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Self-Assembly Approach toward Chiral Bimetallic Catalysts: Bis-Urea-Functionalized (Salen)Cobalt Complexes for the Hydrolytic Kinetic Resolution of Epoxides**

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Abstract: A series of novel bis-urea-functionalized (salen)Co complexes has been developed. The complexes were designed to form self-assembled structures in solution through intermolecular urea–urea hydrogen-bonding interactions. These bis-urea (salen)Co catalysts resulted in rate acceleration (up to 13 times) in the hydrolytic kinetic resolution (HKR) of *rac*-epichlorohydrin in THF by facilitating cooperative activation, compared to the monomeric catalyst. In addition, one of the bis-urea (salen)Co^{III} catalyst efficiently resolves various terminal epoxides even under solvent-free conditions by requiring much shorter reaction time at low catalyst loading (0.03–0.05 mol%). A series of kinetic/mechanistic studies demonstrated that the self-association of two (salen)Co units through urea–urea hydrogen bonds was responsible for the observed rate acceleration. The self-assembly study with the bis-urea (salen)Co by FTIR spectroscopy and with the corresponding (salen)Ni complex by ^{1}H NMR spectroscopy showed that intermolecular hydrogen-bonding interactions exist between the bis-urea scaffolds in THF. This result demonstrates that self-assembly approach by using non-covalent interactions can be an alternative and useful strategy toward the efficient HKR catalysis.

Keywords: bis-urea · cooperative effects · epoxide opening · hydrogen bonds · self-assembly

Introduction

Cooperative activation is a general phenomenon in biochemical transformations and many biological catalysts such as enzymes have evolved to achieve high efficiency and selectivity through dual activation.[1] There have been growing efforts to develop efficient asymmetric catalysts based on the concept of cooperative activation.[2] One of the conventional approaches particularly toward bi- or multimetallic catalyst design involves tethering metal centers through covalent bonds or metal coordination in order to place metal centers in close proximity.[3] For example, a second-order dependence on the chiral (salen)Co (salen = bis-(salicyliden)-ethylendiaminato) catalyst in the hydrolytic kinetic resolution (HKR) of epoxides[4] led to the development of a number of multinuclear (salen)Co structures connected mainly through a covalent linker; these multinuclear complexes been devised to enforce a cooperative pathway. Thus, dimeric,[5] oligomeric,[6] dendritic,[7] polymeric,[8] colloidal,[9] and encapsulated[10] (salen)Co complexes showed much improved catalytic efficiency in the HKR, whereas requiring lower catalyst loading.

It would be possible to replace the covalent bond tether with non-covalent bonding interaction such as hydrogen bonds. This self-assembly approach is a highly attractive strategy because various combinations of homo- and hetero-bimetallic systems can be generated in solution by mixing self-assembling monomeric units, without synthesizing individual bimetallic species. Recently, hydrogen-bonding interactions have drawn much attention in asymmetric catalysis. This relatively weak hydrogen bond plays a crucial role in a number of organocatalytic reactions for the activation and orientation of substrates.[11] Hydrogen-bonding interactions have also been recognized as a structural element to construct supramolecular catalysts[12] such as encapsulated catalysts,[13] artificial metalloenzymes,[14] bidentate ligands,[15] organocatalysts,[16] and dinuclear catalysts.[17]

We previously reported a novel self-assembly-based approach toward the dinuclear (salen)Co catalyst through aminopyridine/2-pyridone hydrogen-bonding interactions; these catalyst resulted in significant rate acceleration in the enan-

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[**] Salen = bis-(salicyliden)ethylendiaminato.

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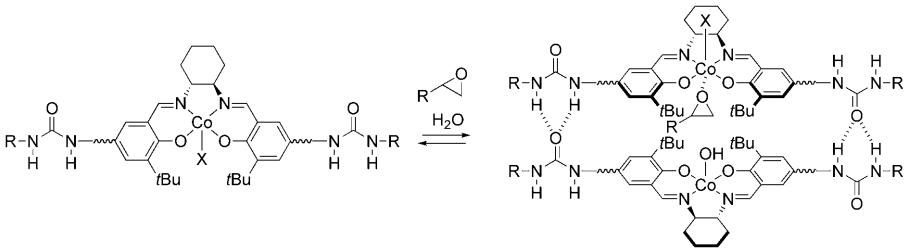
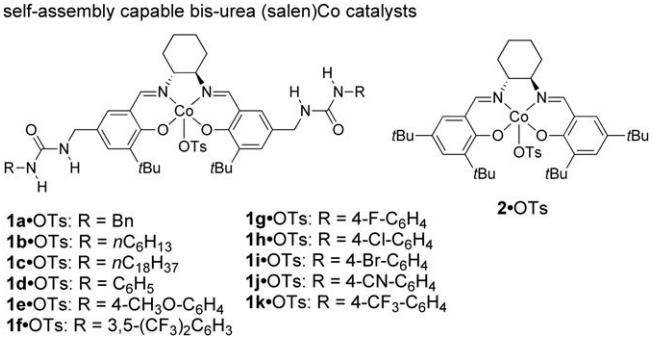
tioselective Henry reactions.[18] It raised an intriguing question whether the self-assembly approach can be applicable to other bimetallic transformations, such as HKR of terminal epoxides. Very recently, Wärnmark and co-workers developed novel supramolecular (salen)Cr catalysts featuring 2-pyridone-containing isoquinolinone and quinolinone hydrogen-bonding pairs to achieve higher reaction rates for *meso*-epoxide opening reactions with $TMSN_3$ (TMS = trimethylsilyl), however, the enantioselectivity observed was generally lower than 10% *ee* (*ee* = enantiomeric excess).[17c] Our initial attempt in HKR with our aminopyridine/2-pyridone-based self-assembled dinuclear catalyst was unsuccessful,[19] prompting us to search for other readily installable hydrogen-bonding pairs that can be systematically varied to modulate self-assembly strength and metal–metal distances. We envisioned that the bis-urea motif could be utilized as a hydrogen-bonding unit in self-assembled (salen)Co catalysts for HKR of epoxides (Scheme 1). Because *N*,*N*′-disubstituted ureas can provide directional hydrogen-bonding interactions between two NH protons and the carbonyl group,[20] the urea motif has been widely applied to the construction of supramolecular architectures such as columns,[21] capsules,[22] nanotubes,[23] channels,[24] supramolecular polymers,[25] and organogels.[26] Furthermore, some bis- and tetra-urea structures have shown self-assembly in polar media such as THF or even in aqueous solution through the combination of hydrogen-bonding and hydrophobic interactions.[22c,27] Herein, we report new bis-urea-functionalized (salen)cobalt catalysts and their improved catalytic efficiency in HKR of epoxides at low catalyst loading (0.03–0.05 mol%).



Scheme 1. Self-association of bis-urea (salen)cobalt complexes (OTs = tosylate).

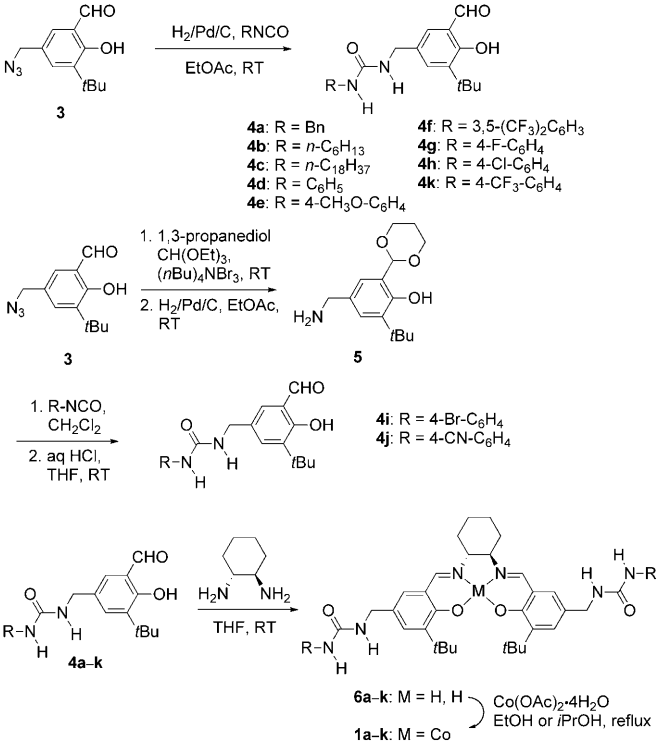
Results and Discussion

Catalysts preparation: In the current ligand design, the CH_2 spacer was employed to connect the *N*,*N*′-disubstituted urea motif to the (salen)cobalt core (Scheme 2). In order to study the influence of different end groups on the urea motif, various alkyl- and aryl-substituted bis-urea (salen)Co complexes were prepared. Prior to the catalytic reactions, the Co^{II} precatalysts **1a–k** were oxidized to the active Co^{III} species **1a–k**•OTs by using 1.1 equivalent of *p*-TsOH (*p*-Ts = *p*-toluenesulfonyl) in the open air.



Scheme 2. Self-assembly capable bis-urea (salen)cobalt complexes.

Bis-urea-functionalized (salen)Co^{II} precatalysts (**1a–k**) were synthesized in four steps from 5-(azidomethyl)-3-*tert*-butyl-2-hydroxybenzaldehyde (**3**) (Scheme 3).[28] The alkyl- and aryl-functionalized urea salicylaldehydes (**4a–h** and **4k**) were conveniently prepared by the reaction of azide **3** with the corresponding isocyanates under catalytic hydrogenation conditions.[29] For the urea compounds bearing reducible functional groups under catalytic hydrogenation conditions (4-Br-C_6H_4- and 4-CN-C_6H_4-), an alternative route was taken to avoid potential reduction of such substituents. Thus, salicy-

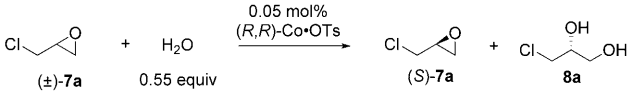


Scheme 3. Synthesis of the bis-urea (salen)Co^{II} precatalysts.

laldehydes **4i** and **4j** were obtained in good overall yields, by the reaction of the acetal-protected amine **5**[30] the with corresponding isocyanates, followed by the removal of the acetal protecting group. Then, the resulting urea-functionalized salicylaldehydes **4a–k** were condensed with (*R*,*R*)-1,2-diaminocyclohexane to afford the bis-urea salen ligands **6a–k**. Finally, the bis-urea (salen)Co^{II} complexes **1a–k** were obtained by the reaction of $Co(OAc)_2{\cdot}4H_2O$ with the corresponding salen ligands in EtOH or *i*PrOH under argon atmosphere. All bis-urea (salen)Co^{II} complexes were characterized by high-resolution mass spectrometry and elemental analysis.

Hydrolytic kinetic resolution: The new bis-urea-functionalized (salen)Co catalysts were evaluated by comparing reaction rates for HKR of *rac*-epichlorohydrin (**7a**) in THF at 23 °C with 0.55 equivalents of H_2O (Table 1). Tosylate was chosen as a counterion for this study and bromobenzene was added as an internal standard. We were pleased to find that all bis-urea (salen)Co·OTs catalysts showed significant rate acceleration (4.2—13 times) compared to the monomeric catalyst **2**·OTs (Table 1, entries 1–11 versus entry 12). The N-aryl end groups (Table 1, entries 4–11) show greater rate acceleration than the N-alkyl end groups (Table 1, entries 1–3). Electron-withdrawing groups on the phenyl ring (Table 1, entries 6–11) appear to be better; however, the substituent effect does not linearly correlate with the Hammett parameter σ. The 4-Cl-C_6H_4- and 4-CF_3-C_6H_4- end groups prove to be the best from the survey (Table 1, entries 8 and 11), and the 4-CF_3-C_6H_4- group (**1k**·OTs) was selected for the further studies.

Table 1. Kinetic data for the HKR of *rac*-epichlorohydrin catalyzed by (salen)Co·OTs catalysts.[a]



Entry	Catalyst	R	k_{obs} [h^{-1}][b,c]	Relative rate[d]
1	**1a**·OTs	Bn[e]	3.2×10^{-1}	4.2
2	**1b**·OTs	*n*-C_6H_{13}	3.5×10^{-1}	4.6
3	**1c**·OTs	*n*-$C_{18}H_{37}$	5.4×10^{-1}	7.2
4	**1d**·OTs	C_6H_5	6.5×10^{-1}	8.6
5	**1e**·OTs	4-CH_3O-C_6H_4	6.5×10^{-1}	8.6
6	**1f**·OTs	3,5-$(CF_3)_2C_6H_3$	7.4×10^{-1}	9.7
7	**1g**·OTs	4-F-C_6H_4	6.7×10^{-1}	8.8
8	**1h·OTs**	**4-Cl-C_6H_4**	**1.0_0**	**13**
9	**1i**·OTs	4-Br-C_6H_4	7.2×10^{-1}	9.5
10	**1j·OTs**	4-CN-C_6H_4	5.1×10^{-1}	6.7
11	**1k·OTs**	**4-CF_3-C_6H_4**	**1.0_4**	**13_7**
12	**2**·OTs	–	7.6×10^{-2}	1.0

[a] Reactions were carried out on a 5.0 mmol scale in THF (1.0 mL) at 23 °C. [b] k_{obs} was determined from plots of $-\ln([epoxide]/[epoxide]_0)$ versus time. [c] Determined by chiral GC-MS (Chiraldex γ-TA) relative to an internal standard (C_6H_5Br). [d] Relative rate per **2**·OTs. [e] Bn = benzyl.

One of the impressive features of HKR catalyzed by (salen)Co complexes is that this reaction can be carried out under solvent-free conditions, which are environment-friendly and cost-effective.[31] Because epoxide substrates and diol products are generally liquid, it is possible to perform HKR under solvent-free or highly concentrated conditions.[4,31] In addition, it would be necessary to avoid the use of solvent particularly for volatile epoxides due to their isolation by vacuum transfer. Therefore, solvent-free conditions for HKR are highly desirable. To examine the catalytic activity under highly-concentrated and solvent-free conditions, kinetic resolution of *rac*-epichlorohydrin (5.0 mmol) was performed at 23 °C with 0.7 equivalents of H_2O and 0.05 mol % of **1k**·OTs in THF (0.1 mL) and under solvent-free conditions. It is important to note that bis-urea catalyst **1k**·OTs exhibited significantly better performance than the monomeric catalyst **2**·OTs under both conditions (Figure 1).

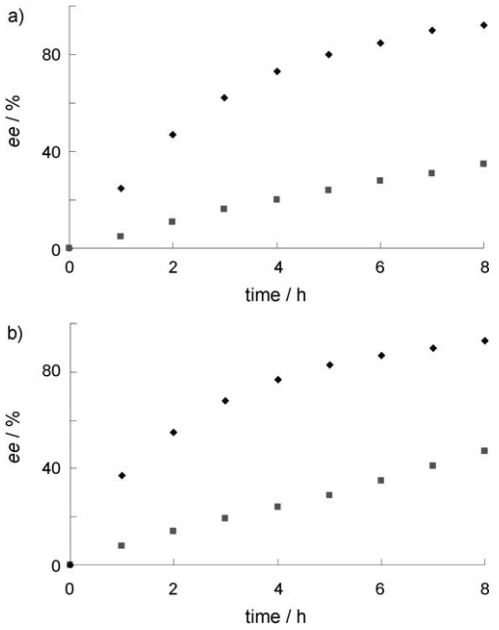
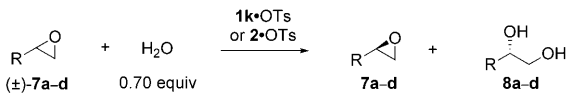


Figure 1. a) HKR of *rac*-epichlorohydrin (5.0 mmol) with 0.05 mol % **1k**·OTs (◆) and **2**·OTs (■) in THF (0.1 mL). b) HKR of *rac*-epichlorohydrin (5.0 mmol) under solvent-free conditions with 0.05 mol % **1k**·OTs (◆) and **2**·OTs (■).

After 8 h, 92 % *ee* (THF) and 93 % *ee* (solvent-free) were achieved with 0.05 mol % **1k**·OTs, whereas only 35 % *ee* (THF) and 47 % *ee* (solvent-free) were achieved with 0.05 mol % **2**·OTs. Note that the self-assembled catalyst that is potentially sensitive to the medium polarity, maintains its catalytic efficiency under solvent-free conditions, although the reaction medium continuously changes as the reaction progresses.[31]

The substrate scope was then studied for solvent-free HKR of epoxides by using 0.03–0.05 mol % bis-urea (salen)Co catalyst **1k**·OTs (Table 2). After the reaction was completed, the remaining epoxide was isolated by vacuum transfer. To our delight, bis-urea (salen)Co catalyst **1k**·OTs displayed improved performance for all four terminal epoxides

Table 2. HKR of terminal epoxides under solvent-free conditions.[a]



(±)-**7a–d** 7a–d 8a–d

Entry	R	Catalyst [mol%]	Time [h]	*ee*[b] [%]	Yield[d] [%]
1	CH_2Cl (**7a**)	**1k**•OTs (0.05)	14	99	41
2	CH_2Cl (**7a**)	**2**•OTs (0.05)	71	96	42
3	CH_2O(allyl) (**7b**)	**1k**•OTs (0.05)	8	99	43
4	CH_2O(allyl) (**7b**)	**2**•OTs (0.05)	32	98	43
5	CH_2CH_3 (**7c**)	**1k**•OTs (0.03)	8	99	43
6	CH_2CH_3 (**7c**)	**2**•OTs (0.03)	24	99	43
7	$(CH_2)_3CH_3$ (**7d**)	**1k**•OTs (0.03)	14	99	41
8	$(CH_2)_3CH_3$ (**7d**)	**2**•OTs (0.03)	42	99	42

[a] Reactions were carried out with 0.7 equiv of H_2O on 10–20 mmol scales under solvent-free conditions at 23 °C. [b] *ee* values of the epoxide. Determined by chiral GC-MS (Chiraldex γ-TA). [c] Yields of isolated epoxides based on *rac*-epoxides (50% theoretical maximum).

examined (Table 2, entries 1, 3, 5, 7 versus entries 2, 4, 6, 8). Compared to the monomeric catalyst **2**•OTs, the bis-urea (salen)Co catalyst **1k**•OTs required much shorter reaction time (8–14 vs. 24–71 h, respectively) to resolve epoxides completely (99% *ee*) in good yields (41–43%) at low catalyst loadings (0.03–0.05 mol%).

Kinetic and mechanistic study: We hypothesized that the rate enhancement can be attributed to the self-association of (salen)Co units through urea–urea hydrogen bonding. A series of kinetic/mechanistic studies was performed mainly in THF to validate the main hypothesis. It is generally assumed that the same mechanisms are operating under solvent-free conditions.[4,31] First, kinetic studies showed that the rate laws were second order in the cobalt concentration for the bis-urea (salen)Co complex **1f**•OTs (Figure 2, rate $\propto$

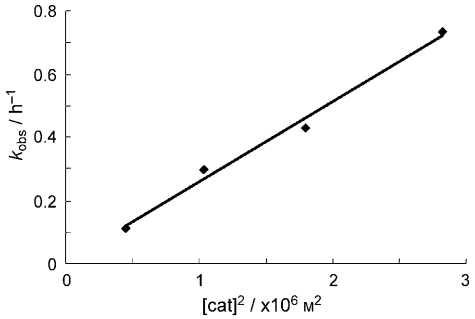


Figure 2. Kinetic analysis of the reaction order of the catalyst concentration (R^2=0.9906).

k_{obs}[(salen)Co]^2). This result indicates that the same bimetallic mechanism is operating with the bis-urea (salen)Co complex as with the monomeric (salen)Co complex **2**•OTs.[4]

Assuming the dimeric aggregate is an actual catalytic species, the rate law can be expressed in terms of the monomer–dimer equilibrium constant K_2 [Eqs. (1)–(3)]. Note that the second-order-like kinetic dependence on the total catalyst concentration, $[cat]_{tot}$ [Eq. (4)], is expected from self-assembled systems with moderate K_2 values under diluted conditions [Eq. (5)], whereas the first-order kinetic dependence is expected from covalently-tethered dimeric catalysts. It is also interesting to note that the kinetics of the current self-assembly conditions show correlation between the observed rate constant (k_{obs}) and the dimerization constant K_2 [Eq. (5)].

$$K_2 = [\text{dimer}]/[\text{monomer}]^2 \quad (1)$$

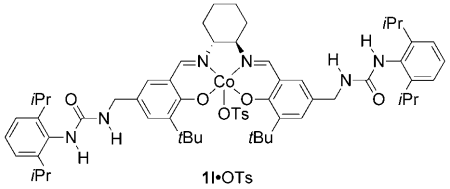
$$\text{rate} \propto k\,[\text{dimer}] \quad (2)$$

$$\text{rate} \propto kK_2\,[\text{monomer}]^2 \quad (3)$$

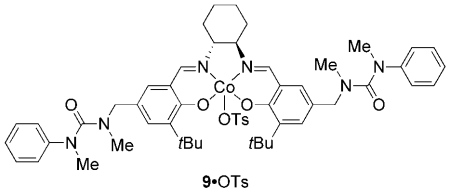
$$[\text{cat}]_{tot} = 2[\text{dimer}]+[\text{monomer}] \quad (4)$$

$$\text{if } [\text{dimer}] \ll [\text{cat}]_{tot}: \quad \text{rate} \propto kK_2\,\{[\text{cat}]_{tot}-2\,[\text{dimer}]\}^2 \approx kK_2\,[\text{cat}]_{tot}^2 \quad (5)$$

Second, control experiments were performed to determine whether the accessible NH groups are crucial for rate acceleration. Two compounds lacking accessible urea NH groups because of bulky *ortho*-isopropyl groups on the aryl substituent (**1l**•OTs) or N–Me substitution (**9**•OTs), were



1l•OTs

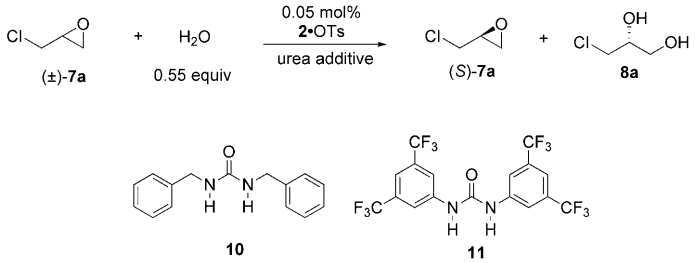


9•OTs

tested for the HKR of *rac*-epichlorohydrin under the same reaction conditions as described in Table 1. Both catalysts resulted in slower reaction rate (relative rate = 0.8 and 0.7 for **1l**•OTs and **9**•OTs, respectively), indicating that accessible urea NH groups are responsible for the observed rate acceleration.

Third, additional control experiments were conducted to rule out an alternative scenario involving electrophilic activation of epoxides by the urea functionality through double hydrogen bonding.[32] Thus, two different *N,N′*-disubstituted urea compounds (**10** and **11**) were added to the reaction mixture in the presence of the monomeric catalyst **2**•OTs (Table 3). Both urea additives decreased the reaction rate in the HKR of *rac*-epichlorohydrin. The electron-richer diben-

Table 3. Kinetic data for the HKR of *rac*-epichlorohydrin catalyzed by **2**•OTs catalysts and urea additive.[a]



Entry	Additive ([mol%])	k_{obs} [h^{-1}][b,c]	Relative rate[d]
1	none	7.6×10^{-2}	1.0
2	**10** (0.1)	3.8×10^{-2}	0.5
3	**11** (0.1)	6.7×10^{-2}	0.9
4	**11** (0.4)	3.2×10^{-2}	0.4

[a] Reactions were carried out on a 5.0 mmol scale in THF (1.0 mL) at 23 °C. [b] k_{obs} was determined from plots of $-\ln([epoxide]/[epoxide]_0)$ versus time. [c] Determined by chiral GC-MS (Chiraldex γ-TA) relative to an internal standard (C_6H_5Br). [d] Relative rate per **2**•OTs.

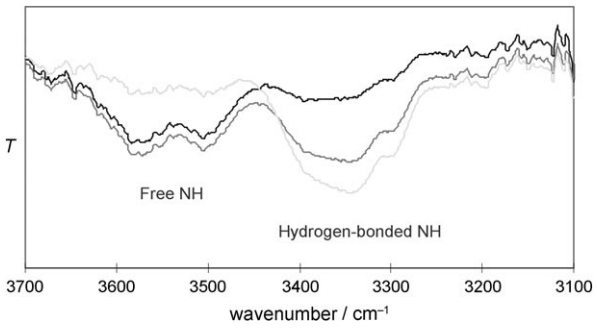


Figure 3. The NH stretching region of the FTIR spectra of **1k** in THF at three different concentration (1 (black), 2 (dark gray), and 3 mM (light gray)) at 25 °C.

zyl urea **10** (Table 3, entry 2) and increased amounts of urea additive (Table 3, entry 3 versus entry 4) resulted in slower reaction rates. These results suggest that the urea additive might function as a competitive inhibitor, presumably through coordination to the metal center. It also explains why electron-deficient R groups showed better reactivity in HKR (Table 1).

Self-association study: More direct experimental evidence was sought for self-association through urea–urea hydrogen bonding in solution. IR spectroscopy has been widely applied for studying self-assembly of urea and bis-urea compounds because free NH groups and hydrogen-bonded NH groups have different frequencies. FTIR experiments with bis-urea (salen)Co **1k** in THF (3 mM) at 25 °C revealed strong hydrogen-bonded NH stretching vibrations ($\tilde{\nu}=3347$ and 3295 cm^{-1}) in comparison to free NH stretching vibrations ($\tilde{\nu}=3571$ and 3505 cm^{-1}). The intensity of hydrogen-bonded NH stretching vibrations was decreased with lowering concentration, but the vibrations were still significant at a 1 mM concentration (Figure 3). This result indicates that the urea NH functionalities of the bis-urea (salen)Co complexes are involved in intermolecular hydrogen-bonding events in THF.

To evaluate the self-association strength, ^1H NMR dilution experiments were performed by using the corresponding bis- and mono-urea (salen)Ni complexes **12** and **13**[33] at 25 °C in [D_8]THF. Two NH proton signals of the urea group in the Ni complexes were monitored upon variation of concentration (0.76–19.1 mM), and the downfield shifts of two urea protons ($\Delta\delta\approx0.2$ ppm) were observed with increasing concentration. The dimerization constants of **12** and **13** were estimated to be (56 ± 22) and $(32\pm3)\,M^{-1}$, respectively, by using the simple monomer–dimer model (Figure 4a and b).[34] Although the monomer–dimer model was used considering the known bimetallic mechanism for the HKR of epoxides, it is also possible that urea and bis-urea molecules can exist as higher aggregates. With the equal K model ($K_2=K_n=K$),[35] K_a values of **12** and **13** were determined to be (70 ± 29) and $(32\pm0)\,M^{-1}$, respectively.[34] Thus, both models indicate that urea (salen)Ni complexes self-assemble in THF with moderate association strength. However, further study will be necessary to elucidate precise dimerization/oligomerization behavior in this system. The mono-urea (salen)Co complex **14**•OTs was also prepared and tested for the HKR of *rac*-epichlorohydrin under the same reaction conditions as described in Table 1 to compare relative rates (Figure 4b). It is interesting to note that the observed self-association strengths of the bis- and mono-urea (salen)Ni complexes (56 vs. 32 M^{-1}) are in accordance with the observed rate enhancements from the corresponding (salen)Co^{III} catalysts (13 vs. 8.4).

X-ray packing structure and MM2 calculation: The X-ray structure of the bis-urea (salen)Ni complex **15** (R = Bn), obtained by slow evaporation in DMF, revealed urea–urea hydrogen bonding between the salen units in the solid state.[36] The crystal packing shows the interstack arrangement between two extensive hydrogen-bond networking layers (Figure 5a), however, the desired head-to-tail bimetallic arrangement is not observed within the hydrogen-bonding network (Figure 5b). Thus, MM2 calculations were carried out to probe feasibility of such dimeric structures capable of dual activation.[37] Optimizations were performed on a simplified bis-urea (salen)Ni complex (R = Me) by using the CAChe program (Fujitsu), and the two resulting plausible energy-minimized structures are shown in Figure 5c.[38] Two (salen)Ni units can be assembled through two urea–urea hydrogen-bonding interactions either in a parallel (P) or an antiparallel (A) mode and the estimated Ni–Ni distances are approximately 6 Å in both modes.[39]

Asymmetric hydrolysis of cyclohexene oxide: The improved catalytic efficiency of the bis-urea (salen)Co catalyst can be demonstrated in asymmetric hydrolysis of cyclohexene oxide, which is known to be very challenging with monomer-

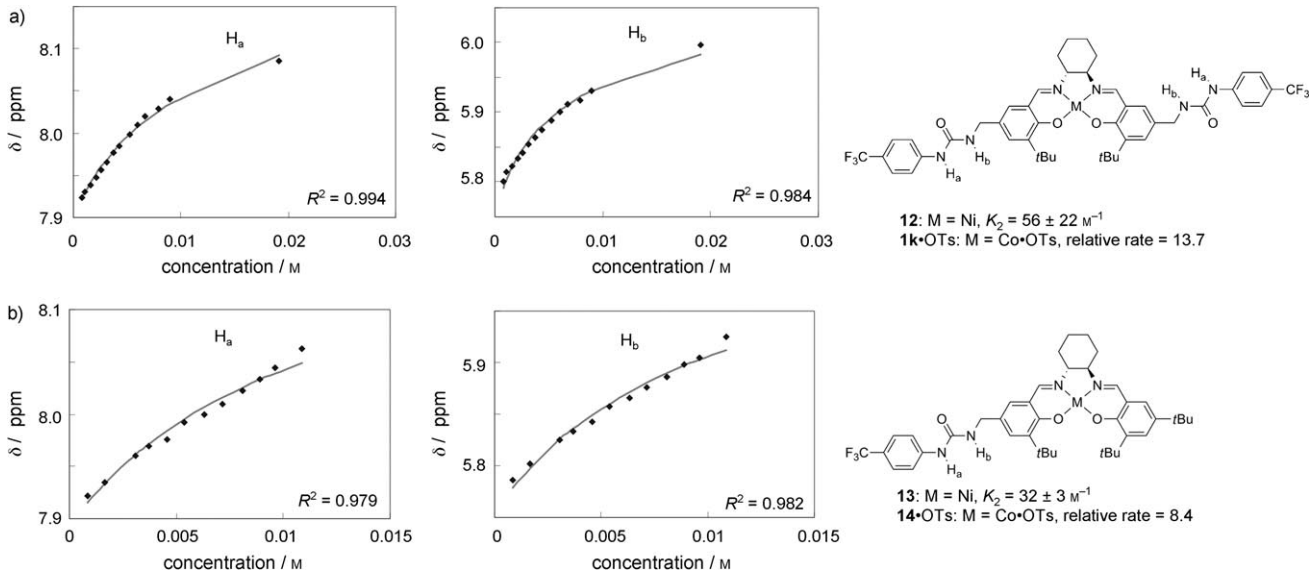


Figure 4. a) Concentration-dependent ^{1}H NMR shift of two urea protons (H_a: aromatic, H_b: aliphatic) of **12** and dimerization constant of (salen)Ni complexe **12** in [D_8]THF at 25 °C. The data were fitted to the monomer–dimer model (solid line). Relative rates for HKR of *rac*-epichlorohydin catalyzed by the corresponding (salen)Co complex **1l**•OTs in THF. b) Concentration-dependent ^{1}H NMR shift of two urea protons (H_a: aromatic, H_b: aliphatic) of **13** and dimerization constant of (salen)Ni complexe **13** in [D_8]THF at 25 °C. The data were fitted to the monomer–dimer model (solid line). Relative rates for HKR of *rac*-epichlorohydin catalyzed by the corresponding (salen)Co complex **14**•OTs in THF.

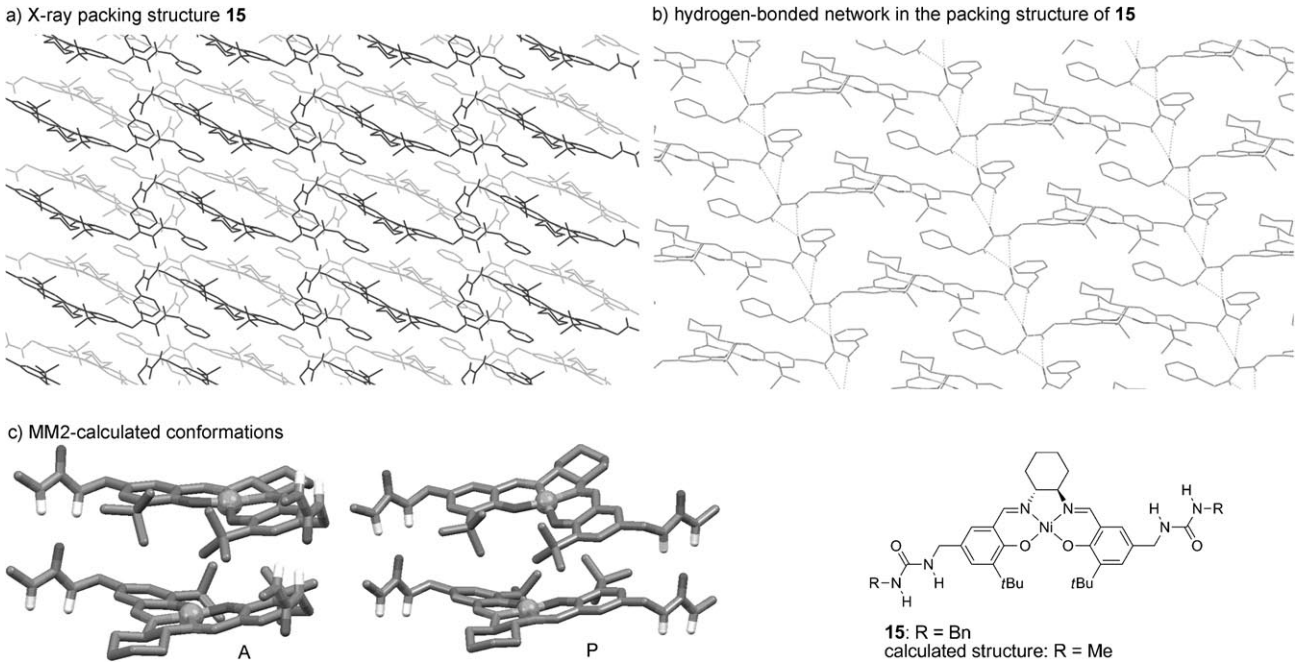
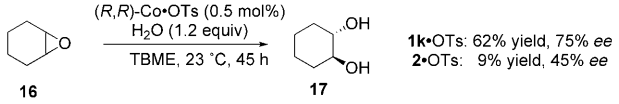


Figure 5. a) X-ray packing structures of **15** showing interstack arrangement between two hydrogen-bond networking layers. b) Observed hydrogen-bonded network in the packing structure of **15**. c) Two plausible structures of the bis-urea (salen)Ni dimer: antiparallel (A) and parallel (P) mode. d) Structure of **15**.

ic (salen)Co catalyst (Scheme 4). After 45 h, **1k**•OTs gave the desired diol product with much higher yield (62%) and enantiomeric excess (75%) than the monomeric catalyst **2**•OTs (9% yield and 45% *ee*).[40]



Scheme 4. Asymmetric hydrolysis of cyclohexene oxide (**16**) (TBME = methyl *tert*-butyl ether).

Conclusion

In conclusion, we have developed novel bis-urea-functionalized (salen)Co catalysts that are designed to self-assemble through urea–urea hydrogen bonding. An optimized bis-urea (salen)Co^{III} catalyst shows improved reaction rate (up to 13 times) in HKR of epoxides. Kinetic/mechanistic study results are consistent with the idea that self-assembly through urea–urea hydrogen bonding is responsible for the observed rate enhancement. This work demonstrates that hydrogen bonding can be utilized to construct chiral bimetallic HKR catalysts. Modifications of ligand structures to further improve the catalytic efficiency are currently in progress.

Experimental Section

General: THF, CH_2Cl_2, and Et_2O were passed through two packed columns of neutral alumina under positive pressure prior to use. All the chemicals used were commercially available and were used as received without further purification. NMR spectra were recorded by using Varian FT-NMR machines, operating at 300 and 500 MHz for ^1H NMR and at 75.4 and 125 MHz for ^{13}C NMR. Fourier transform infrared (FTIR) spectra were recorded with a Perkin–Elmer Spectrum One FTIR Spectrometer in CaF_2 cells of 1 mm path length. High-resolution mass spectra were recorded on a MALDI-TOF spectrometer, an APCI-TOF spectrometer, or an ESI-TOF spectrometer. Enantiomeric excesses were determined by chiral GC-MS analysis by using a Chiraldex γ-TA column.

General procedure for the preparation of bis-urea salen ligands 6a–l: Salicylaldehyde (0.36 mmol, 2.0 equiv) was added to a solution of (1*R*,2*R*)-cyclohexane-1,2-diamine (0.18 mmol) in THF (5 mL) 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 (*n*-hexane/EtOAc 5:1 then 2:1 or 1:2) to give the resulting bis-urea salen as a yellow solid.

6a: 99% yield, yellow solid; ^1H NMR (300 MHz, [D$_6$]DMSO): $\delta=14.02$ (s, 2H), 8.42 (s, 2H), 7.29–7.14 (m, 12H), 6.98 (s, 2H), 6.33–6.25 (m, 4H), 4.18 (d, $J=6.0$ Hz, 4H), 4.05 (d, $J=5.4$ Hz, 4H), 3.45–3.38 (m, 2H), 1.93–1.83 (m, 2H), 1.83–1.74 (m, 2H), 1.69–1.56 (m, 2H), 1.49–1.38 (m, 2H), 1.31 ppm (s, 18H); ^{13}C NMR (75 MHz, [D$_6$]DMSO): $\delta=166.5$, 159.2, 158.6, 141.6, 136.8, 130.4, 129.1, 129.0, 128.8, 127.6, 127.2, 118.4, 71.7, 43.6, 43.3, 35.0, 33.2, 29.8, 24.5 ppm; HRMS (APCI-TOF): *m*/*z* calcd for $C_{46}H_{59}N_6O_4$: 759.4592 $[M+H]^+$; found: 759.4620.

6b: 94% yield, yellow solid; ^1H NMR (300 MHz, $CDCl_3$): $\delta=13.57$ (s, 2H), 7.94 (s, 2H), 6.97 (d, $J=2.0$ Hz, 2H), 6.03 (s, 2H), 5.90 (s, 2H), 5.74 (s, 2H), 3.74–3.53 (m, 4H), 3.28–3.25 (m, 2H), 3.04 (q, $J=6.3$ Hz, 4H), 2.17–2.11 (m, 2H), 1.97–1.94 (m, 2H), 1.81–1.72 (m, 2H), 1.55–1.46 (m, 2H), 1.44–1.37 (m, 4H), 1.28–1.23 (m, 12H), 1.21 (s, 18H), 0.85 ppm (t, $J=6.8$ Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=166.4$, 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 ppm; HRMS (ESI-TOF): *m*/*z* calcd for $C_{44}H_{71}N_6O_4$: 747.5531 $[M+H]^+$; found: 747.5526.

6c: 92% yield, yellow solid; ^1H NMR (300 MHz, $CDCl_3$): $\delta=13.71$ (s, 2H), 8.01 (s, 2H), 7.07 (s, 2H), 6.34 (s, 2H), 5.21 (s, 2H), 5.13 (s, 2H), 3.97–3.74 (m, 4H), 3.28–3.25 (m, 2H), 3.11 (td, $J=6.5$, 6.5 Hz, 4H), 2.13–1.79 (m, 6H), 1.54–1.38 (m, 6H), 1.31 (s, 18H), 1.26 (s, 60H), 0.88 ppm (t, $J=6.8$ Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=166.3$, 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 ppm; HRMS (ESI-TOF): *m*/*z* calcd for $C_{68}H_{119}N_6O_4$: 1083.9287 $[M+H]^+$; found: 1083.9223.

6d: 81% yield, yellow solid; ^1H NMR (300 MHz, [D$_6$]DMSO): $\delta=14.09$ (s, 2H), 8.48 (s, 2H), 8.39 (s, 2H), 7.36–7.16 (m, 10H), 7.07 (s, 2H), 6.88 (t, $J=7.2$ Hz, 2H), 6.43 (t, $J=5.7$ Hz, 2H), 4.12 (d, $J=5.7$ Hz, 4H), 3.45–3.38 (m, 2H), 1.93–1.83 (m, 2H), 1.83–1.74 (m, 2H), 1.69–1.56 (m, 2H), 1.49–1.38 (m, 2H), 1.31 ppm (s, 18H); ^{13}C NMR (75 MHz, [D$_6$]DMSO): $\delta=165.9$, 158.7, 155.0, 140.4, 136.2, 129.1, 128.7, 128.5, 121.0, 117.8, 117.6, 71.0, 42.4, 34.3, 32.5, 29.1, 23.8 ppm; HRMS (APCI-TOF): *m*/*z* calcd for $C_{44}H_{55}N_6O_4$: 731.4279 $[M+H]^+$; found: 731.4291.

6e: 67% yield, yellow solid; ^1H NMR (300 MHz, $CDCl_3$): $\delta=13.63$ (s, 2H), 7.95 (s, 2H), 7.62 (s, 2H), 7.05–7.00 (m, 6H), 6.66 (d, $J=9.1$ Hz, 4H), 6.12 (s, 2H), 6.03 (s, 2H), 3.73–3.63 (m, 4H), 3.70 (s, 6H), 3.31–3.28 (m, 2H), 2.18–2.14 (m, 2H), 2.00–1.97 (m, 2H), 1.84–1.81 (m, 2H), 1.63–1.55 (m, 2H), 1.18 ppm (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=166.4$, 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 ppm; HRMS (APCI-TOF): *m*/*z* calcd for $C_{46}H_{59}N_6O_6$: 791.4491 $[M+H]^+$; found: 791.4493.

6f: 86% yield, yellow solid; ^1H NMR (500 MHz, [D$_6$]DMSO): $\delta=14.09$ (s, 2H), 9.22 (s, 2H), 8.46 (s, 2H), 8.07 (s, 4H), 7.51 (s, 2H), 7.17 (d, $J=2.0$ Hz, 2H), 7.06 (d, $J=1.7$ Hz, 2H), 6.87 (t, $J=5.9$ Hz, 2H), 4.15 (d, $J=6.2$ Hz, 4H), 3.45–3.38 (m, 2H), 1.93–1.83 (m, 2H), 1.83–1.74 (m, 2H), 1.69–1.56 (m, 2H), 1.49–1.38 (m, 2H), 1.25 ppm (s, 18H); ^{13}C NMR (125 MHz, [D$_6$]DMSO): $\delta=165.8$, 158.8, 154.6, 142.6, 136.2, 130.5 (q, $J=32$ Hz), 128.9, 128.6, 128.4, 123.4 (q, $J=271$ Hz), 117.7, 117.1, 113.4, 71.1, 42.4, 34.2, 32.5, 29.0, 23.8 ppm; HRMS (APCI-TOF): *m*/*z* calcd for $C_{48}H_{51}F_{12}N_6O_4$: 1003.3775 $[M+H]^+$; found: 1003.3801.

6g: 52% yield, yellow solid; ^1H NMR (300 MHz, [D$_6$]DMSO): $\delta=14.09$ (s, 2H), 8.48–8.45 (m, 4H), 7.39–7.35 (m, 4H), 7.18 (s, 2H), 7.07–7.01 (m, 4H), 6.41 (s, 2H), 4.13 (s, 4H), 3.43 (m, 2H), 1.93–1.83 (m, 2H), 1.83–1.74 (m, 2H), 1.69–1.56 (m, 2H), 1.49–1.38 (m, 2H), 1.30 ppm (s, 18H); ^{13}C NMR (75 MHz, [D$_6$]DMSO): $\delta=165.9$, 158.8, 156.8 (d, $J=237$ Hz), 155.1, 136.8 (d, $J=2.6$ Hz), 136.2, 129.1, 128.7, 128.6, 119.2 (d, $J=7.4$ Hz), 117.8, 115.0 (d, $J=22$ Hz), 71.0, 42.4, 34.3, 32.5, 29.1, 23.8 ppm; HRMS (ESI-TOF): *m*/*z* calcd for $C_{44}H_{53}F_2N_6O_4$: 767.4091 $[M+H]^+$; found: 767.4087.

6h: 85% yield, yellow solid; ^1H NMR (300 MHz, $CDCl_3$): $\delta=13.69$ (s, 2H), 7.95 (s, 4H), 7.06–6.94 (m, 10H), 6.28 (s, 2H), 6.04 (s, 2H), 3.71–3.64 (m, 4H), 3.31–3.28 (m, 2H), 2.17–2.13 (m, 2H), 2.00–1.97 (m, 2H), 1.84–1.81 (m, 2H), 1.63–1.55 (m, 2H), 1.15 ppm (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=166.1$, 159.2, 157.0, 137.4, 128.8, 128.1, 127.8, 127.4, 127.0, 121.3, 121.0, 117.7, 73.0, 43.0, 34.6, 32.7, 29.0, 24.5 ppm; HRMS (APCI-TOF): *m*/*z* calcd for $C_{44}H_{53}Cl_2N_6O_4$: 799.3500 $[M+H]^+$; found: 799.3531.

6i: 91% yield, yellow solid; ^1H NMR (300 MHz, [D$_6$]DMSO): $\delta=14.09$ (s, 2H), 8.57 (s, 2H), 8.48 (s, 2H), 7.44–7.36 (m, 8H), 7.17 (d, $J=2.0$ Hz, 2H), 7.06 (d, $J=2.0$ Hz, 2H), 6.50 (t, $J=5.8$ Hz, 2H), 4.12 (d, $J=5.8$ Hz, 4H), 3.46 (m, 2H), 1.92–1.88 (m, 2H), 1.88–1.80 (m, 2H), 1.76–1.60 (m, 2H), 1.54–1.44 (m, 2H), 1.30 ppm (s, 18H); ^{13}C NMR (75 MHz, [D$_6$]DMSO): $\delta=165.9$, 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 ppm; HRMS (ESI-TOF): *m*/*z* calcd for $C_{44}H_{53}Br_2N_6O_4$: 887.2490 $[M+H]^+$; found: 887.2469.

6j: 55% yield, yellow solid; ^1H NMR (300 MHz, [D$_6$]DMSO): $\delta=14.10$ (s, 2H), 8.99 (s, 2H), 8.47 (s, 2H), 7.67–7.64 (m, 4H), 7.57–7.54 (m, 4H), 7.18 (d, $J=2.0$ Hz, 2H), 7.07 (d, $J=2.0$ Hz, 2H), 6.69 (t, $J=5.8$ Hz, 2H), 4.14 (d, $J=5.7$ Hz, 4H), 3.46 (m, 2H), 1.94–1.90 (m, 2H), 1.88–1.80 (m, 2H), 1.76–1.60 (m, 2H), 1.54–1.44 (m, 2H), 1.29 ppm (s, 18H); ^{13}C NMR (75 MHz, [D$_6$]DMSO): $\delta=165.9$, 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 ppm; HRMS (ESI-TOF): *m*/*z* calcd for $C_{46}H_{53}N_8O_4$: 781.4184 $[M+H]^+$; found: 781.4170.

6k: 89% yield, yellow solid; ^1H NMR (300 MHz, [D$_6$]DMSO): $\delta=14.10$ (s, 2H), 8.87 (s, 2H), 8.48 (s, 2H), 7.60–7.53 (m, 8H), 7.18 (d, $J=2.0$ Hz, 2H), 7.08 (d, $J=2.0$ Hz, 2H), 6.62 (t, $J=5.7$ Hz, 2H), 4.15 (d, $J=5.7$ Hz, 4H), 3.44 (m, 2H), 1.93–1.83 (m, 2H), 1.83–1.74 (m, 2H), 1.69–1.56 (m, 2H), 1.49–1.38 (m, 2H), 1.29 ppm (s, 18H); ^{13}C NMR (75 MHz, [D$_6$]DMSO): $\delta=165.9$, 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 ppm; HRMS (ESI-TOF): *m*/*z* calcd for $C_{46}H_{53}F_6N_6O_4$: 867.4027 $[M+H]^+$; found: 867.4024.

6l: 92% yield, yellow solid; ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 14.02 (s, 2H), 8.43 (s, 2H), 7.37 (s, 2H), 7.23 (s, 2H), 7.17 (d, J = 7.9 Hz, 2H), 7.08 (m, 4H), 7.03 (s, 2H), 6.46 (s, 2H), 4.11 (s, 4H), 3.46 (m, 2H), 3.10 (m, 2H), 1.94–1.90 (m, 2H), 1.88–1.80 (m, 2H), 1.76–1.60 (m, 2H), 1.54–1.44 (m, 2H), 1.34 (s, 18H), 1.07 ppm (d, J = 6.8 Hz, 24H); ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 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 ppm; HRMS (ESI-TOF): m/z calcd for $C_{56}H_{79}N_6O_4$: 899.6157 $[M+H]^+$; found: 899.6165.

General procedure for the preparation of (salen)cobalt complexes 1a–l: $Co(OAc)_2{\cdot}4H_2O$ (0.21 mmol, 1.0 equiv) was added to a solution or suspension of the appropriate salen ligand (0.21 mmol) in EtOH (5 mL), and heated at reflux for 3 h under argon. The precipitate was collected by filtration, washed with EtOH, and then dried under vacuum for 24 h to give the (salen)cobalt complex.

1a: 68% yield, red solid; HRMS (ESI-TOF): m/z calcd for $C_{46}H_{56}CoN_6O_4$: 815.3690 $[M]^+$; found: 815.3678; elemental analysis calcd (%) for $C_{46}H_{56}CoN_6O_4$: C 55.73, H 5.46, N 8.12; found C 55.73, H 5.46, N 8.12.

1b: 39% yield, red solid; HRMS (ESI-TOF): m/z calcd for $C_{44}H_{68}CoN_6O_4$: 803.4629 $[M]^+$; found: 803.4629; elemental analysis calcd (%) for $C_{44}H_{68}CoN_6O_4$: C 65.73, H 8.53, N 10.45; found C 65.40, H 8.86, N 10.26.

1c: 56% yield, reddish brown solid; HRMS (MALDI-TOF): m/z calcd for $C_{68}H_{116}CoN_6O_4$: 1139.8385 $[M]^+$; found: 1139.8399; elemental analysis calcd (%) for $C_{68}H_{116}CoN_6O_4$: C 71.60, H 10.25, N 7.37; found C 71.61, H 10.56, N 7.19.

1d: 60% yield, red solid; HRMS (ESI-TOF): m/z calcd for $C_{44}H_{52}CoN_6O_4$: 787.3377 $[M]^+$; found: 787.3343; elemental analysis calcd (%) for $C_{44}H_{52}CoN_6O_4$: C 67.08, H 6.65, N 10.67; found C 66.79, H 6.88, N 10.48.

1e: 67% yield, reddish brown solid; HRMS (ESI-TOF): m/z calcd for $C_{46}H_{56}CoN_6O_6$; 847.3588 $[M]^+$; found: 847.3569; elemental analysis calcd (%) for $C_{46}H_{56}CoN_6O_6$: C 65.16, H 6.66, N 9.91; found C 65.39, H 6.92, N 9.81.

1f: 55% yield, reddish brown solid; HRMS (ESI-TOF): m/z calcd for $C_{48}H_{48}CoF_{12}N_6O_4$; 1059.2872 $[M]^+$; found: 1059.2975; elemental analysis calcd (%) for $C_{48}H_{48}CoF_{12}N_6O_4$: C 54.40, H 4.56, N 7.93; found C 54.18, H 4.53, N 7.58.

1g: 79% yield, orange-red solid; HRMS (ESI-TOF): m/z calcd for $C_{44}H_{50}CoF_2N_6O_4$; 823.3188 $[M]^+$; found: 823.3181; elemental analysis calcd (%) for $C_{44}H_{50}CoF_2N_6O_4$: C 64.15, H 6.12, N 10.20; found C 64.39, H 6.54, N 9.95.

1h: 61% yield, reddish brown solid; HRMS (ESI-TOF): m/z calcd for $C_{44}H_{50}Cl_2CoN_6O_4$; 855.2592 $[M]^+$; found: 855.2546; elemental analysis calcd (%) for $C_{44}H_{50}Cl_2CoN_6O_4$: C 61.68, H 5.88, N 9.81; found C 61.28, H 5.98, N 9.59.

1i: 75% yield, reddish brown solid; HRMS (ESI-TOF): m/z calcd for $C_{44}H_{50}Br_2CoN_6O_4$: 945.1572 $[M]^+$; found: 945.1591; elemental analysis calcd (%) for $C_{44}H_{50}Br_2CoN_6O_4$: C 55.88, H 5.33, N 8.89; found C 55.95, H 5.46, N 8.63.

1j: 32% yield, reddish brown solid; HRMS (ESI-TOF): m/z calcd for $C_{46}H_{50}CoN_8O_4$: 837.3287 $[M]^+$; found: 837.3290; elemental analysis calcd (%) for $C_{46}H_{50}CoN_8O_4$: C 65.94, H 6.01, N 13.37; found C 65.56, H 6.06, N 13.03.

1k: 37% yield, reddish brown solid (note: replacement of ethanol with isopropanol in the general procedure afforded **1k** in higher yield (77%)); HRMS (ESI-TOF): m/z calcd for $C_{46}H_{50}CoF_6N_6O_4$; 923.3124 $[M]^+$; found: 923.3140; elemental analysis calcd (%) for $C_{46}H_{50}CoF_6N_6O_4$: C 59.80, H 5.46, N 9.10; found C 59.57, H 5.46, N 8.87.

1l: 56% yield, red solid; HRMS (ESI-TOF): m/z calcd for $C_{56}H_{76}CoN_6O_4$: 955.5255 $[M]^+$; found: 955.5250; elemental analysis calcd (%) for $C_{56}H_{76}CoN_6O$: C 70.34, H 8.01, N 8.79; found C 70.46, H 8.37, N 8.72.

Reaction rates determination: A vial equipped with a stir bar was charged with (salen)cobalt 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 the 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_2O (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 diethyl ether as eluent, and chiral GC-MS analysis (Chiraldex γ-TA, 70 °C, isothermal, t_R(major) = 4.24, t_R(minor) = 4.68 min). The slopes of the least square lines for the plots of $-\ln([\text{epoxide}]/[\text{epoxide}]_0)$ versus time were determined.

General procedure for hydrolytic kinetic resolution of epoxides under solvent-free conditions: A vial equipped with a stir bar was charged with **1k** (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 air for 30 min. After removing the solvent by rotary evaporation, racemic epichlorohydrin (925 mg, 10 mmol) was added. The vial was placed into a water bath at 23 °C and H_2O (126 μL, 0.70 equiv) was added in one portion. The reaction mixture became homogeneous within 30 min. 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 precooled at −78 °C. The recovered epoxide was dried over anhydrous $MgSO_4$ and filtered to give (*S*)-epichlorohydrin **7a** (390 mg, 42%) as a colorless liquid. The *ee* value 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, 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.[4c]

X-ray crystallography: Suitable crystals of **15** were selected and data were collected at 100 K on a Bruker DUO system equipped with an APEX II area detector and a graphite monochromator utilizing $Mo_{K\alpha}$ radiation (λ = 0.71073 Å). Cell parameters were refined by using up to 9999 reflections. A hemisphere of data was collected by using the ω-scan method (0.5° frame width). Absorption corrections by integration were applied based on measured indexed crystal faces. The structure was solved by the direct methods in SHELXTL6,[41] and refined by using full-matrix least squares. The non-hydrogen atoms were treated anisotropically, whereas the hydrogen atoms were calculated in ideal positions and were riding on their respective carbon atoms. There are two disordered regions in the complex. The hexyl ring C1–C6 was refined in two parts with the site occupation factors dependently refined. Similarly, the phenyl ring on C40 is also disordered and was also refined in two parts with the site occupation factors similarly refined. All amino protons were obtained from a difference Fourier map and refined freely. A total of 502 parameters were refined in the final cycle of refinement by using 4506 reflections with $I > 2\sigma(I)$ to yield R_1 and wR_2 of 6.92 and 14.56%, respectively. Refinement was done by using F^2. Refinement details for **15**: $C_{46}H_{56}N_6NiO_4$; M_r = 815.68; T = 100(2) K; wavelength = 0.71073 Å; crystal system: triclinic; space group $P\bar{1}$; a = 8.6817(11), b = 15.721(2), c = 15.803(2); α = 76.708(3), β = 86.868(3), γ = 78.889(3); V = 2059.6(5) Å^3; Z = 2; ρ_{calcd} = 1.315 Mg m^{-3}; μ = 0.523 mm^{-1}; $F(000)$ = 868; crystal size = 0.20 × 0.08 × 0.04 mm^3; θ range = 1.35–25.00°; index ranges: $-10 \le h \le 10$, $-18 \le k \le 14$, $-18 \le l \le 18$; reflections collected 20352, independent reflections 7262 [R(int) = 0.0729], completeness to θ = 25.00°, 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/−0.414 e Å^{-3}.

Molecular mechanics calculations: Molecular mechanics calculations were performed by using augmented MM2 force field parameters, as implemented in CAChe version 6.1.1.[37] Calculations were performed by using a simplified bis-urea (salen)nickel complex. The atomic coordinates in the (salen)Ni fragment were obtained from the crystal structure data of **15**. The (salen)Ni fragment was locked during computation. Steepest descent search was used to locate the energy minimum. Optimization continued until the energy change was less than 0.001 kcal mol^{-1}.

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