg, 0.99 mmol), \(\text{Na}_2\text{CO}_3\) (316 mg, 2.98 mmol), \(\text{Pd(PPh}_3\text{)}_4\) (23 mg, 0.02 mmol), water (0.5 mL), and 1,4-dioxane (3 mL) was heated at reflux under argon for 12 h. The mixture was cooled to room temperature, diluted with ethyl acetate (50 mL), and washed with \(\text{H}_2\text{O}\), and then dried over anhydrous \(\text{Na}_2\text{SO}_4\). Volatiles were removed by evaporation under reduced pressure, then the residue was purified by column chromatography on silica-gel (10%, then 33% ethyl acetate in \(n\)-hexane) to give 2-21 (185 mg, 59%) as a yellow solid. \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 11.83 (s, 1 H), 9.96 (s, 1 H), 8.45 (d, \(J = 2.3 \text{ Hz, 1 H})\), 8.33 (d, \(J = 8.8 \text{ Hz, 1 H})\), 8.07 (s, NH), 7.86 (dd, \(J = 8.6, 2.4 \text{ Hz, 1 H})\), 7.69 (d, \(J = 2.3 \text{ Hz, 1 H})\), 7.56 (d, \(J = 2.3 \text{ Hz, 1 H})\), 1.46 (s, 9 H), 1.35 (s, 9 H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 197.3, 177.3, 161.2, 150.9, 145.7, 139.6, 136.6, 132.8, 132.1, 129.9, 129.0, 121.0, 114.0, 40.1, 35.3, 29.4, 27.7; HRMS (ESI-TOF) calcd for \(\text{C}_{21}\text{H}_{26}\text{N}_{2}\text{O}_{3} [\text{M+H}]^+\): 355.2016, found: 355.2022.
2-22. To a solution of (1\textit{R},2\textit{R})-cyclohexane-1,2-diamine (19 mg, 0.17 mmol) in THF (5 mL), 2-21 (116 mg, 0.33 mmol) was added at room temperature, and allowed to stir overnight. The reaction mixture was concentrated under reduced pressure, and the residue was purified by column chromatography on silica-gel (33% ethyl acetate in \textit{n}-hexane) to give 2-22 (83 mg, 65%) as a yellow solid. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 14.01 (br s, 2 H), 8.36 (s, 2 H), 8.33 (d, $J$ = 1.7 Hz, 2 H), 8.25 (d, $J$ = 8.8 Hz, 2 H), 8.03 (s, 2 NH), 7.74 (dd, $J$ = 8.6, 2.4 Hz, 2 H), 7.40 (d, $J$ = 2.3 Hz, 2 H), 7.15 (d, $J$ = 2.3 Hz, 2 H), 3.38 (dd, $J$ = 5.7, 3.7 Hz, 2 H), 2.05–2.01 (m, 2 H), 1.93-1.91 (m, 2 H), 1.66-1.84 (m, 2 H), 1.46-1.57 (m, 2 H), 1.43 (s, 18 H), 1.32 (s, 18 H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 177.2, 165.7, 160.5, 150.3, 145.5, 138.4, 136.5, 133.0, 128.1, 128.0, 127.3, 119.0, 113.8, 72.7, 40.0, 35.2, 33.2, 29.5, 27.7, 24.5; HRMS (APCI-TOF) calcd for C$_{48}$H$_{62}$N$_6$O$_4$Na [M+Na]$^+$: 809.4725, found: 809.4765; [$\alpha$]$_{D}^{21}$ -41.1 (c 0.57, CH$_2$Cl$_2$).

\begin{figure}
\centering
\includegraphics[width=0.5\textwidth]{2-22.png}
\caption{Structure of 2-22}
\end{figure}

2-18. To a solution of 2-22 (47 mg, 0.06 mmol) in MeOH (3 mL), Co(OAc)$_2$•4H$_2$O (15 mg, 0.06 mmol) in MeOH (1 mL) was added, and the resulting dark brown solution allowed to stir at room temperature for 3 h under argon. The reaction mixture was concentrated under reduced pressure, and the residue was dissolved in CH$_2$Cl$_2$. The resulting solution was filtered through celite, and then concentrated under reduced pressure. The resulting solid was dried under vacuum for 24 h to give bisaminopyridine (salen)Co 2-18 (50 mg, 100%) as a reddish brown solid. HRMS (APCI-TOF) calcd for C$_{48}$H$_{60}$CoN$_6$O$_4$ [M]$^+$: 843.4003, found: 843.4054.
To a suspension of 2-11 (110 mg, 0.37 mmol) and 2-21 (132 mg, 0.37 mmol) in anhydrous THF (10 mL), a solution of (1R,2R)-cyclohexane-1,2-diamine (42 mg, 0.37 mmol) in THF (5 mL) was added at room temperature, and allowed to stir for 15 h. The reaction mixture was concentrated under reduced pressure, and the residue was purified by column chromatography on silica-gel column (33% ethyl acetate in n-hexane, and then pure ethyl acetate) to give 2-23 (212 mg, 78%) as a yellow solid. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 14.59 (br s, 1 H), 13.96 (s, 1 H), 10.72 (br s, NH, 1 H), 8.61 (s, NH, 1 H), 8.35 (d, $J$ = 2.3 Hz, 1 H), 8.24 (d, $J$ = 8.8 Hz, 1 H), 8.21 (s, 1 H), 8.13 (s, 1 H), 7.73 (dd, $J$ = 8.6, 2.4 Hz, 1 H), 7.30-7.43 (m, 3 H), 7.13 (d, $J$ = 1.7 Hz, 1 H), 6.98 (d, $J$ = 2.0 Hz, 1 H), 6.55 (d, $J$ = 9.1 Hz, 1 H), 6.38 (d, $J$ = 6.8 Hz, 1 H), 3.24-3.40 (m, 2 H), 2.01-2.14 (m, 2 H), 1.87-1.98 (m, 2 H), 1.72-1.87 (m, 2 H), 1.51-1.69 (m, 2 H), 1.43 (s, 9 H), 1.37 (s, 9 H), 1.35 (s, 9 H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 177.7, 165.9, 165.1, 164.4, 162.9, 160.5, 150.6, 145.2, 141.1, 138.6, 138.4, 136.8, 133.8, 133.4, 133.1, 129.8, 128.5, 127.9, 127.4, 120.8, 118.8, 118.5, 114.4, 111.0, 110.0, 95.5, 80.7, 72.2, 71.9, 40.1, 35.2, 35.1, 33.0, 33.0, 29.5, 29.3, 27.6, 24.4, 24.4; HRMS (ESI-TOF) calcd for C$_{45}$H$_{54}$N$_{5}$O$_{4}$ [M+H]$^+$: 728.4170, found: 728.4192; [$\alpha$]$_D^{21}$ +108.4 (c 0.31, CH$_2$Cl$_2$).
2-19. To a solution of 2-23 (100 mg, 0.14 mmol) in MeOH (5 mL), Co(OAc)$_2$•4H$_2$O (34 mg, 0.14 mmol) in MeOH (1 mL) was added, and allowed to stir at room temperature for 3 h under argon. Precipitate was collected by filtration, washed with MeOH, and then dried under vacuum for 24 h to give unsymmetrical (salen)Co 2-19 (91 mg, 83%) as a brown solid. HRMS (ESI-TOF) calcd for C$_{45}$H$_{51}$CoN$_5$O$_4$ [M]$^+$: 784.3268, found: 784.3297.

2-24. To a solution of 2-23 (30 mg, 0.04 mmol) in MeOH (3 mL), Ni(OAc)$_2$•4H$_2$O (10 mg, 0.04 mmol) in MeOH (1 mL) was added, and allowed to stir at room temperature overnight under argon. Precipitate was collected by filtration, washed with MeOH, and then dried under vacuum for 24 h to give unsymmetrical (salen)Ni 2-24 (24 mg, 74%) as a greenish yellow solid. Red single crystals suitable for X-ray analysis were obtained by layering chloroform solution with n-hexane and allowing slow diffusion at room temperature. $^1$H NMR (300 MHz, DMSO-d$_6$) δ 11.91 (s, 1 H), 9.77 (s, 1 H), 8.51 (s, 1 H), 8.06 (d, $J$ = 8.1 Hz, 1 H), 7.95 (d, $J$ = 8.1 Hz, 1 H), 7.80 (s, 1 H), 7.74 (s, 1 H), 7.67 (s, 1 H), 7.59 (s, 1 H), 7.41 (s, 1 H), 7.35-7.39 (m, 1 H), 6.39 (s, 1 H), 6.32 (d, $J$ = 9.6 Hz, 1 H), 3.13-3.17 (m, 2 H), 2.52-2.56 (m, 2 H), 1.73- 1.81 (m, 2H), 1.36 (s, 9 H), 1.32 (s, 9 H), 1.23-1.37 (m, 4 H), 1.23 (s, 9 H); HRMS (ESI-TOF) calcd for C$_{45}$H$_{52}$NiN$_5$O$_4$ [M+H]$^+$: 784.3367, found: 784.3370. Refinement details for 2-24: C$_{22}$H$_{24}$Cl$_{0.50}$N$_8$NiO$_{0.75}$; $M_r$ = 488.93; $T$ = 173(2) K; wavelength = 0.71073 Å; crystal system: triclinic; space group P-1; $a = 13.8471(18)$ Å, $b = 16.144(2)$ Å, $c = 24.435(3)$ Å; $\alpha = 88.172(3)^\circ$, $\beta =$
88.307(3)°, γ = 87.923(2)°; V = 5454.0(12) Å³; Z = 8; ρ_{calc} = 1.191 Mg/m³; μ = 0.786 mm⁻¹; F(000) = 2036; crystal size = 0.15 x 0.07 x 0.04 mm³; θ range = 0.83 to 22.50°;

index ranges: -14≤h≤14, -16≤k≤17, -26≤l≤24; reflections collected 24770, independent reflections 14238 [R(int) = 0.0645], completeness to θ = 22.50°, 99.8%; absorption correction: integration; max./min. transmission 0.9692/0.8912;
data/restraints/parameters 14238/0/989; goodness-of-fit on F² 0.955; final R indices [l>2σ(l)]; R₁ = 0.0783, wR₂ = 0.1905 [7574]; R indices (all data): R₁ = 0.1212, wR₂ = 0.2047; largest diff. peak/hole 1.042 and -0.378 e.Å⁻³.

5-tert-Butyl-4-hydroxybiphenyl-3-carbaldehyde (2-37). A stirred mixture of phenylboronic acid (334 mg, 2.74 mmol), 3-tert-butyl-2-hydroxy-5-iodobenzaldehyde 2-7 (757 mg, 2.50 mmol), Na₂CO₃ (529 mg, 4.99 mmol), PdCl₂(PPh₃)₂ (58 mg, 0.14 mmol), water (5 mL), and 1,4-dioxane (15 mL) was heated at reflux under argon for 2 h. The mixture was cooled to room temperature, diluted with ethyl acetate (100 mL), and washed with H₂O, and then dried over anhydrous MgSO₄. Volatiles were removed by evaporation under reduced pressure, the residue was then purified by column chromatography on silica-gel (2.5% ethyl acetate in n-hexane) to give 2-37 (532 mg, 84%) as a yellow solid. ¹H NMR (300 MHz, CDCl₃) δ 11.80 (s, 1 H), 9.96 (s, 1 H), 7.78 (d, J = 2.0 Hz, 1 H), 7.60 (d, J = 2.3 Hz, 1 H), 7.53-7.59 (m, 2 H), 7.46 (t, J = 7.6 Hz, 2 H), 7.36 (t, J = 7.1 Hz, 1 H), 1.49 (s, 9 H); ¹³C NMR (75 MHz, CDCl₃) δ 197.5, 160.9, 140.4, 139.0, 133.4, 132.7, 130.3, 129.2, 127.4, 127.0, 121.0, 35.3, 29.5; HRMS (ESI-TOF) calcd for C₁₇H₁₉O₂ [M+H]⁺: 255.1380, found: 255.1397.
5,5’-(1E,1’E)-(1R,2R)-Cyclohexane-1,2-diylbis(azan-1-yl-1-ylidene)bis(methan-1-yl-1-ylidene)bis(3-tert-butylbiphenyl-4-ol) (2-38). To a solution of (1R,2R)-cyclohexane-1,2-diamine (25 mg, 0.22 mmol) in THF (3 mL), 2-37 (110 mg, 0.43 mmol) was added at room temperature, and allowed to stir for 1 h. The reaction mixture was concentrated under reduced pressure, and the residue was purified by column chromatography on silica-gel (2.5% ethyl acetate in n-hexane) to give 2-38 (109 mg, 86%) as a yellow solid. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 13.96 (br s, 2 H), 8.35 (s, 2 H), 7.48 (d, $J$ = 2.5 Hz, 2 H), 7.34-7.46 (m, 6 H), 7.23-7.31 (m, 4 H), 7.20 (d, $J$ = 2.3 Hz, 2 H), 3.29-3.45 (m, 2 H), 1.96-2.09 (m, 2 H), 1.86-1.95 (m, 2 H), 1.71-1.84 (m, 2 H), 1.49-1.55 (m, 2 H), 1.46 (s, 18 H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 166.0, 160.1, 141.3, 137.7, 131.1, 128.9, 128.7, 128.4, 126.9, 126.7, 118.9, 72.6, 35.2, 33.3, 29.6, 24.5; HRMS (ESI-TOF) calcd for $C_{40}H_{47}N_2O_2$ [M+H]$^+$: 587.3632, found: 587.3634; $[\alpha]_D^{21}$ -131.2 (c 0.17, CH$_2$Cl$_2$).

2-34. To a solution of 2-38 (83 mg, 0.14 mmol) in CH$_2$Cl$_2$ (5 mL), Co(OAc)$_2$•4H$_2$O (35 mg, 0.14 mmol) in MeOH (3 mL) was added, and allowed to stir at room temperature for 1 h under argon. Precipitate was collected by filtration, and then dried
under vacuum for 24 h to give bisphenyl (salen)Co 2-34 (52 mg, 58%) as a dark red solid. HRMS (ESI-TOF) calcd for C₄₀H₄₅CoN₂O₂ [M+H]^+: 643.2729, found: 643.2724.

**General Procedure for Asymmetric Henry Reaction**

To the mixture of (salen)Co catalyst (2 mol%) in CH₂Cl₂ (0.2 mL), aldehyde (0.25 mmol) and nitromethane (0.13 mL, 10 equiv.) were added at room temperature. The resulting mixture was cooled to -30°C, stirred at this temperature for 30 min, and followed by the addition of 0.1 M DIPEA (50 μL, 2 mol%) in CH₂Cl₂. After 14-110 h reaction time, the reaction mixture was purified by column chromatography on silica-gel column (20% ethyl acetate in n-hexane) to give the desired nitroaldol adduct. Enantiomeric excesses were determined by chiral HPLC analysis using Chiralpak IA or Chiralpak IB columns. Absolute configuration of major isomer was determined to be (S) by comparison of the retention time with literature data and by analogy.

![Chemical structure](image)

**(S)-1-(2-Methoxyphenyl)-2-nitroethanol (2-33a).** Colorless oil. ¹H NMR (300 MHz, CDCl₃) δ 7.44 (dd, J = 7.6, 1.7 Hz, 1 H), 7.33 (td, J = 7.9, 1.7 Hz, 1 H), 7.01 (t, J = 7.5 Hz, 1 H), 6.91 (d, J = 8.2 Hz, 1 H), 5.55-5.69 (m, 1 H), 4.64 (dd, J = 13.0, 3.4 Hz, 1 H), 4.56 (dd, J = 13.0, 9.1 Hz, 1 H), 3.88 (s, 3 H), 3.20 (br s, 1 H); ¹³C NMR (75 MHz, CDCl₃) δ 156.2, 130.0, 127.4, 126.1, 121.4, 110.7, 80.1, 68.0, 55.6; HRMS (GC-Cl) calcd for C₉H₁₁O₄ [M]⁺: 197.0688, found: 197.0688; Ee was determined by HPLC with a Chiralpak IB column (90:10 hexane:i-PrOH, 0.8 mL/min, 215 nm); minor tᵣ = 10.7 min; major tᵣ = 11.6 min; 96% ee.
(S)-1-(2-Chlorophenyl)-2-nitroethanol (2-33b). Colorless oil. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.65 (d, $J = 6.8$ Hz, 1 H), 7.23-7.41 (m, 3 H), 5.83 (td, $J = 9.3$, 2.5 Hz, 1 H), 4.66 (dd, $J = 13.6$, 2.5 Hz, 1 H), 4.44 (dd, $J = 13.3$, 9.3 Hz, 1 H), 3.24 (br s, 1 H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 135.8, 131.7, 130.2, 129.9, 127.8, 79.6, 68.1; HRMS (GC-Cl) calcd for C$_8$H$_8$ClNO$_3$ [M]$^+$: 201.0193, found: 201.0208; $\text{Ee}$ was determined by HPLC with a Chiralpak IB column (97.5:2.5 hexane:i-PrOH, 0.8 mL/min, 215 nm); minor $t_r = 21.2$ min; major $t_r = 22.0$ min; 93% ee.

(S)-1-(2-Fluorophenyl)-2-nitroethanol (2-33c). Colorless oil. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.54 (td, $J = 7.6$, 1.8 Hz, 1 H), 7.28-7.42 (m, 1 H), 7.15-7.25 (m, 1 H), 7.01-7.15 (m, 1 H), 5.64-5.79 (m, 1 H), 4.50-4.68 (m, 2 H), 3.26 (br s, 1 H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 159.6 (d, $J_{CF} = 246.2$ Hz), 130.7 (d, $J_{CF} = 8.3$ Hz), 127.8 (d, $J_{CF} = 3.7$ Hz), 125.1 (d, $J_{CF} = 3.4$ Hz), 116.7 (d, $J_{CF} = 21.5$ Hz), 116.0 (d, $J_{CF} = 21.2$ Hz), 80.0 (d, $J_{CF} = 2.0$ Hz), 65.7 (d, $J_{CF} = 2.9$ Hz); HRMS (DART-TOF-MS) calcd for C$_8$H$_7$FNO$_3$ [M-H]$^-$: 184.0415, found: 184.0411; $\text{Ee}$ was determined by HPLC with a Chiralpak IA column (95:5 hexane:i-PrOH, 0.8 mL/min, 215 nm); major $t_r = 16.7$ min; minor $t_r = 17.7$ min; 94% ee.
(S)-2-Nitro-1-(4-(trifluoromethyl)phenyl)ethanol (2-33d). Colorless oil. $^1$H NMR (300 MHz, CDCl$_3$) δ 7.68 (d, $J$ = 7.9 Hz, 2 H), 7.56 (d, $J$ = 7.9 Hz, 2 H), 5.55 (d, $J$ = 8.9 Hz, 1 H), 4.60 (dd, $J$ = 13.6, 8.8 Hz, 1 H), 4.52 (dd, $J$ = 13.6, 3.7 Hz, 1 H), 3.05 (br s, 1 H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 142.1 (q, $J_{CF}$ = 1.3 Hz), 131.4 (q, $J_{CF}$ = 32.0 Hz), 126.6, 126.2 (q, $J_{CF}$ = 3.8 Hz), 122.2, 81.1, 70.5; HRMS (DART-TOF-MS) calcd for C$_9$H$_7$F$_3$NO$_3$ [M-H]: 234.0384, found: 234.0373; Ee was determined by HPLC with a Chiralpak IB column (85:15 hexane:i-PrOH, 0.8 mL/min, 215 nm); minor $t_r$ = 8.2 min; major $t_r$ = 9.2 min; 82% ee.

(S)-1-(4-Fluorophenyl)-2-nitroethanol (2-33e). Colorless oil. $^1$H NMR (300 MHz, CDCl$_3$) δ 7.31-7.49 (m, 2 H), 7.00-7.20 (m, 2 H), 5.45 (d, $J$ = 9.1 Hz, 1 H), 4.58 (dd, $J$ = 13.5, 9.4 Hz, 1 H), 4.49 (dd, $J$ = 13.2, 3.5 Hz, 1 H), 2.94 (d, $J$ = 3.8 Hz, 1 H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 163.1 (d, $J_{CF}$ = 246.8 Hz), 134.1, 128.0 (d, $J_{CF}$ = 8.2 Hz), 116.2 (d, $J_{CF}$ = 21.8 Hz), 81.3, 70.5; HRMS (DART-TOF-MS) calcd for C$_8$H$_7$FNO$_3$ [M-H]: 184.0415, found: 184.0413; Ee was determined by HPLC with a Chiralpak IB column (90:10 hexane:i-PrOH, 0.8 mL/min, 215 nm); minor $t_r$ = 11.5 min; major $t_r$ = 12.6 min; 90% ee.

(S)-1-(4-Methoxyphenyl)-2-nitroethanol (2-33f). Colorless oil. $^1$H NMR (300 MHz, CDCl$_3$) δ 7.27-7.36 (m, 2 H), 6.86-6.96 (m, 2 H), 5.40 (d, $J$ = 9.6 Hz, 1 H), 4.60 (dd, $J$ = 12.7, 9.1 Hz, 1 H), 4.47 (dd, $J$ = 13.3, 3.1 Hz, 1 H), 3.80 (s, 3 H), 2.80 (d, $J$ = 2.3 Hz, 1
H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 160.3, 130.4, 127.5, 114.6, 81.5, 70.9, 55.6; HRMS (DART-TOF-MS) calcd for C$_9$H$_{10}$NO$_4$ [M-H]: 196.0615, found: 196.0608; Ee was determined by HPLC with a Chiralpak IB column (85:15 hexane:i-PrOH, 0.8 mL/min, 215 nm); minor $t_r = 12.0$ min; major $t_r = 13.6$ min; 81% ee.

\[
\begin{array}{c}
\text{(S)-1-}(\text{Naphthalen-1-yl})-2\text{-nitroethanol (2-33g). Yellow oil.} \\
\text{$^1$H NMR (300 MHz, CDCl$_3$) δ 8.02 (d, $J = 8.5$ Hz, 1 H), 7.91 (d, $J = 7.6$ Hz, 1 H), 7.85 (d, $J = 8.2$ Hz, 1 H), 7.75 (d, $J = 7.3$ Hz, 1 H), 7.47-7.63 (m, 3 H), 6.23 (dd, $J = 7.5$, 4.3 Hz, 1 H), 4.58-4.70 (m, 2 H), 2.98 (s, 1 H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 133.9, 133.7, 129.7, 129.6, 129.5, 127.3, 126.3, 125.7, 124.0, 122.0, 81.0, 68.5; HRMS (DART-TOF-MS) calcd for C$_{12}$H$_{10}$NO$_3$ [M-H]: 216.0666, found: 216.0658; Ee was determined by HPLC with a Chiralpak IB column (85:15 hexane:i-PrOH, 1.0 mL/min, 215 nm); minor $t_r = 8.3$ min; major $t_r = 10.7$ min; 91% ee.}
\end{array}
\]

\[
\begin{array}{c}
\text{(S)-1-}(\text{Naphthalen-2-yl})-2\text{-nitroethanol (2-33h). White solid.} \\
\text{$^1$H NMR (300 MHz, CDCl$_3$) δ 7.82-7.93 (m, 4 H), 7.46-7.56 (m, 3 H), 5.65 (dt, $J = 9.3$, 3.4 Hz, 1 H), 4.71 (dd, $J = 13.6$, 9.3 Hz, 1 H), 4.61 (dd, $J = 13.3$, 3.1 Hz, 1 H), 2.86 (d, $J = 3.1$ Hz, 1 H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 135.6, 133.6, 133.4, 129.2, 128.3, 128.0, 126.9, 126.9, 125.5, 123.4, 81.4, 71.4; HRMS (DART-TOF-MS) calcd for C$_{12}$H$_{10}$NO$_3$ [M-H]: 216.0666, found: 216.0664; Ee was determined by HPLC with a Chiralpak IB column (85:15 hexane:i-PrOH, 0.8 mL/min, 215 nm); minor $t_r = 18.0$ min; major $t_r = 23.3$ min; 87% ee.}
\end{array}
\]
**Kinetic Experiments**

To a vial equipped with sealed cap, the cobalt-salen catalyst and CH$_2$Cl$_2$ (1.0 mL) were charged, and then followed by the addition of o-methoxybenzaldehyde (34 mg, 0.25 mmol), nitromethane (0.13 mL, 10 equiv.), and mesitylene (30 mg, 0.25 mmol, internal standard). The reaction does not occur without external base. The resulting mixture was cooled to -30°C, and then allowed to stir for 30 min at that temperature. The reaction was initiated by the addition of 1.0 M DIPEA (25 μL, 0.1 equiv.) in CH$_2$Cl$_2$. The reaction progress was monitored by the removal of 20 μL aliquots from the reaction mixture, filtration through silicagel with 10% isopropanol in n-hexane as the eluent, and HPLC analysis (Chiralpak IB column, 95:5 hexane:i-PrOH, 0.8 mL/min, 215 nm, mesitylene: 4.1 min, o-methoxybenzaldehyde: 7.9 min) for the first 30% or 40% of the reaction. The slopes of the least square lines for the plots of ([SM]$_0$-[SM]) vs. time were determined.
CHAPTER 3
SELF-ASSEMBLED CATALYSTS THROUGH UREA-UREA HYDROGEN BONDS FOR EPOXIDE OPENING REACTIONS

Backgrounds

The urea functional group is composed of one hydrogen-bond acceptor (C=O) and two hydrogen-bond donors (NH). Owing to its unique ability of H-bonding interactions to anions and electrophiles, the urea moiety and its congeners have been widely employed in the development of anion receptors\textsuperscript{118} and H-bond donor organocatalysts\textsuperscript{119} for the past decade. Besides those abilities, symmetrical or unsymmetrical $N,N'$-disubstituted ureas can form strong and directional hydrogen-bonds with other urea molecules in solution and in the solid state.\textsuperscript{120} More interestingly, the good complementarity between donors and acceptors of urea motifs often lead to the formation of robust one-dimensional H-bonded chains (Figure 3-1).

![Figure 3-1. Urea self-assembly](image)

Those intermolecular interactions can be further strengthened and controlled by the introduction of multiple urea motifs in the molecule. In this regard, the compounds bearing bis-, tris- or tetra-urea motifs have been reported, and they can form dimer or higher aggregates through multiple intermolecular hydrogen bonds in solution and in the solid state. By employing multiple urea motifs, a number of self-assembled supramolecular architectures such as capsules, columns, nanotubes, channels, supramolecular polymers, and organogels have been developed.
Rebek and Böhmer independently and extensively studied self-assembled dimeric calix[4]arenes in which tetra-urea motifs have been utilized. The attachment of four urea groups at the upper rim of calix[4]arenes led to formation of a reversible dimeric capsule through a circular array of eight hydrogen-bonded ureas in nonpolar solvents (Figure 3-2). The cavities generated by reversible dimerization can accommodate small solvent molecules such as benzene.

![Figure 3-2. Dimeric self-assembly of tetra-urea calix[4]arene](image)

Similarly, Steed and co-workers reported dimeric self-assembling capsules derived from the tribenzylamine skeleton (Figure 3-3). This molecular self-assembly consist of a circular array of six hydrogen-bonded ureas. The dimerization constant of 3-2•3-2 was found to be very high in CDCl₃ \((K_2 = \sim 83000 \text{ M}^{-1})\). The X-ray structure showed that the resulting cavity of the self-assembled dimer could accommodate one molecule of CH₂Cl₂.

There has been considerable interest in building self-assembled hollow columnar and tubular stacks which can be applicable to ion transport and sensing, antibacterial agents, and reaction vessels. Owing to the strong tendency to form hydrogen-bonded
Figure 3-3. Dimeric self-assembly of tris-urea compounds

one-dimensional network, macrocyclic $N,N'$-oligoureas have been shown to form various supramolecular structures possessing channels (Figure 3-4).\textsuperscript{124} Those macrocyclic bis- or tetra-urea compounds 3-3, 3-4, 3-5, and 3-6 were stacked through 3-points urea-urea H-bonding, and 4.61~4.72 Å of intermolecular space was created in the solid state. The dimension of the channel can be controlled by variation of the length and the type of spacer in the ring. Interestingly, oligomeric ureas with a large ring such as 3-6 can accommodate small guest molecules in the pore.

Gelation is becoming an important area for developing new materials in solar cells, tissue engineering, vehicles for drug release, and pollutant removal.\textsuperscript{125} Traditionally, covalently cross-linked polymers were used to prepare gels. Recently, low molecular weight organic gelators have been developed. The gelation by these organic gelators involves the self-assembly of individual molecules through non-covalent interactions such as hydrogen bonding and hydrophobic interactions, followed by trapping of solvent molecules. In the pioneering work by Hanabusa, Hamilton, and Feringa, cyclic or acyclic bis-urea molecules serve as a good gelator in a variety of
Figure 3-4. X-ray packing structures of macrocyclic bis- and tetra-urea compounds
solvent systems (Figure 3-5). With a high propensity to form infinite H-bonded networks, urea motifs were shown to be effective in gelation in organic and aqueous solution. In addition, urea functionality is easy to incorporate.

![Figure 3-5. Some examples of bis-urea gelators](image)

Another interesting application of bis-urea self-assembly is the formation of supramolecular polymers which are a chain of small molecules held together through reversible noncovalent interactions. The bis-urea based supramolecular polymers have been extensively studied by Bouteiller and co-workers. In contrast to bis-urea gelators, some bis-urea compounds such as 3-10 and 3-11 have a tendency to form dynamic supramolecular polymers through urea-urea hydrogen bonds in nonpolar solvents (Figure 3-6). The molar mass of these unconventional polymers depends on concentration, solvent polarity, and temperature, and they are potentially useful for a wide range of applications including self-healing polymers and stimuli-responsive materials.

![Figure 3-6. Bis-urea monomers for supramolecular polymer](image)
The urea-based self-assembled structures generally formed in non-polar media. However, some bis- and tetra-urea compounds can also self-assemble in polar media such as THF or even in aqueous solution through the combination of hydrogen-bonding and hydrophobic interactions (Figure 3-7).\textsuperscript{128} This behavior is advantageous for the development of effective hydrogelators and supramolecular polymers in aqueous solution.

![Chemical structures](image)

**Figure 3-7.** Urea monomers for the self-assembly in polar media

Although many urea-based self-assembly systems have been reported, examples of the urea system containing transition metals are relatively rare. As one of the few examples, Shinkai and co-workers reported a tetra-urea incorporated (porphyrin)Cu complex 3-15 that forms thermally stable organometallic gel through one-dimensional molecular self-assembly by means of urea-urea hydrogen bonds and porphyrin-porphyrin π-π interactions (Figure 3-8).\textsuperscript{129} Although 3-15 was not tested as a catalyst, this molecular design could have the potential to be a new self-assembling, transition metal catalyst.

In summary, the urea functional group has proved to have a strong tendency to form self-assembled structures with neighboring urea molecules in a predictive and directional way. This self-assembled structure includes dimer, oligomer, and higher
Figure 3-8. (Porphyrin)Cu based tetra-urea gelator aggregates. It seems possible to develop self-assembled bimetallic or multimetallic catalysts if the urea motifs are introduced to the catalytic cores through an appropriate linker.

**Hydrolytic Kinetic Resolution (HKR) of Terminal Epoxides**

Enantiopure terminal epoxides are valuable intermediates for the synthesis of important pharmaceuticals and agricultural compounds. Although a number of excellent methods have been developed for the catalytic enantioselective epoxidation of unfunctionalized alkenes, terminal alkenes are still very challenging substrates for enantioselective epoxidation. As an alternative, Jacobsen and co-workers developed (salen)Co(III) catalyzed hydrolytic kinetic resolution (HKR) of racemic epoxides (Scheme 3-1). This reaction represents one of the most successful applications of chiral (salen)metal catalyst. In this reaction, the Co(II) precatalyst should be oxidized to the active Co(III) species by addition of acid in the air. The chiral (salen)Co(III) complexes efficiently resolve those epoxides up to 99% ee using water as a nucleophile under highly concentrated or solvent-free conditions. In addition, this reaction generates
optically pure 1,2-diol as a by-product which is also a synthetically valuable intermediate. Because racemic epoxides are relatively inexpensive and water is the sole reagent in this reaction, the hydrolytic kinetic resolution (HKR) has become the most powerful and practical method to obtain enantiopure terminal epoxides.

Scheme 3-1. Hydrolytic kinetic resolution using a (salen)Co catalyst

Preliminary mechanistic and kinetic studies by Jacobsen and co-workers have revealed a second-order dependence on cobalt concentration, which suggests that two metal centers are involved in the rate-limiting transition state in a cooperative manner. In this dual activation mechanism, epoxide is activated by one metal-salen unit and cobalt hydroxide species is delivered by the second catalyst unit. Therefore, this reaction could be second order with respect to catalyst concentration. In addition, two limiting geometries were proposed, as described in Figure 3-9. Among them, ‘head-to-tail’ geometry seemed to give better enantioselectivity.

Recently, a more detailed kinetic profile of the HKR of epoxides was disclosed by Jacobsen and Blackmond, where significant counterion dependence was found on the rate of the HKR (Figure 3-10). Their kinetic studies reveal that the maximum rate can be obtained when [Co-OH]_{tot} is equal to [Co-X]_{tot}. Thus, it is important to maintain this partitioning during the course of reaction to achieve the maximum reaction rate. The partitioning of the Co-OH (B) and Co-X (A) is highly dependent on the nature of counterion. Although acetate could be a reasonable choice as a counterion, weaker
nucleophilic tosylate was the much better alternative. Note that Co(OTs) complex displays better catalytic efficiency in HKR of epoxides compared to Co(OAc) in most cases.

Figure 3-9. Two limiting geometries in HKR of epoxides

Figure 3-10. Counterion effect in HKR
Despite the aforementioned advantages, there is also a disadvantage associated with this methodology, arising from the second-order kinetics. The loss of activity is often observed at the late stage of HKR, and the catalytic efficiency is exponentially decreased at low catalyst loadings. There have been numerous attempts to overcome this limitation for the past decade. The general approach to improve catalytic efficiency in HKR is linking multiple salen catalytic units together using a covalent tether. The resulting oligomeric, dendritic, and polymeric multinuclear salen catalysts, indeed, showed improved reactivity and selectivity in HKR reaction by increasing local concentration of the catalytic site. Many of them showed better performance than monomeric catalyst in the HKR to afford lower catalyst loading.

As a pioneering work, Jacobsen and co-workers developed dendritic multinuclear salen complexes for HKR, and the dendritic salen complexes showed dramatic improvement of catalytic efficiency compared to the monomeric salen catalyst (Figure 3-11).\textsuperscript{132} They utilized NH\textsubscript{2}-terminated PAMAM dendrimers as a backbone that was attached by multiple chiral (salen)Co units through covalent linkages. Dendritic catalyst 3-17 demonstrated much enhanced reactivity and lower catalyst loading in HKR of epoxides resulting from intramolecular cooperative reactivity between catalytic units.

Cyclic oligomers have also been realized as a good platform to enhance cooperative activity between the catalytic units. Jacobsen and co-workers reported highly efficient cyclic oligomer salen complexes 3-18 for HKR of epoxides (Figure 3-12).\textsuperscript{133} This catalyst was prepared as a mixture of different ring sizes. These complexes exhibited lower catalyst loading (up to 50 fold) and shorter reaction times, compared to the monomeric catalyst. This remarkable catalytic efficiency can be attributed to the
Figure 3-11. Dendrimeric multinuclear (salen)Co complex 3-17
facile formation of the head-to-tail bimetallic geometry within flexible macrocyclic structures. The kinetic analysis of HKR with 3-18 revealed a first-order dependence on catalyst, consistent with this intramolecular activation.

Weck and co-workers reported macrocyclic oligomeric (salen)Co(III) complexes which were derived from cyclooctene salen monomers using an olefin metathesis strategy (Figure 3-13).\textsuperscript{134} These oligomeric (salen)Co(III) complexes that were prepared as a mixture of cyclic oligomers with different ring sizes, showed remarkable efficiency in the HKR of terminal epoxides. Later, further studies reveal that the ring size is crucial to achieve high efficiency in HKR of terminal epoxides.\textsuperscript{135} They found that the dimeric
(salen)Co complex was the least reactive catalyst, whereas larger ring size macrocycles (tetramer to hexamer mixture) showed superior reactivity in the HKR of epoxides.

Figure 3-12. Macrocyclic oligomeric (salen)Co complexes

![Figure 3-12](image)

3-18: $n = 1-5$

Figure 3-13. Weck’s macrocyclic oligomeric (salen)Co complexes

![Figure 3-13](image)

3-19: $n = 2-10$

The catalytic efficiencies of those oligomeric multinuclear (salen)Co complexes and the monomeric complex are summarized in Table 3-1. Indeed, two oligomeric (salen)Co complexes 3-18 and 3-19 display superior catalytic efficiency and lower catalyst loading. For example, in the HKR of (rac)-epichlorohydrin, relatively high catalyst loading (0.2-0.5 mol%) and longer reaction time (16-18 h) are required with
monomeric catalysts 2-26(OAc) and 2-26(OTs), whereas only 0.01 mol% catalyst loading is required by the multinuclear (salen)Co complexes to achieve the same level of resolution (entry 1). In addition, reaction time (2.5-11 h) is also much shorter than that of the monomeric catalyst (16-18 h). Similarly good results are also obtained with the multinuclear (salen)Co complexes for the HKR of various terminal epoxides (entries 2-5). It is important to note that this remarkable catalytic efficiency is originated from the enforcement of cooperative activation by tethering catalytic units.

Table 3-1. Catalyst efficiency of multinuclear salen systems

<table>
<thead>
<tr>
<th>entry</th>
<th>epoxide</th>
<th>solvent</th>
<th>catalyst</th>
<th>Co (mol%)</th>
<th>time (h)</th>
<th>ee (%)</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>neat</td>
<td>neat</td>
<td>2-26(OAc)</td>
<td>0.5</td>
<td>18</td>
<td>99</td>
<td>42</td>
</tr>
<tr>
<td></td>
<td>neat</td>
<td>neat</td>
<td>2-26(OTs)</td>
<td>0.2</td>
<td>16</td>
<td>99</td>
<td>42</td>
</tr>
<tr>
<td></td>
<td>neat</td>
<td>neat</td>
<td>3-19</td>
<td>0.01</td>
<td>2.5</td>
<td>99</td>
<td>44</td>
</tr>
<tr>
<td></td>
<td>neat</td>
<td>neat</td>
<td>3-18</td>
<td>0.01</td>
<td>11</td>
<td>99</td>
<td>45</td>
</tr>
<tr>
<td>2</td>
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<td>1,2-hexanediol</td>
<td>2-26(OAc)</td>
<td>2.0</td>
<td>48</td>
<td>99</td>
<td>41</td>
</tr>
<tr>
<td></td>
<td>neat</td>
<td>1,2-hexanediol</td>
<td>2-26(OTs)</td>
<td>2.0</td>
<td>48</td>
<td>99</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>neat</td>
<td>1,2-hexanediol</td>
<td>3-19</td>
<td>0.25</td>
<td>48</td>
<td>99</td>
<td>42</td>
</tr>
<tr>
<td>3</td>
<td>neat</td>
<td>THF</td>
<td>2-26(OAc)</td>
<td>0.8</td>
<td>48</td>
<td>99</td>
<td>44</td>
</tr>
<tr>
<td></td>
<td>neat</td>
<td>THF</td>
<td>3-19</td>
<td>0.1</td>
<td>24</td>
<td>99</td>
<td>45</td>
</tr>
<tr>
<td></td>
<td>neat</td>
<td>THF</td>
<td>CH₃CN/CH₂Cl₂</td>
<td>3-18</td>
<td>0.08</td>
<td>2.5</td>
<td>99</td>
</tr>
<tr>
<td>4</td>
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<td>neat</td>
<td>2-26(OAc)</td>
<td>0.5</td>
<td>18</td>
<td>99</td>
<td>43</td>
</tr>
<tr>
<td></td>
<td>neat</td>
<td>neat</td>
<td>2-26(OTs)</td>
<td>0.05</td>
<td>16</td>
<td>99</td>
<td>45</td>
</tr>
<tr>
<td></td>
<td>neat</td>
<td>neat</td>
<td>3-19</td>
<td>0.01</td>
<td>2</td>
<td>99</td>
<td>43</td>
</tr>
<tr>
<td>5</td>
<td>neat</td>
<td>THF</td>
<td>2-26(OAc)</td>
<td>0.5</td>
<td>18</td>
<td>99</td>
<td>47</td>
</tr>
<tr>
<td></td>
<td>neat</td>
<td>THF</td>
<td>3-19</td>
<td>0.01</td>
<td>20</td>
<td>99</td>
<td>46</td>
</tr>
</tbody>
</table>

Immobilization of salen molecules on polymer backbones and inorganic supports is also a well-known strategy for reinforcing the bimetallic activation as well as recycling catalysts. In 1999, Jacobsen and Annis reported polystyrene- and silica-bound (salen)Co complexes for this purpose (Figure 3-14). This polymer-supported system has been proved to be beneficial particularly for purification step and allows repeated recycling without loss of reactivity and enantioselectivity.
Weberskirch and co-workers developed self-assembled nanoreactors for the HKR of terminal epoxides, and they utilized amphiphilic block copolymers as a backbone (Scheme 3-2). The miscellar aggregation of this polymer backbone generates a hydrophobic core which provides high local concentration of catalysts under homogeneous conditions. This catalyst resolves efficiently various terminal epoxides with very low catalyst loading. In addition, this catalyst can be easily separated and recycled without loss of enantioselectivity.

Scheme 3-2. Hydrolytic kinetic resolution catalyzed by 3-22

In general, it is more challenging to precisely control cooperative activation on solid support than on the soluble support. To overcome this limitation, Weck and co-workers have developed polymer bound (salen)Co complexes bearing oligo(ethylene
glycol) linker or a dendron backbone (Figure 3-15).\textsuperscript{138} Those approaches have been found to provide constant cooperative activation over the entire catalyst structures. As a result, those polymer-bounded catalysts 3-23 and 3-24 also showed high efficiency in the HKR of terminal epoxides at low catalyst loadings (0.01-0.06 mol%).

![Figure 3-15. Polymer-supported (salen)Co complexes by Weck](image)

Similarly, Jones and co-workers reported a polystyrene-supported multinuclear (salen)Co complex, where two salen units are linked through a styryl-functionalized bridge (Scheme 3-3).\textsuperscript{139} Notably, like Weck's polystyrene-based (salen)Co complex, this catalyst can provide constant local concentration of cooperative bimetallic environment. This soluble polymeric catalyst 3-25 showed superior reactivity compared to the monomeric catalyst. For example, racemic 1,2-epoxyhexane can be completely resolved within 2 h with only 0.02 mol\% of catalyst loading.

In 2008, Jacobsen and Belser reported (salen)Co(III) complexes immobilized on gold colloids (Figure 3-16).\textsuperscript{140} The self-assembled thiolate monolayers (SAMs) showed remarkable efficiency in the HKR of 1,2-epoxyhexane. Only 0.01 mol\% catalyst was needed to complete the resolution within 4 h.
Recently, nanocages of mesoporous materials have been utilized for this reaction. Li and co-workers developed nano-cage materials in which (salen)Co complexes were
accommodated in the cagelike mesoporous silica SBA-16 (Figure 3-17). As a consequence of high local concentration of catalytic units in the confined space, dramatic rate enhancement was observed in the HKR of racemic propylene oxide. In addition, this solid catalyst can be easily recycled by filtration without significant loss of catalytic efficiency.

![Figure 3-17. HKR on (salen)Co catalysts confined in nanocages](image)

Very recently, Kleij and co-workers used olefin metathesis as a coupling tool for constructing dinuclear cobalt-salen complexes (Figure 3-18). They tested the resulting dimeric catalyst for the HKR and methanolysis of epoxides, however cooperative effect was not significant. The same group also reported a bis-(salen)Co-calix[4]arene hybrid catalyst for the HKR. Similarly, this dimeric catalyst also did not show significant enhancement of the reaction rate. Both results suggest that the precise control of the orientation of catalytic units is challenging but crucial to achieve the effective cooperative activation.
Figure 3-18. Kleij’s dimeric (salen)cobalt complexes

Although there have been tremendous efforts to develop efficient HKR catalysts, covalent tethering or immobilization approaches were mainly pursued. However, those strategies generally require a relatively long synthesis and difficult purification. Thus, the self-assembly approach using non-covalent interactions would be a promising alternative for the efficient catalytic system in many respects.

**Design and Preparation of Bis-Urea (Salen)Co Catalysts**

Based on a wealth of literature precedence on self-assembly of the urea motifs, we envisioned that the urea functional group can be utilized as a hydrogen bonding motif to design new self-assembled catalysts. As described above, tremendous efforts have been devoted into developing more efficient catalysts for HKR of terminal epoxides mainly by the use of a covalent tether. Thus, it would be interesting to utilize non-covalent bonds, particularly hydrogen bonds in designing a multinuclear (salen)Co catalyst. For those reasons, we devised a new bis-urea functionalized (salen)Co complex which can be self-assembled through urea-urea H-bonding interactions to offer a cooperative activity (Figure 3-19).
Figure 3-19. Self-assembly of bis-urea incorporated (salen)Co complexes

The readily accessible linkers such as \( p \)-phenylene, \( m \)-phenylene, and methylene groups have been chosen to install the urea group into the salen core (Figure 3-20). Phenylene type linkers would provide relatively rigid structural framework, while the methylene linker would give more flexibility. All those bis-urea incorporated salen structures were easily synthesized from commercial starting materials.

Figure 3-20. Design of bis-urea (salen)Co complexes

The synthesis of bis-urea (salen)Co complexes \( 3-28(a-f) \) with the \( p \)-phenylene linker is summarized in Scheme 3-4. 4-Aminophenylboronic ester \( 3-31 \) was reacted with an appropriate isocyanate to afford the urea-derived boronic esters in 70-99% yield. Then the urea-boronic ester was converted to the urea-incorporated salicylaldehydes \( 3-33 \) under the Suzuki coupling conditions. After condensation of salicylaldehydes with
\((R,R)\)-1,2-diaminocyclohexane, the resulting salens were reacted with \(\text{Co(OAc)}_2 \cdot 4\text{H}_2\text{O}\) under argon atmosphere to afford the corresponding bis-urea (salen)Co(II) complexes 3-28(a-f).

![Chemical structure](image)

Scheme 3-4. Synthesis of bis-urea (salen)Co complexes containing the \(p\)-phenylene linker

The synthesis of \(m\)-phenylene linked bis-urea (salen)Co(II) complexes 3-29(a-c) was also performed in a similar way from 3-aminophenylboronic ester 3-35 (Scheme 3-5). For this series, three different end groups (4-CF\(_3\)C\(_6\)H\(_4\), 4-MeOC\(_6\)H\(_4\), and 3,5-(CF\(_3\))\(_2\)C\(_6\)H\(_3\)) were employed.
Scheme 3-5. Synthesis of bis-urea (salen)Co complexes containing the m-phenylene linker

Methylene-linked bis-urea (salen)Co complexes were prepared in five steps from commercial t-butyl-salicylaldehyde 2-6 (Scheme 3-6). Compound 3-39 was obtained by reacting 2-6 with formaldehyde in concentrated HCl for 2 days at 40°C. After converting 3-39 to azide compound 3-40, the urea functional group was conveniently introduced by the reaction of 3-40 with an appropriate isocyanate under catalytic hydrogenation conditions. For the urea compounds bearing reducible functional groups under catalytic hydrogenation conditions, an alternative route should be taken. Thus, the acetal-protected amine 3-43 was prepared in a two step sequence. Then, 3-43 was treated
with a corresponding isocyanate, followed by the removal of the acetal protecting group to afford salicylaldehydes \(3-41i\) and \(3-41j\) in good overall yields.

Scheme 3-6. Synthesis of urea functionalized salicylaldehyde

The resulting salicylaldehydes \(3-41(a-k)\) were condensed with \((R,R)-1,2\)-diaminocyclohexane to afford bis-urea salen ligands \(3-44(a-k)\) (Scheme 3-7). Finally, bis-urea (salen)Co(II) complexes \(3-30(a-k)\) were obtained by the reaction of Co(OAc)\(_2\)•4H\(_2\)O with the corresponding salen ligands in EtOH under argon atmosphere. It is interesting to note that the yield was improved by the replacement of ethanol with iso-propanol in the metalation of \(3-44k\) (37% vs 77%). Those methylene linked bis-urea (salen)Co(II) complexes \(3-30(a-k)\) were characterized by high-resolution mass spectroscopy and elemental analysis.
Scheme 3-7. Synthesis of bis-urea (salen)Co complexes containing the methylene linker

**Self-Assembled Bis-Urea (Salen)Co(III) Catalyzed HKR**

To assess the catalytic performance of bis-urea (salen)Co complexes, HKR of (rac)-allyl glycidyl ether was performed under solvent free conditions at 23°C with 0.55 equivalents of H₂O (Scheme 3-8). For this initial study, two different types of bis-urea (salen)Co complexes 3-28e (p-phenylene) and 3-30f (methylen) were chosen. As mentioned earlier, the counter ion effect is crucial in the HKR of epoxides. To avoid potential disruption of self-assembly by binding of acetate to the urea NHs, tosylate was chosen as a counterion for this study. Thus, prior to the catalytic reactions, Co(II) precatalyst 3-28e and 3-30f were oxidized to active Co(III) species 3-28e(OTs) and 3-30f(OTs). Both bis-urea (salen)Co(OTs) catalysts showed much superior reactivity compared to monomeric catalyst 2-26(OTs) at the initial stage (Figure 3-21a). However,
we later found that an induction period existed in HKR of some epoxides such as allyl glycidyl ether and benzyl glycidyl ether at low catalyst loading (0.05 mol%) when monomeric catalyst \(2-26(OTs)\) was used. As shown in Figure 3-21a, in the HKR of allyl glycidyl ether using 0.05 mol% of the monomeric catalyst, almost no reaction occurs for the first 9 h under solvent free conditions. However, after the induction period, monomeric catalyst \(2-26(OTs)\) exhibited comparable reaction rates (Figure 3-21b). This induction period might be attributed to the immiscibility of allyl glycidyl ether with the water. According to the literature,\(^ {131}\) to avoid the immiscibility issue, the addition of 10 mol% of 1,2-hexanediol to reaction mixture could be helpful to obtain more reliable kinetic profile. However, at 0.05 mol% catalyst loading of monomeric catalyst \(2-26(OTs)\), the induction period was still observed (~5 h) even with the addition of 10 mol% of 1,2-hexanediol. Interestingly, this induction period was not observed with both bis-urea catalysts \(3-28e(OTs)\) and \(3-30f(OTs)\) at 0.05 mol% catalyst loading, which can be an advantage of bis-urea (salen)Co catalysts.

![Scheme 3-8. HKR of (rac)-allyl glycidyl ether catalyzed by bis-urea (salen)Co complexes](image-url)
Figure 3-21. Induction period of HKR of allyl glycidyl ether

Although we found that bis-urea (salen)Co complexes had apparent advantage over the monomeric catalyst from these initial experiments, the induction period made it difficult to precise evaluate efficiency of the catalysts. Later we found that such induction period can be eliminated by choosing (rac)-epichlorohydrin as a substrate at 0.05 mol%
catalyst loading in THF. Thus, we decided to use these induction-period free conditions for better analysis.

A series of bis-urea salen catalysts were reevaluated in the HKR of (rac)-epichlorohydrin in THF at 23°C with 0.55 equiv. of H₂O (Scheme 3-9). Tosylate was chosen as a counterion for this study and bromobenzene was added as an internal standard for GC analysis. The results are shown in Table 3-2. Rather unexpectedly, the aminopyridine/pyridone self-assembled catalyst 2-19(OTs) showed much slower reaction rate (entry 1, relative rate = 0.2) compared to monomeric catalyst 2-26(OTs). The m-phenylene linked bis-urea (salen)Co complex 3-29b(OTs) also showed similarly slow reaction (entry 2, relative rate = 0.3). However, the p-phenylene linked bis-urea complex 3-28e(OTs) disclosed noticeable rate acceleration (entry 3, relative rate = 2.6) and the methylene-linked bis-urea complex 3-30f(OTs) showed most significant rate enhancement (entry 4, relative rate = 9.7). From these results, we confirmed that the orientation and geometry of bis-urea functional groups were pivotal to exhibit the cooperative effect. It is not clear why 2-19(OTs) showed rate deceleration in HKR of epoxide in contrast to the rate acceleration in Henry reaction. Presumably, the metal-metal separation (~4 Å) of the 2-pyridone/aminopyridine system might not be optimal for the epoxide opening reactions (5-6 Å).

Aforementioned kinetic studies revealed that methylene-linked bis-urea (salen)Co complexes would be optimal for epoxide opening reactions. Thus, we decided to study further with this rather flexible bis-urea scaffold. To evaluate the end-group effect, a series of bis-urea (salen)Co complexes 3-30(a-k) were tested for the HKR of (rac)-epichlorohydrin under same reaction conditions (Scheme 3-10). We were pleased to
Scheme 3.9. HKR of (rac)-epichlorohydrin catalyzed by (salen)Co(OTs) complexes

Table 3.2. Kinetic data for the HKR of (rac)-epichlorohydrin

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>$k_{obs}$ (h$^{-1}$)</th>
<th>relative rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2-19(OTs)</td>
<td>$1.8 \times 10^{-2}$</td>
<td>0.2</td>
</tr>
<tr>
<td>2</td>
<td>3-29b(OTs)</td>
<td>$2.0 \times 10^{-2}$</td>
<td>0.3</td>
</tr>
<tr>
<td>3</td>
<td>3-28e(OTs)</td>
<td>$2.0 \times 10^{-1}$</td>
<td>2.6</td>
</tr>
<tr>
<td>4</td>
<td>3-30f(OTs)</td>
<td>$7.4 \times 10^{-1}$</td>
<td>9.7</td>
</tr>
<tr>
<td>5</td>
<td>2-26(OTs)</td>
<td>$7.6 \times 10^{-2}$</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Figure 3.22. Rate plots of the HKR of (rac)-epichlorohydrin in THF
find that bis-urea (salen)Co(OTs) catalysts showed significant rate acceleration (4.2-13 times) compared to monomeric catalyst 2-26(OTs) (Table 3-3). It is noteworthy that all bis-urea salen complexes showed rate acceleration regardless of the end-groups. The N-aryl end groups show greater rate acceleration than the N-alkyl end groups (entries 1-3 vs 4-11). Electron-withdrawing groups on the phenyl ring show more rate acceleration. However, the substituent effect does not linearly correlate with the Hammett parameter σ. The bis-urea (salen)Co complexes 3-30h(OTs) and 3-30k(OTs) prove to be the best from the survey (entries 8 and 11), and 3-30k(OTs) was selected for the further studies.

Table 3-3. Kinetic data for the HKR of (rac)-epichlorohydrin

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>R</th>
<th>$k_{obs}$ (h$^{-1}$)</th>
<th>relative rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3-30a(OTs)</td>
<td>Bn</td>
<td>$3.2 \times 10^{-1}$</td>
<td>4.2</td>
</tr>
<tr>
<td>2</td>
<td>3-30b(OTs)</td>
<td>$n$-C$<em>6$H$</em>{13}$</td>
<td>$3.5 \times 10^{-1}$</td>
<td>4.6</td>
</tr>
<tr>
<td>3</td>
<td>3-30c(OTs)</td>
<td>$n$-C$<em>{18}$H$</em>{37}$</td>
<td>5.4</td>
<td>7.2</td>
</tr>
<tr>
<td>4</td>
<td>3-30d(OTs)</td>
<td>C$_6$H$_5$</td>
<td>6.5</td>
<td>8.6</td>
</tr>
<tr>
<td>5</td>
<td>3-30e(OTs)</td>
<td>4-CH$_3$O-C$_6$H$_4$</td>
<td>6.5</td>
<td>8.6</td>
</tr>
<tr>
<td>6</td>
<td>3-30f(OTs)</td>
<td>3,5-(CF$_3$)$_2$-C$_6$H$_3$</td>
<td>7.4</td>
<td>9.7</td>
</tr>
<tr>
<td>7</td>
<td>3-30g(OTs)</td>
<td>4-F-C$_6$H$_4$</td>
<td>6.7</td>
<td>8.8</td>
</tr>
<tr>
<td>8</td>
<td>3-30h(OTs)</td>
<td>4-Cl-C$_6$H$_4$</td>
<td>1.00</td>
<td>13</td>
</tr>
<tr>
<td>9</td>
<td>3-30i(OTs)</td>
<td>4-Br-C$_6$H$_4$</td>
<td>7.2</td>
<td>9.5</td>
</tr>
<tr>
<td>10</td>
<td>3-30j(OTs)</td>
<td>4-CN-C$_6$H$_4$</td>
<td>5.1</td>
<td>6.7</td>
</tr>
<tr>
<td>11</td>
<td>3-30k(OTs)</td>
<td>4-CF$_3$-C$_6$H$_4$</td>
<td>1.04</td>
<td>13.7</td>
</tr>
<tr>
<td>12</td>
<td>2-26(OTs)</td>
<td>-</td>
<td>$7.6 \times 10^{-2}$</td>
<td>1.0</td>
</tr>
</tbody>
</table>

One of the impressive features of the (salen)Co(III)-catalyzed HKR is that this reaction can be performed under solvent-free conditions, which is beneficial in terms of waste-reductions and cost-savings. Because epoxide substrates and 1,2-diol products are generally liquid, it is possible to use solvent-free or highly concentrated
conditions. In addition, since the remaining epoxides are generally isolated by vacuum transfer, it is highly desirable to avoid the use of solvent. Kinetic resolution of (rac)-

Figure 3-23. Rate plots of the HKR of epichlorohydrin (3-30a-f) and 2-26)

Figure 3-24. Rate plots of the HKR of epichlorohydrin (3-30g-k) and 2-26)
epichlorohydrin (5 mmol) was performed at 23°C with 0.7 equivalents of H₂O and 0.05 mol% of 3-30k(OTs) and under solvent-free conditions (Figure 3-25). It should be noted that bis-urea catalyst 3-30k(OTs) displayed significantly better performance than
monomeric catalyst 2-26(OTs) both in THF (Figure 3-25a) and under solvent-free conditions (Figure 3-25b). After 8 h, 3-30k(OTs) gave 92% ee (THF) and 93% ee (solvent-free) for the remaining epoxide, while 2-26(OTs) gave only 35% ee (THF) and 47% ee (solvent-free) at the same catalyst loading (0.05 mol%).

Figure 3-25. HKR of (rac)-epichlorohydrin with 0.05 mol% 3-30k(OTs) and 2-26(OTs) in THF and under solvent-free conditions

Bis-urea (salen)Co catalyst 3-30k(OTs) was employed in the HKR of a variety of terminal epoxides under solvent-free conditions and as low as 0.03-0.05 mol% catalyst loading (Scheme 3-11). After the reaction was completed, the enantioenriched epoxide was isolated by vacuum transfer. Bis-urea (salen)Co catalyst 3-30k(OTs) displayed
improved performance for all four terminal epoxides examined compared to monomeric catalyst 2-26(OTs) (Table 3-3). Bis-urea (salen)Co catalyst 3-30k(OTs) completed the reaction in 8-14 h, whereas the monomeric catalyst require a prolonged reaction time (24-71 h) at the same low catalyst loadings (0.03-0.05 mol%).

Scheme 3-11. HKR of (rac)-epoxides catalyzed by (salen)Co(OTs) complexes

Table 3-4. HKR of terminal epoxides under solvent-free conditions

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>catalyst (mol%)</th>
<th>time (h)</th>
<th>ee (%)</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH₂Cl (1-49b)</td>
<td>3-30k(OTs) (0.05)</td>
<td>14</td>
<td>99</td>
<td>41</td>
</tr>
<tr>
<td>2</td>
<td>CH₂Cl (1-49b)</td>
<td>2-26(OTs) (0.05)</td>
<td>71</td>
<td>96</td>
<td>42</td>
</tr>
<tr>
<td>3</td>
<td>CH₂O(allyl) (1-49a)</td>
<td>3-30k(OTs) (0.05)</td>
<td>8</td>
<td>99</td>
<td>43</td>
</tr>
<tr>
<td>4</td>
<td>CH₂O(allyl) (1-49a)</td>
<td>2-26(OTs) (0.05)</td>
<td>32</td>
<td>98</td>
<td>43</td>
</tr>
<tr>
<td>5</td>
<td>CH₂CH₃ (1-49c)</td>
<td>3-30k(OTs) (0.03)</td>
<td>8</td>
<td>99</td>
<td>43</td>
</tr>
<tr>
<td>6</td>
<td>CH₂CH₃ (1-49c)</td>
<td>2-26(OTs) (0.03)</td>
<td>24</td>
<td>99</td>
<td>43</td>
</tr>
<tr>
<td>7</td>
<td>(CH₂)₂CH₃ (1-49d)</td>
<td>3-30k(OTs) (0.03)</td>
<td>14</td>
<td>99</td>
<td>41</td>
</tr>
<tr>
<td>8</td>
<td>(CH₂)₂CH₃ (1-49d)</td>
<td>2-26(OTs) (0.03)</td>
<td>42</td>
<td>99</td>
<td>42</td>
</tr>
</tbody>
</table>

Kinetic and Mechanistic Study

In order to investigate the origin of the observed rate acceleration, a series of kinetic/mechanistic studies were performed mainly in THF. First, the rate constants ($k_{obs}$) of the HKR of epichlorohydrin with 3-30f(OTs) were measured by changing catalyst loadings in THF (Figure 3-26).
Figure 3-26. Rate plots of the HKR of epichlorohydrin (5.0 mmol) using the bis-urea (salen)Co 3-30f(OTs) (0.02, 0.03, 0.04, and 0.05 mol%) in THF

The kinetic study revealed that the rate laws were second order in catalyst concentration for bis-urea (salen)Co complex 3-30f(OTs) (Figure 3-27). While this result might suggest that the same bimetallic mechanism is operating with the bis-urea (salen)Co complex as with monomeric (salen)Co complex 2-26(OTs), we cannot rule out completely other mechanism such as intermolecular metal/urea activation.

Figure 3-27. Kinetic dependence on catalyst concentration
Assuming the dimeric aggregate of (salen)Co units is an actual catalytic species, the rate law can be expressed in terms of monomer-dimer equilibrium constant $K_2$ (Eqs. 3-1, 3-2, and 3-3). Meanwhile, the initial catalyst concentration $[(\text{salen})\text{Co}]_0$ can be written as the sum of monomer concentration $[(\text{salen})\text{Co}]$ and dimer concentration $[(\text{salen})\text{Co} \text{•} (\text{salen})\text{Co}]$ (Eq. 3-4). By assuming that monomer concentration would be equal to the initial catalyst concentration in relatively weak self-assembled systems ($K_2 << 10^2$), the second order-like kinetic dependence on the initial catalyst concentration $[(\text{salen})\text{Co}]_0$ is expected (Eq. 3-5). In contrast, the first order-like kinetic dependence is expected from strong self-assembled systems ($K_2 >> 10^3$) or covalently tethered systems (Eq. 3-6). Thus, the observed second-order kinetic dependence might suggest that the self-association constant of the bis-urea (salen)Co would be moderate in current reaction media.

$$K_2 = [(\text{salen})\text{Co} \text{•} (\text{salen})\text{Co}] / [(\text{salen})\text{Co}]^2 \quad (3-1)$$

$$\text{Rate} = k_{\text{obs}} [(\text{salen})\text{Co} \text{•} (\text{salen})\text{Co}] \quad (3-2)$$

$$\text{Rate} = k_{\text{obs}} K_2 [(\text{salen})\text{Co}]^2 \quad (3-3)$$

$$[(\text{salen})\text{Co}]_0 = 2[(\text{salen})\text{Co} \text{•} (\text{salen})\text{Co}] + [(\text{salen})\text{Co}] \quad (3-4)$$

i) $K_2 << 10^2$: $[(\text{salen})\text{Co}] \approx [(\text{salen})\text{Co}]_0$

$$\text{Rate} = k_{\text{obs}} K_2 [(\text{salen})\text{Co}]_0^2 \quad \text{(second order)} \quad (3-5)$$

ii) $K_2 >> 10^3$: $[(\text{salen})\text{Co} \text{•} (\text{salen})\text{Co}] \approx [(\text{salen})\text{Co}]_0/2$

$$\text{Rate} = (k_{\text{obs}} /2) [(\text{salen})\text{Co}]_0 \quad \text{(first order)} \quad (3-6)$$
Second, to determine whether the accessible urea NH groups are pivotal for such rate acceleration, we synthesized two other (salen)Co complexes that might not readily form self-assembled dimer because of their bulky end-group or N-Me substitution. For this purpose, 2,6-diisopropylphenylurea derived (salen)Co complex 3-30l was prepared as shown in Scheme 3-12.

Scheme 3-12. Synthesis of 2,6-diisopropylphenylurea (salen)Co complex

Synthesis of N,N'-dimethylated urea (salen)Co complex was summarized in Scheme 3-13. The urea intermediate 3-41d was reacted with excess MeI after deprotonation by NaI to afford N,N'-dimethylurea 3-46. The methyl group on aryl oxygen of 3-46 was removed by the treatment with BBr₃ in CH₂Cl₂ to afford salicylaldehyde 3-47. This resulting intermediate was converted to N,N'-dimethylated bis-urea (salen)Co complex 3-49 using the routine condensation and metatation methods.

Both catalysts 3-30l(OTs) and 3-49(OTs) lacking accessible N-H were tested for the HKR of (rac)-epichlorohydrin under the standard reaction conditions, much slower reaction rates were observed (Figure 3-28). This result clearly indicates that accessible urea NH groups are crucial for the observed rate acceleration.
Scheme 3-13. Synthesis of $N,N'$-dimethylated urea (salen)Co complex

 Third, mono-substituted urea (salen)Co complex 3-51 was synthesized using Weck's protocol for unsymmetrical salens as described in Scheme 3-14. This complex was expected to show slower reaction rate compared to bis-urea catalyst because of the lack of additional H-bonding interactions.

 The resulting mono-urea (salen)Co complex 3-51(OTs) showed less rate acceleration in the HKR of epichlorohydrin (Figure 3-29). However, the rate acceleration (relative rate = 8.4) was still significant compared to that of the corresponding bis-urea (salen)Co catalyst (relative rate = 13.7), which suggests even the mono-urea (salen)Co complex can provide self-assembled structure in a desired orientation with comparable association strength. This phenomenon will be discussed further in later sections.

![Chemical Reaction Diagram]

Scheme 3-15. Epoxide opening reaction catalyzed by thiourea

Figure 3-29. Relative rate of mono-urea (salen)Co complex

Finally, additional control experiment was performed to rule out an alternative mechanism involving electrophilic activation of epoxides by the neighboring urea group through double hydrogen-bonding. According to recent report by Schreiner and co-workers, (thio)urea functional groups can catalyze a certain types of epoxide opening reaction by double hydrogen-bonding activation (Scheme 3-15).\textsuperscript{148}
Because previous kinetic analysis cannot discriminate intermolecular electrophilic activation by the neighboring urea group (Figure 3-30), another control experiment would be required to ensure that bimetallic activation through self-assembly is responsible for observed rate acceleration.

Figure 3-30. Possible urea/metal dual activation scenario

Thus, to examine possible electrophilic activation, two different simple \( N,N \)-disubstituted urea compounds were added to the reaction mixture in the presence of monomeric catalyst 2-26(OTs) (Scheme 3-16). However, the addition of both urea additives decreased reaction rates in the HKR of (rac)-epichlorohydrin (Table 3-5). The addition of electron-rich dibenzylurea 3-52 exhibited a much slower reaction (entry 2). Increasing the amount of urea additive also resulted in slower reaction (entry 4). These results suggest that the urea additive might function as a competitive inhibitor, presumably through coordination to the metal center. Therefore, it is highly unlikely that the rate-acceleration originated from the electrophilic activation of epoxides by the urea moiety. It also explains why electron-deficient end groups showed generally better reactivity in the bis-urea (salen)Co catalyzed HKR.
Scheme 3-16. Kinetic data for the HKR of (rac)-epichlorohydrin catalyzed by 2-26(OTs) and urea additives

Table 3-5. Kinetic data for the HKR of (rac)-epichlorohydrin

<table>
<thead>
<tr>
<th>entry</th>
<th>additive (mol%)</th>
<th>$k_{obs}$ (h$^{-1}$)</th>
<th>relative rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>none</td>
<td>7.6 x 10$^{-2}$</td>
<td>1.0</td>
</tr>
<tr>
<td>2</td>
<td>3-52 (0.1)</td>
<td>3.8 x 10$^{-2}$</td>
<td>0.5</td>
</tr>
<tr>
<td>3</td>
<td>3-53 (0.1)</td>
<td>6.7 x 10$^{-2}$</td>
<td>0.9</td>
</tr>
<tr>
<td>4</td>
<td>3-53 (0.4)</td>
<td>3.2 x 10$^{-2}$</td>
<td>0.4</td>
</tr>
</tbody>
</table>

Self-Assembly Study

To verify the self-assembly of bis-urea salen structures in solution, FT-IR and $^1$H NMR dilution experiments were performed. IR spectroscopy has been widely applied for studying self-assembly of urea compounds because it has been known that free N-H and hydrogen-bonded N-H have different frequencies. Figure 3-31 depicts the NH stretching region of the FT-IR spectra of 3-26k (3 mM, cyan line) in THF and reveals strong hydrogen-bonded N-H stretching vibrations (3347 and 3295 cm$^{-1}$) in comparison to free N-H stretching vibrations (3571 and 3505 cm$^{-1}$). The intensity of hydrogen-bonded N-H stretching vibrations was decreased with lowering concentration, but they were still significant even in diluted (1 mM, dark blue line) solution. This result demonstrates that the urea N-H groups of the bis-urea (salen)Co complex are involved in intermolecular H-bonding events in THF.
Figure 3-31. The NH stretching region of the FTIR spectra of 3-26k in THF

To gain further insight into the self-association strength, $^1$H NMR dilution experiments were also performed using (salen)Ni complexes in THF-$d_6$. Both bis- and mono-urea (salen)Ni complexes 3-54 and 3-55 were readily prepared as a model compound from the corresponding salen ligands (Figure 3-32).

Figure 3-32. Bis-urea (salen)Ni complex and mono-urea (salen)Ni complex

Two NH proton signals of the urea group in the (salen)Ni complexes were monitored upon increasing the concentration (0.76 to 19.1 mM), and the observed chemical shift of the N-H group shifted downfield ($\Delta \delta \approx 0.2$ ppm) as shown in Figure 3-33. By using the simple monomer-dimer model, the dimerization constants of 3-54 and 3-55 were estimated as $56 \pm 22$ M$^{-1}$ and $32 \pm 3$ M$^{-1}$ respectively. As mentioned earlier, it is also possible that mono- and bis-urea (salen)Ni complexes can exist as higher aggregates like many other urea derived compounds. To evaluate the association
strength of the higher aggregate, two mathematical models such as equal $K$ model ($K_2 = K_n = K$) and two $K$ model ($K_2 \neq K_n = K$) have been generally used. When the equal $K$ model ($K_2 = K_n = K$) was applied, $K_{as}$ values of 3-54 and 3-55 were determined as $70 \pm 29 \text{ M}^{-1}$ and $32 \text{ M}^{-1}$ respectively. These results indicate that both urea (salen)Ni complexes are self-assembled in THF through hydrogen-bonds with moderate

![Diagram](image)

Figure 3-33. Concentration-dependent $^1$H NMR shifts of two urea protons

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association strength \( (K_a = 32\text{--}70\ \text{M}^{-1}) \). In addition, as discussed before, this moderate association values are consistent with the observed second-order kinetic dependence on catalyst concentration in this system. It is also worthwhile to mention that the self-association strength of Ni complexes \( (56\ \text{M}^{-1} \text{ vs } 32\ \text{M}^{-1}) \) can be translated into the rate enhancement by the corresponding Co(III) catalysts \( (13 \text{ vs } 8.4) \).

**X-Ray Packing Structures and MM2 Calculation**

To obtain the structural information on the self-assembly of bis-urea (salen)Co complexes, we attempted to grow single crystals. However, our attempts to crystallize (salen)Co complexes were unsuccessful. Instead, a single crystal of the bis-urea (salen)Ni complex \( \text{3-56} \) \( (R = \text{Bn}) \) was obtained by slow evaporation in DMF. The ORTEP view of \( \text{3-56} \) is shown in Figure 3-34.

![ORTEP view of the crystal structure of 3-56. The H atoms of the framework are omitted for clarity](image)

Figure 3-34. ORTEP view of the crystal structure of \( \text{3-56} \). The H atoms of the framework are omitted for clarity

In the crystal packing, the interstack arrangement between two extensive H-bond networking layers was observed (Figure 3-35). However, the desired head-to-tail dimer suitable for bimetallic activation is not found within this H-bonding network (Figure 3-36).
Thus, MM2 calculations were performed by using CAChe program (Fujitsu) to look at the feasibility of the self-assembled dimer capable of bimetallic activation. To simplify the calculation, the bis-urea (salen)Ni structure having the methyl-end groups (R = Me) was used. The atomic coordinates in the (salen)Ni fragment were obtained from the crystal structure data of 3-56, and the (salen)Ni fragment was locked during optimization.
After calculations, two possible energy-minimized structures in the head-to-tail arrangement were obtained as shown in Figure 3-37. Two (salen)Ni units can be assembled through two urea-urea H-bonding interactions either in a parallel (P) or an anti-parallel (A) mode. Interestingly, the Ni-Ni separation was calculated as approximately 6 Å in both modes, which is the optimal metal-metal separation for epoxide opening reactions.42

Figure 3-37. Two plausible structures of bis-urea (salen)Ni dimer: antiparallel (A) and parallel (P)

After performing MM2 calculations, we could obtain an X-ray suitable single crystal of bis-urea (salen)Ni complex 3-57 by slow evaporation in DMF (Figure 3-38). The end group of this bis-urea (salen)Ni complex is the electron-poor and sterically demanding 3,5-(CF₃)₂C₆H₃-moiety.

In the crystal packing, the bis-urea (salen)Ni complex 3-57 forms a self-assembled dimer which adopts anti-parallel head-to-tail conformation (Figure 3-39 and 3-40). In this structure, the intermolecular hydrogen bonding interactions between urea groups are observed (N–H•••O = 2.06, 2.08 Å) at the both ends of the salen and two urea planes are significantly twisted (57.9(8)°). The metal-metal distance was determined as 5.3 Å.
Figure 3.38. X-ray crystal structure of bis-urea (salen)Ni complex 3-57

Figure 3.39. Self-assembled dimeric structure of 3-57 (side view)

Figure 3.40. Self-assembled dimeric structure of 3-57 (top view)
This dimeric structure interacts with the neighboring dimer through extended urea-urea hydrogen bonds (Figure 3-41). However, in this association, only the alkyl urea N-H involves in the formation of intermolecular N–H···O interaction of 2.05 Å with the neighboring dimer. The aryl urea N-H forms N–H···O interactions of 2.28 Å with one DMF molecule. The urea-urea plane is also twisted with the angle of 53.4(1)°. The metal-metal distance between neighboring dimers was measured as 4.9 Å.

![Figure 3-41. Hydrogen-bond packing structure of bis-urea (salen)Ni complex](image)

Interestingly, less reactive bis-urea salen complex (R = Bn) reveals the oligomeric structure in the solid state, whereas more reactive bis-urea salen (R = 3,5-(CF₃)₂C₆H₃) shows the desired dimeric structure. This result is rather unexpected, because it is generally accepted that the electron-rich alkyl urea can form more stable self-assembled structures. Although it is possible to have different self-association pattern in solution, the bis-urea salen bearing the electron-deficient end-group may have a stronger tendency to form the dimeric structure adopting the desired conformation. Taken together, those MM2 calculations and X-ray packing structures demonstrate that
the current bis-urea salen scaffold provides optimal metal-metal separation (5~6 Å) through H-bonds for effective bimetallic activation.

**Asymmetric Hydrolysis of Cyclohexene Oxide**

Although the chiral (salen)Co(III) complexes are very efficient for the HKR of terminal epoxides, the asymmetric hydrolysis of *meso*-epoxides still remains a challenge. Thus, we investigated asymmetric hydrolysis of cyclohexene oxide 3-58 as a model reaction to explore the scope of the bis-urea (salen)Co catalyst (Scheme 3-17). After 45 h, bis-urea (salen)Co complex 3-30k(OTs) afforded the desired trans-1,2-cyclohexanediol product with much higher yield (62%) and enantiomeric excess (75%) compared to monomeric catalyst 2-26(OTs) (9% yield and 45% ee). This result demonstrates that our approach will be applicable to more challenging substrates as well.

![Scheme 3-17. Asymmetric hydrolysis of cyclohexene oxide](image)

**Design of Bis-Urea Spacing Dimeric (Salen)Co Complexes**

In the previous section, we successfully developed the self-assembled catalyst mediated by urea-urea hydrogen bonds for HKR of epoxides. Thus, it is interesting to utilize the urea motif for a new self-assembled system. We envisioned that the bis-urea motif could be used as a spacer for linking two (salen)Co units (Figure 3-42). As a result, two bimetallic reaction sites can be generated at the both ends of the self-assembled dimer. We expected that the resulting dimeric catalysts could provide stronger, but more flexible self-assembling system for bimetallic reactions.
Based on this idea, various bis-urea spacing dimeric (salen)cobalt complexes were prepared. Bis-urea spacing salicylaldehydes 3-61(a-e) were readily synthesized by reacting amine compound 3-43 with an appropriate commercial diisocyanate, followed by deprotection (Scheme 3-18).

Scheme 3-18. Synthesis of bis-urea spacing salicylaldehyde intermediates
From this salicylaldehyde intermediates, the corresponding bis-urea dimeric salen ligands were obtained using Weck’s protocol\textsuperscript{147} as depicted in Scheme 3-19. Subsequent metation of the resulting dimeric salen ligands afforded the desired bis-urea spacing dimeric (salen)Co complexes 3-62(a-e).

Scheme 3-19. Synthesis of bis-urea spacing dimeric (salen)Co complexes

It is also interesting to see the catalytic efficiency and the self-assembly of the analogous mono-urea spacing dimeric (salen)Co complex. For this reason, mono-urea intermediate 3-63 was prepared by the reaction of amino compound 3-43 with carbodiimidazole (CDI), followed by deprotection of acetal group (Scheme 3-20). From salicylaldehyde intermediate 3-63, mono-urea dimeric (salen)Co complex 3-64 was obtained by using Weck’s protocol\textsuperscript{147} and subsequent metation.

Those newly prepared dimeric (salen)Co complexes were tested for the hydrolytic desymmetrization of cyclohexene oxide (Scheme 3-21). As mentioned earlier, this reaction has been known for very challenging with the simple monomeric (salen)Co catalyst. As low as 0.25 mol\% of catalyst loading and 1.2 equivalent of H\textsubscript{2}O were used for this reaction. In the initial screening, those all bis-urea spacing dimeric (salen)Co
complexes demonstrated superior reactivity and enantioselectivity compared to monomeric catalyst 2-26(OTs) (Table 3-6, entry 1 vs entries 3-7). Among them, the

![Scheme](image)

Scheme 3-20. Synthesis of mono-urea spacing dimeric (salen)Co complex 3-64 dimeric catalysts linked with 1,3-phenylene type spacers (3-62a(OTs) and 3-62b(OTs)) showed better performance than bis-urea monomeric catalyst 3-26k(OTs) in terms of reactivity and enantioselectivity (entry 2 vs entries 3-4). Linear aliphatic and 1,4-phenylene spacers were found to be less efficient than bis-urea monomeric catalyst 3-26k(OTs) in terms of reactivity (entry 2 vs entries 5-7). Interestingly, the mono-urea analogue 3-64(OTs) exhibited slightly low but comparable reactivity and similar enantioselectivity (entry 8).

Those promising results demonstrate that the bis-urea spacing dimeric scaffolds can provide a versatile and powerful self-assembled catalytic system for epoxide opening reactions. In addition, the different types of chiral ligands such as tridentate Schiff base can be easily installed at the both ends of the bis-urea spacer. Although more detailed structural and mechanistic studies are required to elucidate this novel
self-assembled catalytic system, it would be a powerful solution for efficient bimetallic catalysis.

\[
\begin{align*}
\text{3-58} & + \text{H}_2\text{O} \rightarrow \text{3-59} \\
& \text{1.2 equiv} \quad \frac{(R,R)-\text{Co(OTs)}}{(0.25-0.5 \text{ mol})} \quad \text{TBME, 23°C, 45 h}
\end{align*}
\]

**monomeric salen**

\[
\begin{align*}
R^1 &= \text{t-Bu}, 2-26(\text{OTs}) \\
R^1 &= \text{H}, 3-30k(\text{OTs})
\end{align*}
\]

**dimeric salen**

\[
\begin{align*}
3-62a(\text{OTs}) & \\
3-62b(\text{OTs}) & \\
3-62c(\text{OTs}) & \\
3-62d(\text{OTs}) & \\
3-62e(\text{OTs}) & \\
3-64(\text{OTs}) & \\
\end{align*}
\]

Scheme 3-21. Desymmetrization of cyclohexene oxide catalyzed by (salen)Co complexes

**Table 3-6. Desymmetrization of cyclohexene oxide**

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst (mol%)</th>
<th>yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2-26(OTs) (0.5)</td>
<td>9</td>
<td>45</td>
</tr>
<tr>
<td>2</td>
<td>3-30k(OTs) (0.5)</td>
<td>62</td>
<td>75</td>
</tr>
<tr>
<td>3</td>
<td>3-62a(OTs) (0.25)</td>
<td>69</td>
<td>81</td>
</tr>
<tr>
<td>4</td>
<td>3-62b(OTs) (0.25)</td>
<td>72</td>
<td>81</td>
</tr>
<tr>
<td>5</td>
<td>3-62c(OTs) (0.25)</td>
<td>45</td>
<td>71</td>
</tr>
<tr>
<td>6</td>
<td>3-62d(OTs) (0.25)</td>
<td>38</td>
<td>72</td>
</tr>
<tr>
<td>7</td>
<td>3-62e(OTs) (0.25)</td>
<td>43</td>
<td>76</td>
</tr>
<tr>
<td>8</td>
<td>3-64(OTs) (0.25)</td>
<td>59</td>
<td>80</td>
</tr>
</tbody>
</table>
Summary

In summary, we developed novel chiral bis-urea (salen)Co catalysts which were self-assembled through intermolecular urea-urea hydrogen bonds in the solution. These catalysts were successfully employed to hydrolytic kinetic resolution of racemic epoxides, exhibiting significant rate acceleration up to 13 times compared to the unfunctionalized analogue. The observed rate acceleration can be rationalized by the self-assembly of catalytic units through intermolecular hydrogen bonds. To the best of our knowledge, this is the first example of H-bonded self-assembling catalyst for the hydrolytic kinetic resolution of epoxides. In addition, as an extension of this strategy, bis-urea spacing dimeric (salen)Co catalysts were developed. These catalysts exhibited superior performance in the hydrolytic desymmetrization of meso-epoxide in terms of reactivity and enantioselectivity.

Experimental

General Remarks

All reactions were conducted in flame-dried glassware under an inert atmosphere of dry argon. THF, CH₂Cl₂, Et₂O and toluene were purified under positive pressure of dry nitrogen by Meyer Solvent Dispensing System prior to use. All the chemicals used were purchased from Sigma-Aldrich Co., Acros Organics, TCI America, and Strem Chemical Incs. and were used as received without further purification. NMR spectra were recorded using a Mercury 300 FT-NMR, operating at 300 MHz for ¹H NMR and at 75.4 MHz for ¹³C NMR. All chemical shifts for ¹H and ¹³C NMR spectroscopy were referenced to residual signals from CDCl₃ (¹H) 7.26 ppm and (¹3C) 77.23 ppm. High resolution mass spectra were recorded on a GC/MS spectrometer or a TOF-LC/Ms
spectrometer. Enantiomeric ratios were determined by chiral GC-MS analysis using a Chiraldex γ-TA column.

**General Procedure for the Preparation of Ureidophenyl-Boronic Esters**

To a solution of 4-aminophenylboronic acid pinacol ester (161 mg, 0.74 mmol) in CH$_2$Cl$_2$ (2 mL), isocyanate (0.74 mmol) was added at room temperature, and then allowed to stir for 2 h. The solution was concentrated under reduced pressure, and the residue was then triturated with ethyl acetate/n-hexane to give **3-32** as a solid.

**1-Benzy1-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)urea (3-32a).**

White solid (95%); $^1$H NMR (300 MHz, DMSO-$d_6$) δ 8.69 (s, 1 H), 7.52 (d, $J = 8.5$ Hz, 2 H), 7.40 (d, $J = 8.5$ Hz, 2 H), 7.35-7.18 (m, 5 H), 6.66 (t, $J = 5.8$ Hz, 1 H), 4.28 (d, $J = 5.7$ Hz, 2 H), 1.25 (s, 12 H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 155.6, 144.1, 140.9, 136.1, 129.0, 127.9, 127.5, 127.4, 117.3, 83.9, 43.4, 25.4; HRMS (ESI-TOF) calcd for C$_{20}$H$_{26}$BN$_2$O$_3$ [M+H]$^+$: 353.2035, found: 353.2042.

**1-Hexyl-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)urea (3-32b).**

White solid (100%); $^1$H NMR (300 MHz, DMSO-$d_6$) δ 8.53 (s, 1 H), 7.51 (d, $J = 8.5$ Hz, 2 H), 7.38 (d, $J = 8.5$ Hz, 2 H), 6.16 (t, $J = 5.5$ Hz, 1 H), 3.05 (q, $J = 6.6$ Hz, 2 H), 1.50-1.35 (m, 6 H), 1.25 (s, 12 H), 0.84 (t, $J = 6.6$ Hz, 3 H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ...
155.6, 144.3, 136.0, 117.1, 83.9, 39.7, 31.7, 30.4, 26.8, 25.4, 22.8, 14.6; HRMS (APCI-TOF) calcd for C$_{19}$H$_{32}$BN$_2$O$_3$ [M+H]$^+$: 347.2500, found: 347.2530.

![Compound 3-32c](image)

1-Phenyl-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)urea (3-32c).

White solid (97%). $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 8.80 (s, 1 H), 8.69 (s, 1 H), 7.65-7.53 (m, 2 H), 7.47 (d, $J=6.2$ Hz, 2 H), 7.44 (d, $J=6.2$ Hz, 2 H), 7.27 (t, $J=7.8$ Hz, 2 H), 7.03–6.90 (m, 1 H), 1.26 (s, 12 H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$ 153.0, 143.4, 140.2, 136.1, 129.5, 122.7, 122.6, 119.0, 117.8, 84.0, 25.4; HRMS (ESI-TOF) calcd for C$_{19}$H$_{24}$BN$_2$O$_3$ [M+H]$^+$: 339.1878, found: 339.1888.

![Compound 3-32d](image)

1-(4-Methoxyphenyl)-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)urea (3-32d). White solid (99%); $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 8.71 (s, 1 H), 8.49 (s, 1 H), 7.56 (d, $J=8.5$ Hz, 2 H), 7.44 (d, $J=8.5$ Hz, 2 H), 7.34 (d, $J=9.1$ Hz, 2 H), 6.85 (d, $J=9.1$ Hz, 2 H), 3.70 (s, 3 H), 1.26 (s, 12 H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$ 155.3, 153.2, 143.6, 136.1, 133.2, 120.8, 117.6, 114.7, 84.0, 55.8, 25.4; HRMS (APCI-TOF) calcd for C$_{20}$H$_{26}$BN$_2$O$_4$ [M+H]$^+$: 369.184, found: 369.186.
1-(3,5-Bis(trifluoromethyl)phenyl)-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)urea (3-32e). White solid (90%); $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 9.40 (s, 1 H), 9.12 (s, 1 H), 8.12 (s, 2 H), 7.63 (s, 1 H), 7.60 (d, $J = 7.8$ Hz, 2 H), 7.50 (d, $J = 7.8$ Hz, 2 H), 1.27 (s, 12 H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$ 152.9, 142.7, 142.4, 136.1, 131.4 (q, $J = 32$ Hz), 124.0 (q, $J = 272$ Hz), 118.8, 118.7, 118.4, 84.1, 25.4; HRMS (APCI-TOF) calcd for C$_{21}$H$_{22}$BF$_6$N$_2$O$_3$ [M+H]$^+$: 475.1626, found: 475.1639.

1-(4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-3-(4-(trifluoromethyl)-phenyl)urea (3-32f). White solid (100%); $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 9.11 (s, 1 H), 8.94 (s, 1 H), 7.62 (d, $J = 3.0$ Hz, 4 H), 7.59 (d, $J = 8.1$ Hz, 2 H), 7.47 (d, $J = 8.1$ Hz, 2 H), 1.27 (s, 12 H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$ 152.8, 144.0, 143.0, 136.1, 126.8 (d, $J = 3.7$ Hz), 125.2 (q, $J = 270$ Hz), 122.6 (q, $J = 32$ Hz), 118.6, 118.0, 84.1, 25.4; HRMS (APCI-TOF) calcd for C$_{20}$H$_{23}$BF$_3$N$_2$O$_3$ [M+H]$^+$: 407.1752, found: 407.1760.

**General Procedure for the Preparation of Ureidophenyl-Salicylaldehydes**

A stirred mixture of urea-functionalized boronic acid pinacol ester 3-32 (0.50 mmol), 3-tert-butyl-2-hydroxy-5-iodobenzaldehyde 2-7 (0.50 mmol, 1 equiv.), K$_2$CO$_3$ (1.50 mmol, 3 equiv.), PdCl$_2$(PPh$_3$)$_2$ (0.02 mmol, 4 mol%), water (2 mL), and CH$_3$CN (5 mL) was heated at 70°C under argon for 3-12 h. The mixture was cooled to room temperature, diluted with ethyl acetate (50 mL), and washed with H$_2$O, and then dried over anhydrous Na$_2$SO$_4$. Volatiles were removed by evaporation under reduced
pressure, then the residue was purified by column chromatography on silica-gel (10%, then 33% ethyl acetate in n-hexane) to give the resulting salicylaldehydes 3-33 (38-72% yield) as a solid. The yields were not optimized.

1-Benzyl-3-(3’-tert-butyl-5’-formyl-4’-hydroxybiphenyl-4-yl)urea (3-33a). Yellow solid (66%); ¹H NMR (300 MHz, DMSO-d₆) δ 11.76 (s, 1 H), 10.04 (s, 1 H), 8.66 (s, NH), 7.90 (d, J = 2.3 Hz, 1 H), 7.73 (d, J = 2.3 Hz, 1 H), 7.56-7.48 (m, 4 H), 7.35-7.20 (m, 5 H), 6.63 (t, J = 5.9 Hz, NH), 4.30 (d, J = 5.9 Hz, 2 H), 1.42 (s, 9 H); ¹³C NMR (75 MHz, DMSO-d₆) δ 199.7, 159.5, 155.9, 141.0, 140.5, 138.3, 132.6, 132.4, 132.1, 130.3, 129.0, 127.8, 127.4, 127.2, 121.6, 118.8, 43.5, 35.3, 29.8; HRMS (APCI-TOF) calcd for C₂₅H₂₇N₂O₃ [M+H]^+: 403.2016, found: 403.2043.

1-(3’-tert-Butyl-5’-formyl-4’-hydroxybiphenyl-4-yl)-3-hexylurea (3-33b). Yellow solid (50%); ¹H NMR (300 MHz, DMSO-d₆) δ 11.76 (s, 1 H), 10.03 (s, 1 H), 8.48 (s, NH), 7.89 (d, J = 2.3 Hz, 1 H), 7.72 (d, J = 2.3 Hz, 1 H), 7.58-7.42 (m, 4 H), 6.12 (t, J = 5.5 Hz, NH), 3.07 (q, J = 5.9 Hz, 2 H), 1.42 (s, 9 H), 1.26 (m, 8 H), 0.86 (t, J = 6.6 Hz, 3 H); ¹³C NMR (75 MHz, DMSO-d₆) δ 199.7, 159.5, 155.8, 140.7, 138.2, 132.4, 131.1, 130.3,
127.2, 121.6, 118.6, 39.7, 35.3, 31.7, 30.4, 29.8, 26.8, 22.8, 14.6; HRMS (APCI-TOF) calcd for C$_{24}$H$_{32}$N$_2$O$_3$Na [M+Na]$^+$: 419.2305, found: 419.2327.

![Chemical Structure](image)

1-(3'-*tert*-Butyl-5'-formyl-4'-hydroxybiphenyl-4-yl)-3-phenylurea (3-33c). Beige solid (72%); $^1$H NMR (300 MHz, DMSO-$d_6$) δ 11.79 (s, 1 H), 10.05 (s, 1 H), 8.77 (s, NH), 8.67 (s, NH), 7.92 (d, $J = 2.3$ Hz, 1 H), 7.74 (d, $J = 2.3$ Hz, 1 H), 7.57 (m, 4 H), 7.45 (m, 2 H), 7.27 (t, $J = 7.9$ Hz, 2 H), 6.96 (m, 2 H), 1.43 (s, 9 H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 199.7, 159.6, 153.2, 140.3, 139.7, 138.3, 133.3, 132.5, 132.0, 130.4, 129.5, 127.4, 122.6, 121.6, 119.3, 118.9, 35.3, 29.8; HRMS (ESI-TOF) calcd for C$_{24}$H$_{25}$N$_2$O$_3$ [M+H]$^+$: 389.1860, found: 389.1879.

![Chemical Structure](image)

1-(3'-*tert*-Butyl-5'-formyl-4'-hydroxybiphenyl-4-yl)-3-(4-methoxyphenyl)urea (3-33d). Yellow solid (38%); $^1$H NMR (300 MHz, DMSO-$d_6$) δ 11.77 (s, 1 H), 10.05 (s, 1 H), 8.68 (s, NH), 8.47 (s, NH), 7.92 (d, $J = 2.3$ Hz, 1 H), 7.74 (d, $J = 2.3$ Hz, 1 H), 7.64-7.46 (m, 4 H), 7.43-7.27 (m, 2 H), 6.77-6.95 (m, 2 H), 3.70 (s, 3 H), 1.43 (s, 9 H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 199.7, 159.6, 155.2, 153.4, 139.9, 138.3, 133.3, 133.1, 132.5, 130.4, 127.3, 121.7, 120.8, 119.2, 114.7, 55.9, 35.3, 29.8; HRMS (APCI-TOF) calcd for C$_{25}$H$_{27}$N$_2$O$_4$ [M+H]$^+$: 419.1965, found: 419.1972.

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1-(3,5-Bis(trifluoromethyl)phenyl)-3-(3'-tert-butyl-5'-formyl-4'-hydroxybiphenyl-4-yl)urea (3-33e). Yellow solid (60%); \(^1\)H NMR (300 MHz, DMSO-\(d_6\)) \(\delta\) 11.78 (s, 1 H), 10.05 (s, 1 H), 9.39 (s, NH), 9.09 (s, NH), 8.14 (s, 2 H), 7.93 (d, \(J = 2.1\) Hz, 1 H), 7.75 (d, \(J = 2.1\) Hz, 1 H), 7.63-7.56 (m, 5 H), 1.43 (s, 9 H); \(^{13}\)C NMR (75 MHz, DMSO-\(d_6\)) \(\delta\) 199.7, 159.7, 153.1, 142.5, 139.0, 138.3, 134.0, 132.5, 131.8, 131.4 (q, \(J = 33\) Hz), 130.8, 130.5, 127.3, 124.0 (q, \(J = 272\) Hz), 121.7, 120.0, 118.7, 35.3, 29.8; HRMS (ESI-TOF) calcd for C\(_{26}\)H\(_{23}\)F\(_6\)N\(_2\)O\(_3\) [M+H]\(^+\): 525.1607, found: 525.1613.

1-(3'-tert-Butyl-5'-formyl-4'-hydroxybiphenyl-4-yl)-3-(4-(trifluoromethyl)-phenyl) urea (3-33f). Yellow solid (59%); \(^1\)H NMR (300 MHz, DMSO-\(d_6\)) \(\delta\) 11.78 (s, 1 H), 10.05 (s, 1 H), 9.10 (s, NH), 8.90 (s, NH), 7.93 (d, \(J = 2.0\) Hz, 1 H), 7.75 (d, \(J = 2.3\) Hz, 1 H), 7.68-7.55 (m, 8 H), 1.43 (s, 9 H); \(^{13}\)C NMR (75 MHz, DMSO-\(d_6\)) \(\delta\) 199.6, 159.7, 152.9, 144.1, 139.3, 138.3, 133.7, 132.5, 131.9, 130.5, 127.4, 126.8, 125.2 (q, \(J = 270\) Hz), 122.5 (q, \(J = 32\) Hz), 121.7, 119.6, 118.6, 35.3, 29.8; HRMS (ESI-TOF) calcd for C\(_{25}\)H\(_{24}\)F\(_3\)N\(_2\)O\(_3\) [M+H]\(^+\): 457.1734, found: 457.1749.
General Procedure for the Preparation of Ureidophenyl-Salen Ligands

To a solution of (1R,2R)-cyclohexane-1,2-diamine (0.20 mmol) in THF (8 mL), urea functionalized salicylaldehyde 3-33 (0.40 mmol) was added at room temperature, and then allowed to stir for 3-20 h. The solution was concentrated under reduced pressure, and the residue was purified by column chromatography on silica-gel (ethyl acetate) to give the resulting salen as a yellow solid. The yields were not optimized.

3-34a. Yellow solid (71%); \(^1\)H NMR (300 MHz, DMSO-\(d_6\)) \(\delta\) 14.15 (s, 2 H), 8.60 (s, 2 H), 8.52 (s, 2 H), 7.43-7.20 (m, 12 H), 6.59 (t, \(J = 6.0\) Hz, 2 H), 4.30 (d, \(J = 5.7\) Hz, 4 H), 3.46-3.38 (m, 2 H), 2.01-1.91 (m, 2 H), 1.86-1.76 (m, 2 H), 1.75-1.60 (m, 2 H), 1.52-1.41 (m, 2 H), 1.36 (s, 18 H); \(^{13}\)C NMR (75 MHz, DMSO-\(d_6\)) \(\delta\) 167.1, 159.6, 155.8, 141.0, 139.9, 137.3, 133.5, 130.4, 129.0, 128.0, 127.8, 127.4, 126.9, 119.0, 118.7, 71.6, 43.4, 35.2, 33.1, 29.8, 24.5; HRMS (APCI-TOF) calcd for C\(_{56}\)H\(_{62}\)N\(_6\)O\(_4\)Na [M+Na]\(^+\): 905.4725, found: 905.4718.

3-34b. Yellow solid (72%); \(^1\)H NMR (300 MHz, DMSO-\(d_6\)) \(\delta\) 14.14 (s, 2 H), 8.52 (s, 2 H), 8.41 (s, 2 H), 7.42-7.28 (m, 8 H), 6.08 (t, \(J = 5.7\) Hz, 2 H), 3.47-3.40 (m, 2 H), 3.06 (q, \(J = 6.5\) Hz, 4 H), 2.02-1.91 (m, 2 H), 1.88-1.76 (m, 2 H), 1.75-1.60 (m, 2 H), 1.50-1.47 (m, 2 H), 1.35 (s, 18 H), 1.31-1.19 (m, 16 H), 0.86 (t, \(J = 6.5\) Hz, 6 H); \(^{13}\)C NMR (75
MHZ, DMSO-\textit{d}_6) \delta 167.1, 159.6, 155.8, 140.0, 137.3, 133.2, 130.4, 127.9, 127.8, 126.8, 119.0, 118.5, 71.6, 39.7, 35.2, 33.0, 31.7, 30.4, 29.8, 26.7, 24.5, 22.8, 14.6; HRMS (APCI-TOF) calcd for C_{54}H_{75}N_{6}O_{4} [M+H]^+: 871.5844, found: 871.5858.

3-34c. Yellow solid (88%); \(^1\)H NMR (300 MHz, DMSO-\textit{d}_6) \delta 14.18 (s, 2 H), 8.70 (s, 2 H), 8.64 (s, 2 H), 8.54 (s, 2 H), 7.48-7.35 (m, 16 H), 7.27 (t, J = 7.6 Hz, 4 H), 6.95 (t, J = 7.2 Hz, 2 H), 3.51-3.41 (m, 2 H), 2.02-1.92 (m, 2 H), 1.88-1.78 (m, 2 H), 1.75-1.62 (m, 2 H), 1.54-1.43 (m, 2 H), 1.37 (s, 18 H); \(^{13}\)C NMR (75 MHz, DMSO-\textit{d}_6) \delta 167.1, 159.7, 153.1, 140.3, 139.1, 137.4, 143.2, 130.2, 129.4, 128.0, 127.9, 127.0, 122.5, 119.1, 119.0, 118.9, 71.6, 35.2, 33.1, 29.8, 24.5; HRMS (APCI-TOF) calcd for C_{54}H_{59}N_{6}O_{4} [M+H]^+: 855.4594, found: 855.4593.

3-34d. Yellow solid (83%); \(^1\)H NMR (300 MHz, DMSO-\textit{d}_6) \delta 14.14 (s, 2 H), 8.59 (s, 2 H), 8.51 (s, 2 H), 8.41 (s, 2 H), 7.41 (d, J = 8.7 Hz, 4 H), 7.35-7.29 (m, 12 H), 6.82 (d, J = 8.9 Hz, 4 H), 3.66 (s, 6 H), 3.44-3.42 (m, 2 H), 1.97-1.91 (m, 2 H), 1.82-1.77 (m, 2 H), 1.70-1.60 (m, 2 H), 1.49-1.39 (m, 2 H), 1.33 (s, 18 H); \(^{13}\)C NMR (75 MHz, DMSO-\textit{d}_6) \delta 167.6, 159.7, 155.1, 153.3, 139.3, 137.3, 133.9, 133.3, 132.2, 130.3, 128.2, 127.0, 120.7, 119.1, 119.0, 114.6, 71.1, 55.9, 35.2, 33.1, 29.8, 23.1; HRMS (APCI-TOF) calcd for C_{56}H_{63}N_{6}O_{6} [M+H]^+: 915.4804, found: 915.4817.
3-34e. Yellow solid (86%); \(^1\)H NMR (300 MHz, DMSO-\(\text{d}_6\)) \(\delta\) 14.20 (s, 2 H), 9.37 (s, 2 H), 9.02 (s, 2 H), 8.54 (s, 2 H), 7.62 (s, 2 H), 7.52-7.37 (m, 12 H), 3.46-3.44 (m, 2 H), 1.99-1.96 (m, 2 H), 1.83-1.81 (m, 2 H), 1.70-1.68 (m, 2 H), 1.50-1.47 (m, 2 H), 1.37 (s, 18 H); \(^{13}\)C NMR (75 MHz, DMSO-\(\text{d}_6\)) \(\delta\) 167.1, 159.9, 153.0, 142.5, 138.4, 137.4, 134.9, 132.0, 131.4 (q, \(J\) = 32 Hz), 130.1, 128.1, 127.9, 127.0, 124.0 (q, \(J\) = 271 Hz), 199.8, 119.1, 118.6, 71.6, 35.2, 33.0, 29.8, 24.9; HRMS (APCI-TOF) calcd for C\(_{58}\)H\(_{55}\)F\(_{12}\)N\(_6\)O\(_4\) [M+H]\(^+\): 1127.4088, found: 1127.4098.

3-34f. Yellow solid (46%); \(^1\)H NMR (300 MHz, DMSO-\(\text{d}_6\)) \(\delta\) 14.19 (s, 2 H), 9.07 (s, 2 H), 8.84 (s, 2 H), 8.54 (s, 2 H), 7.69-7.58 (m, 8 H), 7.52-7.34 (m, 12 H), 3.49-3.42 (m, 2 H), 2.03-1.92 (m, 2 H), 1.87-1.79 (m, 2 H), 1.75-1.63 (m, 2 H), 1.54-1.44 (m, 2 H), 1.37 (s, 18 H); \(^{13}\)C NMR (75 MHz, DMSO-\(\text{d}_6\)) \(\delta\) 167.1, 159.8, 152.9, 144.1, 138.7, 137.4, 134.6, 130.2, 128.1, 128.0, 127.0, 126.7, 125.2 (q, \(J\) = 270 Hz), 122.4 (q, \(J\) = 32 Hz), 119.4, 119.1, 118.5, 71.6, 35.2, 33.1, 29.8, 24.5; HRMS (APCI-TOF) calcd for C\(_{56}\)H\(_{57}\)F\(_6\)N\(_6\)O\(_4\) [M+H]\(^+\): 991.4340, found: 991.4364.

**General Procedure for the Preparation of Bis-Urea (Salen)Co Complexes**

To a solution or suspension of an appropriate salen ligand 3-34 (0.21 mmol) in EtOH (5 mL), Co(OAc)\(_2\)•4H\(_2\)O (0.21 mmol, 1.0 equiv) was added, and heated at reflux
for 3 h under argon. Precipitate was collected by filtration, washed by EtOH, and then
dried under vacuum for 24 h to give a (salen)cobalt complex.

3-28a. Reddish brown solid (72%); HRMS (APCI-TOF) calcd for C$_{56}$H$_{60}$CoN$_{6}$O$_{4}$

3-28b. Brown solid (81%); HRMS (ESI-TOF) calcd for C$_{54}$H$_{72}$CoN$_{6}$O$_{4}$ [M]$^+$: 927.4942, found: 927.4896.

3-28c. Reddish brown solid (87%); HRMS (ESI-TOF) calcd for C$_{54}$H$_{56}$CoN$_{6}$O$_{4}$ [M]$^+$: 911.3690, found: 911.3704.

3-28d. Reddish brown solid (57%); HRMS (ESI-TOF) calcd for C$_{58}$H$_{60}$CoN$_{6}$O$_{6}$
[M]$^+$: 971.3901, found: 971.3861.
3-28e. Reddish brown solid (81%); HRMS (APCI-TOF) calcd for C\textsubscript{58}H\textsubscript{52}CoF\textsubscript{12}N\textsubscript{6}O\textsubscript{4} [M]\textsuperscript{+}: 1183.3190, found: 1183.3168.

3-28f. Red solid (83%); HRMS (ESI-TOF) calcd for C\textsubscript{56}H\textsubscript{54}CoF\textsubscript{6}N\textsubscript{6}O\textsubscript{4} [M]\textsuperscript{+}: 1047.3437, found: 1047.3419.

**General Procedure for the Preparation of Ureidomethylene-salicylaldehydes**

This reaction was carried out using known procedures. To a solution of 5-(azidomethyl)-3-tert-butyl-2-hydroxybenzaldehyde 3-40 (1.26 mmol) in ethyl acetate (10mL), an appropriate isocyanate (1.26 mmol, 1.0 equiv) was added. After addition of Pd-C (10 wt %, ~30 mg), the mixture was then allowed to stir overnight under a hydrogen balloon. This reaction mixture was filtered through Celite, and washed with ethyl acetate. The filtrate was concentrated under reduced pressure, and the residue was purified by column chromatography on silica-gel (n-hexane:EtOAc 2:1) to give the resulting salicylaldehyde. Yields were not optimized.
1-Benzyl-3-(3-<sup>tert</sup>-butyl-5-formyl-4-hydroxybenzyl)urea (3-40a). White solid (63%). <sup>1</sup>H NMR (300 MHz, DMSO-<em>d</em><sub>6</sub>) δ 11.72 (s, 1 H), 9.93 (s, 1 H), 7.50-7.46 (m, 2 H), 7.31-7.18 (m, 5 H), 6.46 (t, <em>J</em> = 6.0 Hz, 2 H), 4.22 (d, <em>J</em> = 6.6 Hz, 2 H), 4.20 (d, <em>J</em> = 6.3 Hz, 2 H), 1.36 (s, 9 H); <sup>13</sup>C NMR (75 MHz, DMSO-<em>d</em><sub>6</sub>) δ 198.5, 158.7, 158.1, 140.9, 137.1, 133.7, 132.0, 132.4, 126.8, 126.5, 120.3, 42.9, 42.3, 34.4, 29.0; HRMS (ESI-TOF) calcd for C<sub>20</sub>H<sub>25</sub>N<sub>2</sub>O<sub>3</sub> [M+H]^+: 341.1860, found: 341.1861.

![Chemical Structure](image)

1-(3-<sup>tert</sup>-Butyl-5-formyl-4-hydroxybenzyl)-3-hexylurea (3-40b). Colorless oil (83%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 11.65 (s, 1 H), 9.70 (s, 1 H), 7.33 (d, <em>J</em> = 2.3 Hz, 1 H), 7.18 (d, <em>J</em> = 2.3 Hz, 1 H), 5.75 (t, <em>J</em> = 5.3 Hz, 1 H), 5.37 (t, <em>J</em> = 5.3 Hz, 1 H), 4.15 (d, <em>J</em> = 5.7 Hz, 2 H), 3.04 (q, <em>J</em> = 6.7 Hz, 2 H), 1.41-1.36 (m, 2 H), 1.34 (s, 9 H), 1.27-1.14 (m, 6 H), 0.83 (t, <em>J</em> = 6.8 Hz, 3 H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 196.8, 160.1, 158.8, 138.4, 133.3, 130.2, 129.9, 120.2, 43.4, 40.4, 34.7, 31.5, 30.2, 29.1, 26.5, 22.5, 14.0; HRMS (APCI-TOF) calcd for C<sub>19</sub>H<sub>31</sub>N<sub>2</sub>O<sub>3</sub> [M+H]^+: 335.2329, found: 335.2318.

1-(3-<sup>tert</sup>-Butyl-5-formyl-4-hydroxybenzyl)-3-octadecylurea (3-40c). White solid (66%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 11.73 (s, 1 H), 9.84 (s, 1 H), 7.43 (d, <em>J</em> = 2.3 Hz, 1 H), 7.34 (d, <em>J</em> = 2.3 Hz, 1 H), 4.70 (t, <em>J</em> = 5.8 Hz, 1 H), 4.40 (t, <em>J</em> = 5.5 Hz, 1 H), 4.32 (d, <em>J</em> = 5.9 Hz, 2 H), 3.19-3.13 (m, 2 H), 1.49-1.45 (m, 2 H), 1.40 (s, 9 H), 1.25 (s, 30 H), 0.88
(t, J = 6.8 Hz, 3 H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 197.0, 160.5, 158.0, 138.7, 133.7, 130.5, 130.0, 120.4, 43.9, 40.7, 34.9, 31.9, 30.2, 29.7, 29.7, 29.6, 29.6, 29.4, 29.4, 29.2, 26.9, 22.7, 14.1; HRMS (ESI-TOF) calcd for C$_{31}$H$_{55}$N$_2$O$_3$ [M+H]$^+$: 503.4207, found: 503.4200.

1-(3-tert-Butyl-5-formyl-4-hydroxybenzyl)-3-phenylurea (3-40d). White solid (72%). $^1$H NMR (300 MHz, DMSO-d$_6$) δ 11.75 (s, 1 H), 9.96 (s, 1 H), 8.54 (s, 1 H), 7.55-7.52 (m, 2 H), 7.40 (d, J = 8.4 Hz, 2 H), 7.22 (t, J = 8.0 Hz, 2 H), 6.88 (t, J = 7.4 Hz, 1 H), 6.61 (t, J = 6.0 Hz), 4.26 (d, J = 6.0 Hz, 2 H), 1.35 (s, 9 H); $^{13}$C NMR (125 MHz, DMSO-d$_6$) δ 198.6, 158.9, 155.2, 140.4, 137.1, 133.5, 131.4, 130.5, 128.6, 121.1, 120.4, 117.7, 42.1, 34.4, 29.0; HRMS (ESI-TOF) calcd for C$_{19}$H$_{23}$N$_2$O$_3$ [M+H]$^+$: 327.1703, found: 327.1702.

1-(3-tert-Butyl-5-formyl-4-hydroxybenzyl)-3-(4-methoxyphenyl)urea (3-40e).

White solid (42%). $^1$H NMR (300 MHz, CDCl$_3$) δ 11.69 (s, 1 H), 9.73 (s, 1 H), 7.37 (d, J = 2.0 Hz, 2 H), 7.23 (s, 1 H), 7.12 (d, J = 8.8 Hz, 2 H), 6.78 (d, J = 8.8 Hz, 2 H), 5.40 (s, 1 H), 4.27 (d, J = 5.7 Hz, 2 H), 3.74 (s, 3 H), 1.37 (s, 9 H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 196.9, 160.4, 156.9, 156.8, 138.6, 133.4, 130.7, 130.3, 129.7, 124.4, 120.3, 114.5, 55.4,
43.4, 34.8, 29.1; HRMS (ESI-TOF) calcd for C_{20}H_{24}N_{2}O_{4}Na [M+Na]^+: 379.1628, found: 379.1634.

1-(3,5-Bis(trifluoromethyl)phenyl)-3-(3-tert-butyl-5-formyl-4-hydroxybenzyl)-urea (3-40f). White solid (68%). \(^1\)H NMR (300 MHz, DMSO-\(d_6\)) \(\delta\) 11.77 (s, 1 H), 9.98 (s, 1 H), 9.38 (s, 1 H), 8.11 (s, 2 H), 7.56-7.55 (m, 3 H), 7.05 (t, \(J = 5.7\) Hz, 1 H), 4.31 (d, \(J = 5.9\) Hz, 2 H), 1.38 (s, 9 H); \(^{13}\)C NMR (75 MHz, DMSO-\(d_6\)) \(\delta\) 198.6, 158.9, 154.8, 142.5, 137.2, 133.4, 131.2, 131.0, 130.6 (q, \(J = 32\) Hz), 130.5, 123.4 (q, \(J = 271\) Hz), 120.4, 117.3, 42.2, 34.4, 29.0; HRMS (ESI-TOF) calcd for C_{21}H_{24}F_{6}N_{3}O_{3} [M+NH\_4]^+: 480.1716, found: 480.1743.

1-(3-tert-Butyl-5-formyl-4-hydroxybenzyl)-3-(4-fluorophenyl)urea (3-40g).

White solid (73%). \(^1\)H NMR (300 MHz, DMSO-\(d_6\)) \(\delta\) 11.77 (s, 1 H), 9.97 (s, 1 H), 8.60 (s, 1 H), 7.55-7.53 (m, 2 H), 7.43-7.38 (m, 2 H), 7.09-7.03 (m, 2 H), 6.62 (t, \(J = 5.9\) Hz, 1 H), 4.27 (d, \(J = 5.9\) Hz, 2 H), 1.38 (s, 9 H); \(^{13}\)C NMR (75 MHz, DMSO-\(d_6\)) \(\delta\) 198.6, 158.9, 156.9 (d, \(J = 236\) Hz), 155.3, 137.1, 136.8 (d, \(J = 2.6\) Hz), 133.5, 131.4, 130.5, 120.4, 119.3 (d, \(J = 7.7\) Hz), 115.1 (d, \(J = 22\) Hz), 42.2, 34.4, 29.1; HRMS (ESI-TOF) calcd for C_{19}H_{22}F_{2}N_{2}O_{3} [M+H]^+: 345.1609, found: 345.1614.

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1-(3-tert-Butyl-5-formyl-4-hydroxybenzyl)-3-(4-chlorophenyl)urea (3-40h).

White solid (65%). $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 11.76 (s, 1 H), 9.97 (s, 1 H), 8.71 (s, 1 H), 7.54-7.53 (m, 2 H), 7.45-7.42 (m, 2 H), 7.27-7.24 (m, 2 H), 6.67 (t, $J$ = 5.9 Hz, 1 H), 4.27 (d, $J$ = 5.9 Hz, 2 H), 1.38 (s, 9 H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$ 198.6, 158.9, 155.0, 139.4, 137.1, 133.5, 131.2, 130.5, 128.4, 124.5, 120.4, 119.2, 42.1, 34.4, 29.0; HRMS (ESI-TOF) calcd for C$_{19}$H$_{22}$N$_2$O$_3$ [M+H]$^+$: 361.1313, found: 361.1325.

1-(3-tert-Butyl-5-formyl-4-hydroxybenzyl)-3-(4-(trifluoromethyl)phenyl)urea (3-40k). White solid (71%). $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 11.77 (s, 1 H), 9.97 (s, 1 H), 9.03 (s, 1 H), 7.63-7.54 (m, 6 H), 6.81 (t, $J$ = 5.9 Hz, 1 H), 4.29 (d, $J$ = 5.9 Hz, 2 H), 1.38 (s, 9 H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$ 198.6, 158.9, 154.9, 144.2, 137.2, 133.5, 131.1, 130.5, 126.0, 124.6 (q, $J$ = 270 Hz), 121.0 (q, $J$ = 32 Hz), 120.4, 117.3, 42.2, 34.4, 29.0; HRMS (ESI-TOF) calcd for C$_{20}$H$_{22}$F$_3$N$_2$O$_3$ [M+H]$^+$: 395.1577, found: 395.1580.
1-(3-tert-Butyl-5-formyl-4-hydroxybenzyl)-3-(2,6-diisopropylphenyl)urea (3-40I). White solid (66%). $^1$H NMR (300 MHz, DMSO-$d_6$) δ 11.71 (s, 1 H), 9.95 (s, 1 H), 7.57 (s, 1 H), 6.64 (s, 1 H), 4.24 (s, 2 H), 3.13 (m, 2 H), 1.38 (s, 9 H), 1.09 (d, $J = 6.8$ Hz, 12 H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 198.2, 158.7, 157.0, 146.7, 137.0, 133.2, 133.0, 132.2, 130.3, 126.9, 122.7, 120.2, 42.3, 34.4, 29.0, 27.9, 23.6; HRMS (ESI-TOF) calcd for C$_{25}$H$_{35}$N$_2$O$_3$ [M+H]$^+$: 411.2642, found: 411.2632.

Synthesis of 4-(Aminomethyl)-2-tert-butyl-6-(1,3-dioxan-2-yl)phenol

![Image](https://via.placeholder.com/150)

4-(Azidomethyl)-2-tert-butyl-6-(1,3-dioxan-2-yl)phenol (3-42). To a mixture of 5-(azidomethyl)-3-tert-butyl-2-hydroxybenzaldehyde 3-40 (596 mg, 2.56 mmol), 1,3-propanediol (0.74 mL, 10.23 mmol), and a catalytic amount of tetra-n-butyrammonium tribromide (123 mg, 0.25 mmol) was added. After stirring at room temperature for 20 h, the reaction was quenched by adding saturated aqueous NaHCO$_3$ solution. The mixture was extracted twice with EtOAc and the combined organic layers were washed with brine. After drying over anhydrous Na$_2$SO$_4$, the solvent was removed in vacuo. The residue was purified by column chromatography on silica-gel (n-hexane:EtOAc 5:1) to give 3-42 (506 mg, 68%) as a colorless oil. $^1$H NMR (300 MHz, CDCl$_3$) δ 8.20 (s, 1 H), 7.18 (d, $J = 2.0$ Hz, 1 H), 7.03 (d, $J = 2.3$ Hz, 1 H), 5.63 (s, 1 H), 4.34-4.28 (m, 2 H), 4.23 (s, 2 H), 4.05-3.96 (m, 2 H), 2.33-2.21 (m, 1 H), 1.54-1.47 (m, 1 H), 1.42 (s, 9 H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 154.4, 137.9, 127.9, 125.7, 125.6, 122.7, 103.2, 67.5, 54.8,
34.9, 29.4, 25.6; HRMS (ESI-TOF) calcd for C_{15}H_{22}N_{3}O_{3} [M+H]^+: 292.1656, found: 292.1656.

![Chemical Structure](image)

**4-(Aminomethyl)-2-tert-butyl-6-(1,3-dioxan-2-yl)phenol (3-43)**. To a solution of 3-42 (506 mg, 1.74 mmol) in ethyl acetate (10 mL), Pd-C (10 wt %, 40 mg) was added. The mixture was then allowed to stir overnight under a hydrogen balloon. This reaction mixture was filtered through Celite, and washed with ethyl acetate. The filtrate was concentrated under reduced pressure to give 3-43 (446 mg, 77%) as a white solid. This crude compound was used for the next step without further purification. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.01 (s, 1 H), 7.17 (d, $J = 1.7$ Hz, 1 H), 7.01 (d, $J = 2.3$ Hz, 1 H), 5.62 (s, 1 H), 4.35-4.29 (m, 2 H), 4.01 (t, $J = 12.2$ Hz, 2 H), 3.75 (s, 2 H), 2.32-2.22 (m, 1 H), 1.54-1.47 (m, 1 H), 1.40 (s, 9H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 153.1, 137.5, 133.5, 126.8, 124.3, 122.4, 103.6, 67.5, 46.2, 34.9, 29.6, 25.6.

**General Procedure for the Preparation of 3-41g and 3-41h**

To a solution of 4-(aminomethyl)-2-tert-butyl-6-(1,3-dioxan-2-yl)phenol 3-43 (0.25 mmol) in CH$_2$Cl$_2$ (3.0 mL) at 0°C, an appropriate isocyanate (0.25 mmol, 1.0 equiv) was added. After stirring at this temperature for 1 h, the reaction mixture was allowed to warm up to room temperature. After stirring overnight at room temperature, the solvent was removed under reduced pressure. The residue was dissolved in EtOAc (10 mL), and then the organic layer was washed with aqueous 2 N HCl (10 mL). After removing the solvent under reduced pressure, the residue was dissolved in THF (3 mL), and then
10% HCl (0.2 mL) was added to this solution at room temperature. After stirring for 2 h at this temperature, the solvent was removed under reduced pressure. The residue was dissolved in EtOAc (10 mL), and then the organic layer was washed with water and saturated aqueous NaHCO₃. After drying over anhydrous Na₂SO₄, the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica-gel (n-hexane:EtOAc 2:1) to give the resulting salicylaldehyde.

\[
\text{1-(4-Bromophenyl)-3-(3-tert-butyl-5-formyl-4-hydroxybenzyl)urea (3-41g).}
\]
Beige solid (66%). \(^1\)H NMR (300 MHz, DMSO-\(d_6\)) \(\delta\) 11.76 (s, 1 H), 9.97 (s, 1 H), 8.72 (s, 1 H), 7.55 (s, 1 H), 7.54 (s, 1 H), 7.39 (s, 4 H), 6.68 (t, \(J = 5.8\) Hz, 1 H), 4.27 (d, \(J = 5.9\) Hz, 2 H), 1.38 (s, 9 H); \(^{13}\)C NMR (75 MHz, DMSO-\(d_6\)) \(\delta\) 198.5, 158.8, 155.0, 139.8, 137.1, 133.4, 131.3, 131.2, 130.4, 120.3, 119.6, 112.4, 42.1, 34.4, 29.1; HRMS (ESI-TOF) calcd for C\(_{19}\)H\(_{22}\)BrN\(_2\)O\(_3\) [M+H]\(^+\): 405.0808, found: 405.0812.

\[
\text{1-(3-tert-Butyl-5-formyl-4-hydroxybenzyl)-3-(4-cyanophenyl)urea (3-41h).}
\]
White solid (85%). \(^1\)H NMR (300 MHz, DMSO-\(d_6\)) \(\delta\) 11.77 (s, 1 H), 9.98 (s, 1 H), 9.14 (s, 1 H), 7.68-7.65 (m, 2 H), 7.60-7.56 (m, 2 H), 7.56 (d, \(J = 2.4\) Hz, 1 H), 7.54 (d, \(J = 2.4\) Hz, 1 H), 6.87 (t, \(J = 5.7\) Hz, 1 H), 4.29 (d, \(J = 5.9\) Hz, 2 H), 1.38 (s, 9 H); \(^{13}\)C NMR (75 MHz, DMSO-\(d_6\)) \(\delta\) 198.5, 158.9, 154.6, 144.8, 137.1, 133.5, 133.1, 131.0, 130.5, 120.3,
119.4, 117.5, 102.4, 42.2, 34.4, 29.0; HRMS (ESI-TOF) calcd for C_{20}H_{21}N_{3}O_{3}Na [M+Na]^+ 374.1475, found: 374.1468.

**General Procedure for the Preparation of Bis-Urea Salen Ligands (3-44)**

To a solution of (1\textit{R},2\textit{R})-cyclohexane-1,2-diamine (0.18 mmol) in THF (5 mL), salicylaldehyde 3-41 (0.36 mmol, 2.0 equiv) was added at room temperature, and then allowed to stir for 3-20 h. The solution was concentrated under reduced pressure, and the residue was purified by column chromatography on silica-gel (\textit{n}-hexane:EtOAc 5:1 then 2:1 or 1:2) to give the resulting bis-urea salen as a yellow solid.

![Chemical Structure of 3-44a](image)

**3-44a.** Yellow solid (99%). ^1H NMR (300 MHz, DMSO-\textit{d}_6) δ 14.03 (s, 2 H), 8.44 (s, 2 H), 7.29-7.14 (m, 12 H), 7.00 (s, 2 H), 6.33-6.25 (m, 4 H), 4.19 (d, J = 6.0 Hz, 4 H), 4.06 (d, J = 5.4 Hz, 4 H), 3.45-3.38 (m, 2 H), 1.93-1.83 (m, 2 H), 1.83-1.74 (m, 2 H), 1.69-1.56 (m, 2 H), 1.49-1.38 (m, 2 H), 1.32 (s, 18 H); ^13C NMR (75 MHz, DMSO-\textit{d}_6) δ 165.9, 158.6, 157.9, 140.9, 136.1, 129.7, 128.4, 128.1, 126.9, 126.5, 117.7, 71.0, 42.9, 42.6, 34.3, 32.5, 29.1, 23.8; HRMS (APCI-TOF) calcd for C_{46}H_{59}N_{6}O_{4} [M+H]^+: 759.4592, found: 759.4620.
3-44b. Yellow solid (94%). $^1$H NMR (300 MHz, CDCl$_3$) δ 13.57 (s, 2 H), 7.94 (s, 2 H), 6.97 (d, $J = 2.0$ Hz, 2 H), 6.03 (s, 2 H), 5.90 (s, 2 H), 5.74 (s, 2 H), 3.74-3.53 (m, 4 H), 3.28-3.25 (m, 2 H), 3.04 (q, $J = 6.3$ Hz, 4 H), 2.17-2.11 (m, 2 H), 1.97-1.94 (m, 2 H), 1.81-1.72 (m, 2 H), 1.55-1.46 (m, 2 H), 1.44-1.37 (m, 4 H), 1.28-1.23 (m, 12 H), 1.21 (s, 18 H), 0.85 (t, $J = 6.8$ Hz, 6 H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 166.4, 159.4, 158.9, 137.0, 128.3, 128.2, 128.0, 117.6, 72.8, 43.2, 40.3, 34.6, 32.7, 31.6, 30.3, 29.5, 29.1, 26.7, 22.6, 14.0; HRMS (ESI-TOF) calcd for C$_{44}$H$_{71}$N$_6$O$_4$ [M+H]$^+$: 747.5531, found: 747.5526.

3-44c. Yellow solid (92%). $^1$H NMR (300 MHz, CDCl$_3$) δ 13.71 (s, 2 H), 8.01 (s, 2 H), 7.07 (s, 2 H), 6.34 (s, 2 H), 5.21 (s, 2 H), 5.13 (s, 2 H), 3.97-3.74 (m, 4 H), 3.28-3.25 (m, 2 H), 3.11 (td, $J = 6.5$, 6.5 Hz, 4 H), 2.13-1.79 (m, 6 H), 1.54-1.38 (m, 6 H), 1.31 (s, 18H), 1.26 (s, 60 H), 0.88 (t, $J = 6.8$ Hz, 6 H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 166.3, 159.2, 158.7, 137.2, 128.4, 128.1, 117.8, 72.5, 43.8, 40.5, 34.7, 32.7, 32.0, 30.4, 29.7, 29.5, 29.4, 29.3, 27.0, 24.4, 22.7, 14.1; HRMS (ESI-TOF) calcd for C$_{68}$H$_{119}$N$_6$O$_4$ [M+H]$^+$: 1083.9287, found: 1083.9223.

3-44d. Yellow solid (81%). $^1$H NMR (300 MHz, DMSO-d$_6$) δ 14.09 (s, 2 H), 8.48 (s, 2 H), 8.39 (s, 2 H), 7.36-7.16 (m, 10 H), 7.07 (s, 2 H), 6.88 (t, $J = 7.2$ Hz, 2 H), 6.43 (t, $J$
1H NMR (300 MHz, CDCl3) δ 13.63 (s, 2 H), 7.95 (s, 2 H), 7.62 (s, 2 H), 7.05-7.00 (m, 6 H), 6.66 (d, J = 9.1 Hz, 4 H), 6.12 (s, 2 H), 6.03 (s, 2 H), 3.73-3.63 (m, 4 H), 3.70 (s, 6 H), 3.31-3.28 (m, 2 H), 2.18-2.14 (m, 2 H), 2.00-1.97 (m, 2 H), 1.84-1.81 (m, 2 H), 1.63-1.55 (m, 2 H), 1.18 (s, 18 H); 13C NMR (75 MHz, CDCl3) δ 166.4, 159.0, 157.5, 155.5, 137.1, 131.9, 128.2, 127.7, 122.2, 117.6, 114.0, 73.0, 55.3, 43.0, 34.5, 32.7, 29.1, 24.6; HRMS (APCI-TOF) calcd for C46H59N6O6 [M+H]+: 791.4491, found: 791.4493.

3-44f. Yellow solid (86%). 1H NMR (300 MHz, DMSO-d6) δ 14.10 (s, 2 H), 9.22 (s, 2 H), 8.47 (s, 2 H), 8.07 (s, 4 H), 7.53 (s, 2 H), 7.16 (d, J = 2.0 Hz, 2 H), 7.06 (d, J = 1.7 Hz, 2 H), 6.87 (t, J = 5.9 Hz, 2 H), 4.14 (d, J = 6.2 Hz, 4 H), 3.45-3.38 (m, 2 H), 1.93-1.83 (m, 2 H), 1.83-1.74 (m, 2 H), 1.69-1.56 (m, 2 H), 1.49-1.38 (m, 2 H), 1.25 (s, 18 H); HRMS (APCI-TOF) calcd for C46H59N6O6 [M+H]+: 791.4493, found: 791.4493.
\[ ^{13}C \text{ NMR} (75 \text{ MHz, DMSO-d}_6) \delta 165.8, 158.7, 154.6, 142.5, 136.2, 130.5 (q, J = 32 \text{ Hz}), 128.9, 128.6, 128.4, 123.4 (q, J = 271 \text{ Hz}), 117.7, 117.1, 113.4, 71.1, 42.4, 34.2, 32.5, 29.0, 23.8; \text{ HRMS (APCI-TOF) calcd for C}_{48}H_{51}F_{12}N_{6}O_{4} [M+H]^+: 1003.3775, \text{ found: 1003.3801.} \]

3-44g. Yellow solid (52%). \(^1H\) NMR (300 MHz, DMSO-d\(_6\)) \(\delta 14.09 \text{ (s, 2 H)}, 8.48-8.45 \text{ (m, 4 H)}, 7.39-7.35 \text{ (m, 4 H)}, 7.18 \text{ (s, 2 H)}, 7.07-7.01 \text{ (m, 4 H)}, 6.41 \text{ (s, 2 H)}, 4.13 \text{ (s, 4 H)}, 3.43 \text{ (m, 2 H)}, 1.93-1.83 \text{ (m, 2 H)}, 1.83-1.74 \text{ (m, 2 H)}, 1.69-1.56 \text{ (m, 2 H)}, 1.49-1.38 \text{ (m, 2 H)}, 1.30 \text{ (s, 18 H)}; \(^{13}C\) NMR (75 MHz, DMSO-d\(_6\)) \(\delta 165.9, 158.8, 156.8 \text{ (d, J = 237 Hz)}, 155.1, 136.8 \text{ (d, J = 2.6 Hz)}, 136.2, 129.1, 128.7, 128.6, 119.2 \text{ (d, J = 7.4 Hz)}, 117.8, 115.0 \text{ (d, J = 22 Hz)}, 71.0, 42.4, 34.3, 32.5, 29.1, 23.8; \text{ HRMS (ESI-TOF) calcd for C}_{44}H_{53}F_{2}N_{6}O_{4} [M+H]^+: 767.4091, \text{ found: 767.4087.} \]

3-44h. Yellow solid (85%). \(^1H\) NMR (300 MHz, CDCl\(_3\)) \(\delta 13.69 \text{ (s, 2 H)}, 7.95 \text{ (s, 4 H)}, 7.06-6.94 \text{ (m, 10 H)}, 6.28 \text{ (s, 2 H)}, 6.04 \text{ (s, 2 H)}, 3.71-3.64 \text{ (m, 4 H)}, 3.31-3.28 \text{ (m, 2 H)}, 2.17-2.13 \text{ (m, 2 H)}, 2.00-1.97 \text{ (m, 2 H)}, 1.84-1.81 \text{ (m, 2 H)}, 1.63-1.55 \text{ (m, 2 H)}, 1.15 \text{ (s, 18 H)}; \(^{13}C\) NMR (75 MHz, CDCl\(_3\)) \(\delta 166.1, 159.2, 157.0, 137.4, 128.8, 128.1, 127.8, 178
127.4, 127.0, 121.3, 121.0, 117.7, 73.0, 43.0, 34.6, 32.7, 29.0, 24.5; HRMS (APCI-TOF) calcd for C_{44}H_{53}Cl_{2}N_{6}O_{4} [M+H]^+: 799.3500, found: 799.3531.

3-44i. Yellow solid (91%). $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 14.09 (s, 2 H), 8.57 (s, 2 H), 8.48 (s, 2 H), 7.44-7.36 (m, 8 H), 7.17 (d, $J = 2.0$ Hz, 2 H), 7.06 (d, $J = 2.0$ Hz, 2 H), 6.50 (t, $J = 5.8$ Hz, 2 H), 4.12 (d, $J = 5.8$ Hz, 4 H), 3.46 (m, 2 H), 1.92-1.88 (m, 2 H), 1.88-1.80 (m, 2 H), 1.76-1.60 (m, 2 H), 1.54-1.44 (m, 2 H), 1.30 (s, 18 H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$ 165.9, 158.9, 155.0, 139.9, 136.4, 131.6, 131.4, 129.1, 128.7, 119.7, 117.9, 112.5, 71.1, 42.5, 34.4, 32.6, 29.2, 23.9; HRMS (ESI-TOF) calcd for C_{44}H_{53}Br_{2}N_{6}O_{4} [M+H]^+: 887.2490, found: 887.2469.

3-44j. Yellow solid (55%). $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 14.10 (s, 2 H), 8.99 (s, 2 H), 8.47 (s, 2 H), 7.67-7.64 (m, 4 H), 7.57-7.54 (m, 4 H), 7.18 (d, $J = 2.0$ Hz, 2 H), 7.07 (d, $J = 2.0$ Hz, 2 H), 6.69 (t, $J = 5.8$ Hz, 2 H), 4.14 (d, $J = 5.7$ Hz, 4 H), 3.46 (m, 2 H), 1.94-1.90 (m, 2 H), 1.88-1.80 (m, 2 H), 1.76-1.60 (m, 2 H), 1.54-1.44 (m, 2 H), 1.29 (s, 18 H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$ 165.9, 158.9, 154.5, 144.9, 136.3, 133.1, 128.8, 128.7, 119.4, 117.8, 117.4, 102.4, 71.0, 42.4, 34.3, 32.5, 29.1, 23.8; HRMS (ESI-TOF) calcd for C_{46}H_{53}N_{8}O_{4} [M+H]^+: 781.4184, found: 781.4170.
3-44k. Yellow solid (89%). $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 14.10 (s, 2 H), 8.87 (s, 2 H), 8.48 (s, 2 H), 7.60-7.53 (m, 8 H), 7.18 (d, $J$ = 2.0 Hz, 2 H), 7.08 (d, $J$ = 2.0 Hz, 2 H), 6.62 (t, $J$ = 5.7 Hz, 2 H), 4.15 (d, $J$ = 5.7 Hz, 4 H), 3.44 (m, 2 H), 1.93-1.83 (m, 2 H), 1.83-1.74 (m, 2 H), 1.69-1.56 (m, 2 H), 1.49-1.38 (m, 2 H), 1.29 (s, 18 H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$ 165.9, 158.8, 154.7, 144.2, 136.3, 128.9, 128.7, 128.6, 125.9, 124.6 (q, $J$ = 270 Hz), 121.0 (q, $J$ = 32 Hz), 117.8, 117.2, 71.0, 42.4, 34.3, 32.5, 29.0, 23.8; HRMS (ESI-TOF) calcd for C$_{46}$H$_{53}$F$_6$N$_6$O$_4$ [M+H]$^+$: 867.4027, found: 867.4024.

3-44l. Yellow solid (92%). $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 14.02 (s, 2 H), 8.43 (s, 2 H), 7.37 (s, 2 H), 7.23 (s, 2 H), 7.17 (d, $J$ = 7.9 Hz, 2 H), 7.08 (m, 4 H), 7.03 (s, 2 H), 6.46 (s, 2 H), 4.11 (s, 4 H), 3.46 (m, 2 H), 3.10 (m, 2 H), 1.94-1.90 (m, 2 H), 1.88-1.80 (m, 2 H), 1.76-1.60 (m, 2 H), 1.54-1.44 (m, 2 H), 1.34 (s, 18 H), 1.07 (d, $J$ = 6.8 Hz, 24 H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$ 165.7, 158.6, 156.9, 146.7, 136.1, 133.0, 129.9, 128.3, 126.8, 122.7, 117.6, 71.0, 42.5, 34.3, 32.6, 29.1, 27.8, 23.8, 23.6; HRMS (ESI-TOF) calcd for C$_{56}$H$_{79}$N$_6$O$_4$ [M+H]$^+$: 899.6157, found: 899.6165.
**General Procedure for the Preparation of Bis-Urea (Salen)Co Complexes (3-30)**

To a solution or suspension of an appropriate salen ligand (0.21 mmol) in EtOH (5 mL), Co(OAc)$_2$$\cdot$4H$_2$O (0.21 mmol, 1.0 equiv) was added, and heated at reflux for 3 h under argon. Precipitate was collected by filtration, washed by EtOH, and then dried under vacuum for 24 h to give a (salen)cobalt complex.

![Diagram of 3-30a](image)

**3-30a.** Red solid (68%). HRMS (ESI-TOF) calcd for C$_{46}$H$_{56}$CoN$_6$O$_4$ [M]$^+$: 815.3690, found: 815.3678; elemental analysis calcd (%) for C$_{46}$H$_{56}$CoN$_6$O$_4$: C 55.73, H 5.46, N 8.12; found C 55.73, H 5.46, N 8.12.

![Diagram of 3-30b](image)

**3-30b.** Red solid (39%). HRMS (ESI-TOF) calcd for C$_{44}$H$_{68}$CoN$_6$O$_4$ [M]$^+$: 803.4629, found: 803.4629; elemental analysis calcd (%) for C$_{44}$H$_{68}$CoN$_6$O$_4$: C 65.73, H 8.53, N 10.45; found C 65.40, H 8.86, N 10.26.
3-30c. Reddish brown solid (56%). HRMS (MALDI-TOF) calcd for C\textsubscript{68}H\textsubscript{116}CoN\textsubscript{6}O\textsubscript{4} [M]\textsuperscript{+}: 1139.8385, found: 1139.8399; elemental analysis calcd (%) for C\textsubscript{68}H\textsubscript{116}CoN\textsubscript{6}O\textsubscript{4}: C 71.60, H 10.25, N 7.37; found C 71.61, H 10.56, N 7.19.

3-30d. Red solid (60%). HRMS (ESI-TOF) calcd for C\textsubscript{44}H\textsubscript{52}CoN\textsubscript{6}O\textsubscript{4} [M]\textsuperscript{+}: 787.3377, found: 787.3343; elemental analysis calcd (%) for C\textsubscript{44}H\textsubscript{52}CoN\textsubscript{6}O\textsubscript{4}: C 67.08, H 6.65, N 10.67; found C 66.79, H 6.88, N 10.48.

3-30e. Reddish brown solid (67%). HRMS (ESI-TOF) calcd for C\textsubscript{46}H\textsubscript{56}CoN\textsubscript{6}O\textsubscript{6} [M]\textsuperscript{+}: 847.3588, found: 847.3569; elemental analysis calcd (%) for C\textsubscript{46}H\textsubscript{56}CoN\textsubscript{6}O\textsubscript{6}: C 65.16, H 6.66, N 9.91; found C 65.39, H 6.92, N 9.81.

3-30f. Reddish brown solid (55%). HRMS (ESI-TOF) calcd for C\textsubscript{48}H\textsubscript{48}CoF\textsubscript{12}N\textsubscript{6}O\textsubscript{4} [M]\textsuperscript{+}: 1059.2872, found: 1059.2975; elemental analysis calcd (%) for C\textsubscript{48}H\textsubscript{48}CoF\textsubscript{12}N\textsubscript{6}O\textsubscript{4}: C 54.40, H 4.56, N 7.93; found C 54.18, H 4.53, N 7.58.
**3-30g.** Orange-red solid (79%). HRMS (ESI-TOF) calcd for C\textsubscript{44}H\textsubscript{50}CoF\textsubscript{2}N\textsubscript{6}O\textsubscript{4} [M]\textsuperscript{+}; 823.3188, found: 823.3181; elemental analysis calcd (%) for C\textsubscript{44}H\textsubscript{50}CoF\textsubscript{2}N\textsubscript{6}O\textsubscript{4}: C 64.15, H 6.12, N 10.20; found C 64.39, H 6.54, N 9.95.

**3-30h.** Reddish brown solid (61%). HRMS (ESI-TOF) calcd for C\textsubscript{44}H\textsubscript{50}Cl\textsubscript{2}CoN\textsubscript{6}O\textsubscript{4} [M]\textsuperscript{+}; 855.2592, found: 855.2546; elemental analysis calcd (%) for C\textsubscript{44}H\textsubscript{50}Cl\textsubscript{2}CoN\textsubscript{6}O\textsubscript{4}: C 61.68, H 5.88, N 9.81; found C 61.28, H 5.98, N 9.59.

**3-30i.** Reddish brown solid (75%). HRMS (ESI-TOF) calcd for C\textsubscript{44}H\textsubscript{50}Br\textsubscript{2}CoN\textsubscript{6}O\textsubscript{4} [M]\textsuperscript{+}: 945.1572, found: 945.1591; elemental analysis calcd (%) for C\textsubscript{44}H\textsubscript{50}Br\textsubscript{2}CoN\textsubscript{6}O\textsubscript{4}: C 55.88, H 5.33, N 8.89; found C 55.95, H 5.46, N 8.63.
**3-30j.** Reddish brown solid (32%). HRMS (ESI-TOF) calcd for C_{46}H_{50}CoN_{8}O_{4} [M]^+: 837.3287, found: 837.3290; elemental analysis calcd (%) for C_{46}H_{50}CoN_{8}O_{4}: C 65.94, H 6.01, N 13.37; found C 65.56, H 6.06, N 13.03.

![Chemical structure](image)

**3-30k.** Reddish brown solid (37%). The replacement of ethanol with isopropanol in the general procedure afforded **3-30k** in higher yield (77%). HRMS (ESI-TOF) calcd for C_{46}H_{50}CoF_{6}N_{6}O_{4} [M]^+: 923.3124, found: 923.3140; elemental analysis calcd (%) for C_{46}H_{50}CoF_{6}N_{6}O_{4}: C 59.80, H 5.46, N 9.10; found C 59.57, H 5.46, N 8.87.

![Chemical structure](image)

**3-30l.** Red solid (56%). HRMS (ESI-TOF) calcd for C_{56}H_{76}CoN_{6}O_{4} [M]^+: 955.5255, found: 955.5250; elemental analysis calcd (%) for C_{56}H_{76}CoN_{6}O_{4}: C 70.34, H 8.01, N 8.79; found C 70.46, H 8.37, N 8.72.

**Synthesis of Mono-Urea (Salen)Co Complex (3-51)**

![Chemical structure](image)
3-50. To a solution of (1\textsubscript{R},2\textsubscript{R})-cyclohexane-1,2-diamine (55 mg, 0.48 mmol) in absolute EtOH (3 mL), 2 M HCl in ethyl ether (0.24 mL, 0.48 mmol, 1.0 equiv) was added at 0°C, and then allowed to stir for 3 h at this temperature under argon. To this reaction mixture 3,5-di-\textit{tert}-butyl-2-hydroxybenzaldehyde (113 mg, 0.48 mmol, 1.0 equiv) in EtOH (3 mL) was added at 0°C. Then, the reaction mixture was stirred for an additional 3 h at this temperature, followed by the addition of 3-41k (190 mg, 0.48 mmol, 1.0 equiv) in EtOH (5 mL) and NE\textsubscript{t}\textsubscript{3} (0.13 mL, 0.96 mmol, 2 equiv). The reaction mixture was allowed to stir at room temperature overnight. The solution was concentrated under reduced pressure, and the residue was purified by column chromatography on silica-gel (\textit{n}-hexane:EtOAc 5:1 then 2:1) to give the resulting mono-urea salen 3-50 (216 mg, 63%) as a yellow solid. \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) \(\delta\) 13.90 (s, 1 H), 13.73 (s, 1 H), 8.31 (s, 1 H), 8.20 (s, 1 H), 7.44 (d, \(J = 6.2\) Hz, 2 H), 7.36-7.27 (m, 2 H), 7.30 (d, \(J = 2.5\) Hz, 1 H), 7.13 (s, 1 H), 6.98 (d, \(J = 2.5\) Hz, 1 H), 6.91 (s, 1 H), 6.37 (s, 1 H), 5.09 (s, 1 H), 4.27-4.13 (m, 2 H), 3.37-3.20 (m, 2 H), 1.96-1.85 (m, 4 H), 1.79-1.62 (m, 2 H), 1.49-1.40 (m, 2 H), 1.38 (s, 9 H), 1.37 (s, 9 H), 1.21 (s, 9 H); \textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}) \(\delta\) 165.8, 164.9, 159.8, 158.0, 155.1, 142.0, 140.2, 137.7, 136.6, 128.8, 128.6, 127.0, 126.9, 126.1 (q, \(J = 3.6\) Hz), 126.0, 124.4 (q, \(J = 33\) Hz), 124.2 (q, \(J = 270\) Hz), 118.5, 118.3, 117.7, 72.4, 72.2, 43.9, 34.9, 34.7, 34.0, 33.1, 33.0, 31.3, 29.4, 29.2, 24.2; HRMS (APCI-TOF) calcd for C\textsubscript{41}H\textsubscript{54}F\textsubscript{3}N\textsubscript{4}O\textsubscript{3} [M+H]\(^{+}\): 707.4143, found: 707.4173.
3-51. To a solution of salen ligand 3-50 (79 mg, 0.11 mmol) in isopropanol (3 mL), Co(OAc)$_2$•4H$_2$O (28 mg, 0.11 mmol) was added, and heated at reflux for 3 h under argon. Precipitate was collected by filtration, washed by isopropanol, and then dried under vacuum for 24 h to give 3-51 (70 mg, 83%) as a reddish brown solid. HRMS (APCI-TOF) calcd for C$_{41}$H$_{52}$CoF$_3$N$_4$O$_3$ [M+H]$^+$: 764.3318, found: 764.3336. elemental analysis calcd (%) for C$_{41}$H$_{51}$CoF$_3$N$_4$O$_3$: C 64.47, H 6.73, N 7.34; found C 64.26, H 6.95, N 7.09.

**Synthesis of Urea (Salen)Ni Complexes**

To a solution or suspension of an appropriate salen ligand (0.1 mmol) in MeOH (3 mL), Ni(OAc)$_2$•4H$_2$O (0.1 mmol, 1.0 equiv) was added, and stirred at room temperature for 6 h under argon. Precipitate was collected by filtration, washed by MeOH, and then dried under vacuum for 24 h to give a (salen)Ni complex.

3-54. Greenish yellow solid (86%). $^1$H NMR (300 MHz, DMSO-$d_6$) δ 8.91 (s, 2 H), 7.66 (s, 2 H), 7.62-7.55 (m, 8 H), 7.16 (s, 2 H), 7.11 (s, 2 H), 6.59 (t, $J$ = 5.5 Hz, 2 H), 4.14 (d, $J$ = 5.1 Hz, 4 H), 3.07 (s, 2 H), 1.76 (s, 2 H), 1.32 (s, 18 H), 1.25 (s, 6 H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 162.2, 158.7, 154.7, 144.3, 139.3, 130.3, 130.0, 126.0, 124.7 (q, $J$ = 270 Hz), 124.1, 120.9 (q, $J$ = 32 Hz), 120.1, 117.2, 69.7, 42.6, 35.1, 29.5, 28.4, 24.0; HRMS (APCI-TOF) calcd for C$_{46}$H$_{51}$F$_6$N$_6$NiO$_4$ [M+H]$^+$: 923.3224, found: 923.3228.
3-55. Greenish yellow solid (81%). $^1$H NMR (300 MHz, DMSO-d$_6$) δ 8.93 (s, 1 H), 7.67 (s, 1 H), 7.66 (s, 1 H), 7.62-7.55 (m, 4 H), 7.18 (s, 2 H), 7.15 (s, 1 H), 7.11 (s, 1 H), 6.60 (t, $J$ = 5.5 Hz, 1 H), 4.14 (d, $J$ = 4.8 Hz, 2 H), 3.06 (s, 2 H), 1.77 (s, 2 H), 1.32 (s, 18 H), 1.26 (s, 6 H), 1.23 (s, 9 H); $^{13}$C NMR (125 MHz, DMSO-d$_6$) δ 162.3, 161.1, 159.1, 158.6, 154.7, 144.3, 139.3, 138.4, 134.8, 130.3, 129.9, 127.6, 127.2, 126.0 (q, $J$ = 3.6 Hz), 125.4 (q, $J$ = 271 Hz), 124.7, 120.9 (q, $J$ = 32 Hz), 120.0, 119.7, 117.2, 69.7, 69.6, 42.6, 35.3, 35.1, 33.5, 31.3, 29.6, 29.5, 28.5, 28.3, 24.0, 23.9; HRMS (APCI-TOF) calcd for C$_{41}$H$_{52}$F$_3$N$_4$NiO$_3$ [M+H]$^+$: 763.3340, found: 763.3354.

3-56. Greenish yellow solid (84%). Orange single crystals suitable for X-ray analysis were obtained by slow evaporation in DMF at room temperature. $^1$H NMR (300 MHz, DMSO-d$_6$) δ 7.61 (s, 2 H), 7.29-7.16 (m, 10 H), 7.08 (s, 4 H), 6.34 (s, 2 H), 6.24 (s, 2 H), 4.22 (d, $J$ = 5.4 Hz, 4 H), 4.06 (d, $J$ = 3.4 Hz, 4 H), 3.08 (s, 2 H), 1.77 (s, 2 H), 1.31 (s, 18 H), 1.28-1.21 (m, 6 H); $^{13}$C NMR (125 MHz, DMSO-d$_6$) δ 162.1, 158.6, 158.1, 141.0, 139.2, 130.0, 129.8, 128.2, 127.0, 126.6, 125.0, 119.9, 69.7, 42.9, 42.8, 35.1, 29.5, 28.4, 24.0; HRMS (APCI-TOF) calcd for C$_{46}$H$_{57}$N$_6$NiO$_4$ [M+H]$^+$: 815.3789, found: 815.3763. Refinement details for 3-56: C$_{46}$H$_{56}$N$_6$NiO$_4$; $M_r$ = 815.68; $T$ = 100(2) K;
wavelength = 0.71073 Å; crystal system: triclinic; space group P-1; \(a = 8.6817(11) \text{ Å}, b = 15.721(2) \text{ Å}, c = 15.803(2) \text{ Å}; \alpha = 76.708(3)^\circ; \beta = 86.868(3)^\circ, \gamma = 78.889(3)^\circ; V = 2059.6(5) \text{ Å}^3; Z = 2; \rho_{\text{calcd}} = 1.315 \text{ Mg/m}^3; \mu = 0.523 \text{ mm}^{-1}; F(000) = 868; \) crystal size = 0.20 x 0.08 x 0.04 mm\(^3\); \(\theta \text{ range} = 1.35 \text{ to } 25.00^\circ; \) index ranges: -10\(\leq h \leq 10, -18 \leq k \leq 14, -18 \leq l \leq 18\); reflections collected 20352, independent reflections 7262 \([R(\text{int}) = 0.0729], \) completeness to \(\theta = 25.00^\circ, 100.0\%; \) absorption correction: none; max./min. transmission 0.9819/0.9031; data/restraints/parameters 7262/0/502; goodness-of-fit on \(F^2\) 1.116; final \(R\) indices \([I>2\sigma(I)]; R_1 = 0.0692, wR_2 = 0.1456 [4506]; R\) indices (all data): \(R_1 = 0.1136, wR_2 = 0.1542; \) largest diff. peak/hole 0.373 and -0.414 e.Å\(^{-3}\).

3-57. Greenish yellow solid (80%). Orange single crystals suitable for X-ray analysis were obtained by slow evaporation in DMF at room temperature. Refinement details for 3-57: \(C_{51}H_{55}F_{12}N_{7}\text{Ni}O_{5}; M_r = 1132.73; T = 100(2) \text{ K}; \) wavelength = 0.71073 Å; crystal system: triclinic; space group P-1; \(a = 9.3525(13) \text{ Å}, b = 13.0965(17) \text{ Å}, c = 20.515(3) \text{ Å}; \alpha = 91.018(3)^\circ, \beta = 97.294(2)^\circ, \gamma = 94.674(3)^\circ; V = 2483.2(6) \text{ Å}^3; Z = 2; \rho_{\text{calcd}} = 1.515 \text{ Mg/m}^3; \mu = 0.492 \text{ mm}^{-1}; F(000) = 1172; \) crystal size = 0.31 x 0.12 x 0.05 mm\(^3\); \(\theta \text{ range} = 1.56 \text{ to } 27.50^\circ; \) index ranges: -12\(\leq h \leq 12, -14 \leq k \leq 17, -26 \leq l \leq 24\); reflections collected 27913, independent reflections 11151 \([R(\text{int}) = 0.0294], \) completeness to \(\theta = 27.50^\circ, 97.9\%; \) absorption correction: none; max./min. transmission 0.9768/0.8632; data/restraints/parameters 11151/0/686; goodness-of-fit on \(F^2\) 1.158; final \(R\) indices 188
[I>2σ(I)]; \( R_1 = 0.0551, wR_2 = 0.1103 \) [9198]; \( R \) indices (all data): \( R_1 = 0.0695, wR_2 = 0.1151 \); largest diff. peak/hole 0.585 and -0.615 eÅ⁻³.

**Preparation of Bis-(\( N,N' \)-Dimethyl-Phenyurea)-(Salen)Cobalt Complex**

\[
\begin{align*}
\text{CHO} & \\
\text{Me} & \\
\text{t-Bu} & \\
\text{Me} & \\
\text{N} \quad \text{O} & \\
\end{align*}
\]

**1-(3-\text{tert-Butyl-5-formyl-4-methoxybenzyl})-1,3-dimethyl-3-phenylurea (3-46).**

1-(3-\text{tert-Butyl-5-formyl-4-hydroxybenzyl})-3-phenylurea 3-41d (214 mg, 0.66 mmol) was dissolved in dry DMF (3.0 mL) and 60% NaH (105 mg, 2.63 mmol) was added at room temperature under argon. After stirring for 30 min at this temperature, iodomethane (0.4 mL, 6.41 mmol) was added, and then the reaction mixture was allowed to stir at room temperature overnight. The reaction mixture was diluted with EtOAc (20 mL) and washed with water and brine. After drying over anhydrous Na₂SO₄, the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica-gel (\( n \)-hexane:EtOAc 10:1 then 5:1) to give 3-46 (173 mg, 72%) as a colorless oil. \( ^1 \text{H NMR} \) (300 MHz, CDCl₃) \( \delta \) 10.30 (s, 1 H), 7.48 (d, \( J = 2.3 \) Hz, 1 H), 7.44 (d, \( J = 2.5 \) Hz, 1 H), 7.34-7.29 (m, 2 H), 7.12-7.07 (m, 3 H), 4.37 (s, 2 H), 3.93 (s, 3 H), 3.25 (s, 3 H), 2.47 (s, 3 H), 1.41 (s, 9 H); \( ^{13} \text{C NMR} \) (75 MHz, CDCl₃) \( \delta \) 190.3, 162.6, 162.0, 146.7, 144.0, 133.1, 132.9, 129.5, 126.9, 124.7, 124.2, 66.1, 53.0, 40.1, 36.4, 35.1, 30.7; HRMS (ESI-TOF) calcd for C₂₂H₂₉N₂O₃ [M+H]⁺: 369.2173, found: 369.2183.

\[
\begin{align*}
\text{CHO} & \\
\text{Me} & \\
\text{t-Bu} & \\
\text{Me} & \\
\text{N} \quad \text{O} & \\
\end{align*}
\]
1-(3-tert-Butyl-5-formyl-4-hydroxybenzyl)-1,3-dimethyl-3-phenylurea (3-47). 1-(3-tert-Butyl-5-formyl-4-methoxybenzyl)-1,3-dimethyl-3-phenylurea 3-46 (153 mg, 0.42 mmol) in dry CH$_2$Cl$_2$ (2.0 mL) was cooled to -78°C and 1 M BBr$_3$ in CH$_2$Cl$_2$ (0.5 mL, 1.2 eq.) was added. After stirring at this temperature for 1 h, the reaction mixture was allowed to warm up to room temperature and then stirred overnight. After quenching by adding saturated NaHCO$_3$, the mixture was extracted with CH$_2$Cl$_2$. The organic layer was dried over anhydrous Na$_2$SO$_4$ and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica-gel (n-hexane:EtOAc 5:1 then 2:1) to give 3-47 (117 mg, 80%) as a yellow oil. $^1$H NMR (300 MHz, CDCl$_3$) δ 11.73 (s, 1 H), 9.82 (s, 1 H), 7.37 (d, $J = 2.3$ Hz, 1 H), 7.34-7.28 (m, 2 H), 7.23 (d, $J = 2.0$ Hz, 1 H), 7.13-7.07 (m, 3 H), 4.34 (s, 2 H), 3.23 (s, 3 H), 2.46 (s, 3 H), 1.39 (s, 9 H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 197.0, 161.9, 160.4, 146.7, 138.4, 134.0, 131.0, 129.4, 128.3, 124.6, 124.1, 120.2, 52.8, 40.0, 36.1, 34.7, 29.1; HRMS (ESI-TOF) calcd for C$_{21}$H$_{27}$N$_2$O$_3$ [M+H]$^+$: 355.2016, found: 355.2022.

3-48. To a solution of (1R,2R)-cyclohexane-1,2-diamine (17 mg, 0.15 mmol) in THF (3.0 mL), salicylaldehyde 3-47 (108 mg, 0.30 mmol, 2.0 equiv) was added at room temperature, and then allowed to stir for 20 h. The solution was concentrated under reduced pressure, and the residue was purified by column chromatography on silica-gel (n-hexane:EtOAc 5:1 then 2:1) to give 3-48 (100 mg, 84%) as a yellow solid. $^1$H NMR (300 MHz, CDCl$_3$) δ 13.80 (s, 2 H), 8.24 (s, 2 H), 7.28-7.22 (m, 4 H), 7.06-7.03 (m, 6 H),
7.01 (s, 2 H), 6.81 (d, J = 2.3 Hz, 2 H), 4.20 (s, 4 H), 3.33-3.30 (m, 4 H), 3.21 (s, 6 H),
2.37 (s, 6 H), 1.98-1.87 (m, 2 H), 1.74-1.71 (m, 2 H), 1.64-1.55 (m, 2 H), 1.50-1.43 (m, 2 H), 1.37 (s, 18 H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 165.2, 161.9, 159.6, 146.8, 137.3, 129.4, 129.3, 129.2, 126.4, 124.2, 123.9, 118.2, 72.3, 53.1, 39.8, 35.8, 34.7, 33.1, 29.3, 24.2; HRMS (ESI-TOF) calcd for C$_{48}$H$_{62}$N$_6$O$_4$Na [M+Na]$^+$: 809.4725, found: 809.4711.

3-49. To a solution of salen 3-48 (73 mg, 0.093 mmol) in EtOH (2.0 mL), Co(OAc)$_2$•4H$_2$O (23 mg, 0.093 mmol) was added, and heated at reflux for 2 h under argon. Precipitate was collected by filtration, washed by EtOH, and then dried under vacuum for 24 h to give 3-49 (50 mg, 64%) as a red solid. HRMS (ESI-TOF) calcd for C$_{48}$H$_{60}$CoN$_6$O$_4$ [M]$^+$: 843.4003, found: 843.3989; elemental analysis calcd (%) for C$_{48}$H$_{60}$CoN$_6$O$_4$: C 68.31, H 7.17, N 9.96; found C 67.94, H 7.44, N 9.69.

**Reaction Rate Determination**

A vial equipped with stir bar was charged with (salen)Co catalyst (2.5 μmol, 0.05 mol%). A solution of p-toluenesulfonic acid monohydrate in THF (0.01 M, 0.55 mL, 1.1 equiv per catalyst) was added and the solution was stirred in air for 30 min. After removing solvent by rotary evaporation, racemic epichlorohydrin (426 mg, 5.0 mmol), bromobenzene (50 μL, internal standard), and THF (1.0 mL) were added to the oxidized (salen)Co complex. The vial was placed into a water bath at 23°C and H$_2$O (50 μL, 0.55 equiv) was added in one portion. The reaction progress was monitored by the removal of aliquots from the reaction mixture, filtration through silica-gel with diethylether as an
eluent, and chiral GC-MS analysis (Chiraldex γ-TA, 70°C, isothermal, $t_R$(major) = 4.24 min, $t_R$(minor) = 4.68 min). The slopes of the least square lines for the plots of $-\ln([\text{epoxide}]/[\text{epoxide}]_0)$ vs. time were determined.

**General Procedure for Hydrolytic Kinetic Resolution of Epoxides**

(S)-Epichlorohydrin (1-49b). A vial equipped with a stir bar was charged with 3-30k (4.6 mg, 5 μmol, 0.05 mol%). A solution of $p$-toluenesulfonic acid monohydrate in THF (0.01 M, 1.1 mL, 1.1 equiv per catalyst) was added and the solution was stirred in the open air for 30 min. After removing solvent by rotary evaporation, racemic epichlorohydrin (925 mg, 10 mmol) was added. The reaction mixture became homogeneous within 30 min. The vial was placed into a water bath at 23°C and H$_2$O (126 μL, 0.70 equiv) was added in one portion. After the reaction was stirred at 23°C for 14 h, the remaining epoxide was isolated by vacuum-transfer (rt, 0.5 Torr) into a receiving flask pre-cooled at -78°C. The recovered epoxide was dried over anhydrous MgSO$_4$ and filtered to give (S)-epichlorohydrin 1-49b (390 mg, 42%) as a colorless liquid. The ee of the recovered epichlorohydrin was determined to be 99% by chiral GC-MS analysis (Chiraldex γ-TA, 70°C, isothermal, $t_R$(major) = 4.24 min, $t_R$(minor) = 4.68 min). Absolute configuration of the major isomer was determined to be (S) by comparison of the retention time with literature data.

(R)-Allyl glycidyl ether (1-49a). A vial equipped with a stir bar was charged with 3-30k (4.6 mg, 5 μmol, 0.05 mol%). A solution of $p$-toluenesulfonic acid monohydrate in THF (0.01 M, 0.55 mL, 1.1 equiv per catalyst) was added and the solution was stirred in the open air for 30 min. After removing solvent by rotary evaporation, racemic allyl glycidyl ether (1.14 g, 10 mmol) was added. The vial was placed into a water bath at 23°C and H$_2$O (126 μL, 0.70 equiv) was added in one portion. After the reaction was
stirred at 23°C for 9 h, the remaining epoxide was isolated by vacuum-transfer (40°C, 0.1 Torr) into a receiving flask pre-cooled at -78°C. The recovered epoxide was dried over anhydrous MgSO₄ and filtered to give (R)-allyl glycidyl ether 1-49a (491 mg, 43%) as a colorless liquid. The recovered allyl glycidyl ether was determined to be 99% ee by chiral GC-MS analysis (Chiraldex γ-TA, 75°C, isothermal, tₘᵣₐ(jor) = 7.35 min, tₘᵣₐ(minor) = 8.69 min). Absolute configuration of the major isomer was determined to be (R) by comparison of the retention time with literature data.

(R)-1,2-Epoxybutane (1-49c). A vial equipped with a stir bar was charged with 3-30k (5.6 mg, 6 μmol, 0.03 mol%). A solution of p-toluenesulfonic acid monohydrate in THF (0.01 M, 0.66 mL, 1.1 equiv per catalyst) was added and the solution was stirred in the open air for 30 min. After removing solvent by rotary evaporation, racemic 1,2-epoxybutane (1.44 g, 20 mmol) was added. The vial was placed into a water bath at 23°C and H₂O (252 μL, 0.70 equiv) was added in one portion. After the reaction was stirred at 23°C for 8 h, the remaining epoxide was isolated by vacuum-transfer (rt, 0.5 Torr) into a receiving flask pre-cooled at -78°C. The recovered epoxide was dried over anhydrous MgSO₄ and filtered to give (R)-1,2-epoxybutane 1-49c (615 mg, 43%) as a colorless liquid. The recovered (R)-1,2-epoxybutane was determined to be 99% ee by chiral GC-MS analysis (Chiraldex γ-TA, 28°C, isothermal, tₘᵣₐ(maj) = 4.91 min, tₘᵣₐ(min) = 5.36 min). Absolute configuration of the major isomer was determined to be (R) by comparison of the retention time with literature data.

(R)-1,2-Epoxyhexane (1-49d). A vial equipped with a stir bar was charged with 3-30k (2.8 mg, 3 μmol, 0.03 mol%). A solution of p-toluenesulfonic acid monohydrate in THF (0.01 M, 0.33 mL, 1.1 equiv per catalyst) was added and the solution was stirred in
the open air for 30 min. After removing solvent by rotary evaporation, racemic 1,2-
epoxyhexane (1.0 g, 10 mmol) was added. The vial was placed into a water bath at
23°C and H₂O (126 μL, 0.70 equiv) was added in one portion. After the reaction was
stirred at 23°C for 14 h, the remaining epoxide was isolated by vacuum-transfer (rt, 0.5
Torr) into a receiving flask pre-cooled at -78°C. The recovered epoxide was dried over
anhydrous MgSO₄ and filtered to give (R)-1,2-epoxyhexane 1-49d (410 mg, 41%) as a
colorless liquid. The recovered (R)-1,2-epoxyhexane was determined to be 99% ee by
chiral GC-MS analysis (Chiraldex γ-TA, 50°C, isothermal, tᵣ(minor) = 8.29 min,
tᵣ(major) = 8.87 min). Absolute configuration of the major isomer was determined to be
(R) by comparison of the retention time with literature data.

**Asymmetric Hydrolysis of Cyclohexene Oxide**

\textbf{(1S,2S)-trans-1,2-Cyclohexanediol (3-59).} A vial equipped with a stir bar was
charged with 3-30k (2.8 mg, 3 μmol, 0.5 mol%). A solution of p-toluenesulfonic acid
monohydrate in THF (0.01 M, 0.33 mL, 1.1 equiv per catalyst) was added and the
solution was stirred in the open air for 30 min. After removing solvent by rotary
evaporation, TBME (0.5 mL) was charged to dissolve the catalyst. Cyclohexene oxide
3-58 (49 mg, 0.5 mmol) and H₂O (12 μL, 1.2 equiv) was added and solution was stirred
for 45 h at 23°C. The reaction mixture was applied to a pad of silica gel and the pad was
washed with EtOAc. The solvent was removed under reduced pressure to give 3-59 (36
mg, 62 %) as a white solid. The bis-TFA ester derivative was prepared to determine
enantiomeric excess (Chiraldex γ-TA, 90°C, isothermal, tᵣ(minor) = 8.29 min, tᵣ(major)
= 8.87 min). The ester derivative was determined to be 75% ee. Absolute configuration
of the major isomer was determined to be (1S,2S) by comparison of the retention time
with literature data.
Molecular Mechanics Calculations

Molecular mechanics calculations were performed using augmented MM2 force field parameters, as implemented in CAChe version 6.1.1. Calculations were performed using a simplified bis-urea (salen)nickel complex (R = Me). The atomic coordinates in the (salen)Ni fragment were obtained from the crystal structure data of 3-56 (R = Bn). The (salen)Ni fragment was locked during computation. Steepest descent search will be used to locate the energy minimum. Optimization continues until the energy change is less than 0.001 kcal/mol.

General Procedure for the Preparation of Bis-Urea Salicylaldehydes

To a solution of 4-(aminomethyl)-2-tert-butyl-6-(1,3-dioxan-2-yl)phenol 3-43 (0.25 mmol, 2 equiv) in CH₂Cl₂ (3.0 mL) at room temperature, an appropriate diisocyanate (0.25 mmol, 1 equiv) was added. After stirring overnight at room temperature, precipitate was filtered and washed with CH₂Cl₂. The resulting solid was dissolved in THF (3 mL), and then 10% HCl (0.2 mL) was added to this solution at room temperature. After stirring for 2 h at this temperature, the solvent was removed under reduced pressure. The residue was dissolved in EtOAc (10 mL), and then the organic layer was washed with water and saturated NaHCO₃. After drying over anhydrous Na₂SO₄, the solvent was removed under reduced pressure. The residue was triturated with CH₂Cl₂/hexanes to give the resulting bis-urea salicylaldehyde.
1,1'-(1,3-Phenylen)bis(3-(3-tert-butyl-5-formyl-4-hydroxybenzyl)urea) (3-61a).

White solid (54%). $^1$H NMR (300 MHz, DMSO-$d_6$) δ 11.77 (s, 2 H), 9.97 (s, 2 H), 8.50-8.56 (m, 2 H), 7.52-7.57 (m, 4 H), 7.52 (br. s., 1 H), 6.95-7.08 (m, 3 H), 6.55 (s, 2 H), 4.26 (dd, $J = 6.0$, 0.2 Hz, 4 H), 1.38 (s, 18 H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 198.5, 158.8, 155.1, 140.7, 137.1, 133.4, 131.4, 130.4, 128.7, 120.3, 110.8, 107.2, 42.1, 40.3, 34.4, 29.1, 22.7; HRMS (ESI) calcd for C$_{32}$H$_{38}$N$_4$O$_6$Na [M+Na]$^+$: 597.2684, found 597.2702.

![Chemical Structure](image)

1,1'-(4-Methyl-1,3-phenylene)bis(3-(3-tert-butyl-5-formyl-4-hydroxybenzyl)urea) (3-61b). White solid (48%). $^1$H NMR (300 MHz, DMSO-$d_6$) δ 11.75-11.79 (m, 2 H), 9.94-10.00 (m, 2 H), 7.75-7.78 (m, 1 H), 7.51-7.58 (m, 4 H), 7.11-7.16 (m, 1 H), 6.93-7.01 (m, 2 H), 6.46-6.53 (m, 1 H), 4.23-4.30 (m, 4 H), 2.09 (s, 3 H), 1.36-1.47 (m, 18 H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 198.5, 158.5, 155.3, 155.2, 138.4, 138.0, 137.1, 133.4, 131.5, 131.3, 130.5, 130.4, 129.9, 120.3, 119.7, 112.0, 110.6, 42.2, 34.4, 29.1, 17.2; HRMS (APCI) calcd for C$_{33}$H$_{41}$N$_4$O$_6$ [M+H]$^+$: 589.3021, found 589.3031.

![Chemical Structure](image)

1,1'-(1,4-Phenylen)bis(3-(3-tert-butyl-5-formyl-4-hydroxybenzyl)urea) (3-61c).

White solid (44%). $^1$H NMR (300 MHz, DMSO-$d_6$) δ 11.75 (s, 2 H), 9.95 (s, 2 H), 8.35 (s, 2 H), 7.52 (d, $J = 2.9$ Hz, 2 H), 7.24 (s, 4 H), 6.52 (t, $J = 5.9$ Hz, 2 H), 4.24 (d, $J = 5.8$ Hz,
4 H), 1.36 (s, 18 H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 199.3, 159.5, 156.1, 137.8, 135.0, 134.2, 132.2, 131.2, 121.0, 119.2, 42.8, 35.1, 29.7; HRMS (APCI) calcd for C$_{32}$H$_{39}$N$_4$O$_6$ [M+H]$^+$: 575.2864, found 575.2861.

1,1''-(Hexane-1,6-diyl)bis(3-(3-tert-butyl-5-formyl-4-hydroxybenzyl)urea) (3-61d). White solid (47%). $^1$H NMR (300 MHz, DMSO-$d_6$) δ 11.73 (s, 2 H), 9.94 (s, 2 H), 7.47 (s, 4 H), 6.26-6.32 (m, 2 H), 5.90-5.96 (m, 2 H), 4.16 (d, $J = 6.1$ Hz, 4 H), 2.98-3.03 (m, 4 H), 2.48-2.52 (m, 4 H), 1.36 (s, 18 H), 1.25 (m, 4 H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 198.6, 158.8, 158.1, 137.0, 133.4, 132.1, 130.3, 120.3, 42.3, 34.4, 30.1, 29.1, 26.1; HRMS (APCI) calcd for C$_{32}$H$_{47}$N$_4$O$_6$ [M+H]$^+$: 583.3490, found 583.3484.

1,1''-(Dodecane-1,12-diyl)bis(3-(3-tert-butyl-5-formyl-4-hydroxybenzyl)urea) (3-61e). White solid (62%). $^1$H NMR (300 MHz, DMSO-$d_6$) δ 11.73 (s, 2 H), 9.93-9.98 (m, 2 H), 7.47 (s, 4 H), 6.30 (s, 2 H), 5.89 - 5.95 (m, 2 H), 4.16 (dd, $J = 6.1$, 0.1 Hz, 4 H), 2.92-3.02 (m, 4 H), 1.36 (s, 18 H), 1.22-1.29 (m, 20 H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 198.5, 158.8, 158.1, 137.0, 133.3, 132.1, 130.3, 120.3, 42.3, 34.4, 30.1, 29.1, 28.9, 26.4; HRMS (APCI) calcd for C$_{38}$H$_{59}$N$_4$O$_6$ [M+H]$^+$: 667.4429, found 667.4447.
1,3-Bis(3-tert-butyl-5-formyl-4-hydroxybenzyl)urea (3-63). White solid (47%).

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 11.71 (s, 2 H), 9.77 (s, 2 H), 7.40 (d, $J$ = 2.1 Hz, 2 H), 7.28 (d, $J$ = 2.1 Hz, 2 H), 4.90 (br s, 2 H), 4.29 (d, $J$ = 5.7 Hz, 4 H), 1.37 (s, 18 H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 197.1, 160.8, 139.1, 133.9, 130.7, 129.9, 120.6, 44.2, 35.1, 29.4.

Bis-Urea Spacing Dimeric (Salen)Co Complexes

3-62a. HRMS (ESI) calcd for C$_{74}$H$_{98}$N$_8$O$_6$Co$_2$ [M]$^+$: 1312.6268, found 1320.6265.

3-62b. HRMS (ESI) calcd for C$_{75}$H$_{100}$N$_8$O$_6$Co$_2$ [M]$^+$: 1326.6424, found 1326.6344.

3-62c. HRMS (ESI) calcd for C$_{74}$H$_{98}$N$_8$O$_6$Co$_2$ [M]$^+$: 1312.6268, found 1312.6226.
3-62d. HRMS (ESI) calcd for C_{74}H_{106}N_{8}O_{6}Co_{2} [M]^+: 1320.6894, found 1320.6885.

3-62e. HRMS (ESI) calcd for C_{80}H_{119}N_{8}O_{6}Co_{2} [M+H]^+: 1405.7911, found 1405.7878.
CHAPTER 4
CONCLUSION

The synergistic dual activation has emerged as a powerful theme to develop more efficient and selective asymmetric catalysis. As one of those approaches, chiral bimetallic catalysts linked by a covalent tether have been extensively reported and studied. Indeed, those catalysts have shown improved efficiency and enantioselectivity for a number of bimetallic transformations. Recently, the merge of supramolecular chemistry and catalysis has been envisioned as a powerful new strategy to achieve multifunctional catalysis because of the facile construction of complicated systems through self-assembly. Based on this concept, we devised a novel self-assembled dinuclear catalytic system mediated by hydrogen bonds. The key to success of this approach was the identification of suitable intermolecular interactions that are strong enough to hold two metal centers in close proximity and that are still compatible with the metal-substrate interactions. In addition, the orientation and geometry of the self-assembled catalyst should be controlled to position two metal centers within the optimal distance for cooperative activation.

Chapter 2 described the development of the self-assembled dinuclear (salen)Co(II) complex featuring two complementary 2-pyridone/aminopyridine hydrogen bonding interactions. This self-assembled dinuclear (salen)Co(II) catalyst results in significant rate acceleration (48 times faster) as well as high enantioselectivity compared to the non-functionalized (salen)Co(II) catalyst. The single crystal X-ray analysis reveals that the self-assembled dimer adopts the antiparallel “head-to-tail” geometry where the metal-metal distance was measured as 4.05 Å. The strength of
self-association ($K_{\text{dim}}$) was estimated as $53 \pm 21 \text{ M}^{-1}$ in 25% CD$_3$NO$_2$/CDCl$_3$ from $^1$H NMR experiments.

Chapter 3 discussed the development of novel bis-urea (salen)Co catalysts that can self-assemble through intermolecular urea-urea hydrogen bonding interactions. These catalysts successfully promoted hydrolytic kinetic resolution of racemic epoxides, exhibiting significant rate acceleration up to 13 times compared to the unfunctionalized analogue. The single crystal X-ray analysis and MM2 calculation reveal that the bis-urea salen scaffold can provide the optimal metal-metal distance (5~6 Å) for epoxide opening reactions through intermolecular H-bonds. In addition, as an extension of this strategy, the bis-urea spacing dimeric (salen)Co catalysts were developed, and they showed superior performance in the hydrolytic desymmetrization of cyclohexene epoxide in terms of reactivity and enantioselectivity.

In all cases, the observed rate acceleration can be rationalized by the facile formation of the dimeric catalyst through intermolecular hydrogen bonds. Thus, this novel self-assembly strategy represents a powerful approach to develop more efficient dual activation catalysts and can be applicable to wide range of asymmetric reactions.
LIST OF REFERENCES


BIOGRAPHICAL SKETCH

Jongwoo Park was born and grew up in Seoul, Korea. After getting BS and MS in chemistry at Yonsei University in Seoul, he joined LG chemical company as a research scientist. After working for LG Chem and LG Life sciences, Jongwoo went on to pursue his PhD in organic chemistry at the University of Florida under the supervision of Dr. Sukwon Hong. He received his Ph. D. from the University of Florida in December 2011.