

THE DEVELOPMENT OF CHIRAL CATALYSTS FOR ASYMMETRIC REACTIONS

By

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To my family

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The body of this work is focused on the development of new chiral catalysts for asymmetric reactions. Chiral catalysts can provide an atom economical route to a variety of synthetically important chiral molecules including compounds of biological and pharmacological interest to novel materials with superior structural properties. The efficiency of a chiral catalyst can be measured in both its ability to accelerate a reaction and to promote a highly selective reaction pathway, yielding reaction products with a high degree of optical purity. In many cases, these two criteria are best met when two or more reaction partners are cooperatively activated and organized by a single catalytic species. The latter portion of this work is focused on the development of transition metal catalysts designed to self-assemble in solution to yield multimetallic catalysts capable of activating multiple reaction partners. The first portion is focused on the application of novel, chelating nitrogen donor ligands synthesized *en route* to *N*-heterocyclic carbene ligands.

CHAPTER 1 INTRODUCTION

***N,N*-Ligands in Asymmetric Catalysis**

Nitrogen-containing ligands have earned a position of significant importance in asymmetric catalysis due in part to their relative ease of synthesis from a readily available, enantiopure chiral pool and their ability to coordinate a variety of metals. A great number of highly enantioselective transformations are possible using Lewis acids supported by chiral ligands based on amine, imine, pyridine, oxazoline, pyrrole and many other nitrogen donor groups.

The use of chiral catalysts for asymmetric transformations is a highly attractive process for increasing a substrate's structural complexity with relatively low expenditures in terms of materials, labor and cost. Synthetic routes for a given target can be greatly shortened by using chiral catalysts, avoiding direct use of enantiopure starting materials. Atom economy can also be improved by avoiding the attachment and subsequent removal of stoichiometric chiral auxiliaries. Additionally, reaction conditions are often more mild, yielding less by-products and easing purification.

The development of successful catalysts is highly dependent on the generation of new ligands that will support the central metal. The approach to the development of new ligands is often a mixture of careful observations, rational design and luck. There are, however, several principles that lend themselves to the development of successful ligands: (1) the synthesis should be modular, preferably at more than one point along the synthesis. The ability to quickly and easily tune the ligand in terms of electronics and sterics is highly desirable (2) the synthesis should be short and relatively straight forward with as many high yielding steps as possible (3) the basic ligand framework

should allow for additional elaboration so that future “generations” of the catalyst family can be created.

The variety of nitrogen donor ligands is vast and in an effort to focus this discussion, those that most closely resemble the structural framework of the ligands developed in the course of this research will be reviewed here. These sections will describe the design and application of these ligand types.

Diimine-Based Chiral Ligands

Developed nearly 70 year ago, diimine ligands are easily synthesized via Schiff base condensation of carbonyl compounds and primary amines.¹ One of the first examples of chiral imine ligands was reported by Uhlemann² who investigated the metal selectivity with Schiff bases synthesized from *ortho*-substituted ketones and (1*R*,2*R*)-*trans*-diaminocyclohexane. The C_2 -symmetry created by these ligands is a common and popular approach, found in both nitrogen based and chelating phosphine ligands. In this way, the number of diastereomeric pathways an asymmetric reaction can take are limited. The incorporation of C_2 -symmetry has been pillar of ligand design since the introduction of DIOP ligands by Kagan³ 40 years ago. A quadrant analogy is often used to simplify and predict the interactions between catalyst and substrate.



Figure 1-1. Quadrant analogy as applied to C_2 -symmetric ligands.

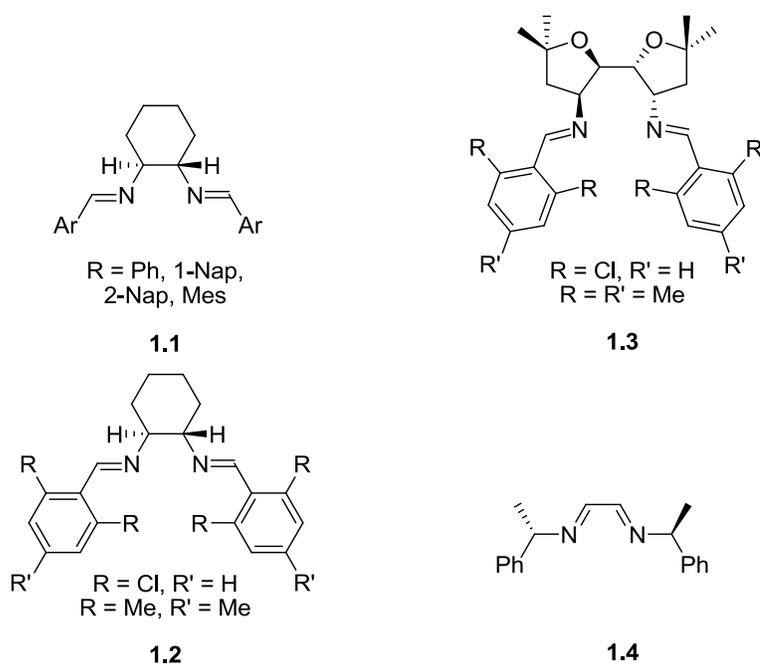


Figure 1-2. A selection of C_2 -symmetric diimine ligands.

One of the attractive features of diimine ligands are their simple synthesis, either by condensation of achiral carbonyl compounds with chiral *trans*-diamines (types **1.1-1.3**) or by condensation of dialdehydes with chiral monoamines (type **1.4**). Steric bulk and electronics can be easily modified and a variety of chiral amines are readily available.

The successful application of C_2 -symmetric diimine ligands varies. While yield and selectivity suffers in some cases, exceptions are the Cu(II) catalyzed aziridination of olefins by types **1.2**⁴ and **1.3**⁵ and the reduction of ketones with polymeric silanes and diethyl zinc with ligand type **1.1**⁶

Salen Ligands

Modifications to the C_2 -symmetric diimine ligands include the tetradentate salen ligands formed through the condensation of chiral diamines and salicylaldehyde derivatives. The commercial synthesis of the most universal salen ligand (**1.5a**) starts

from inexpensive raw materials and is available on a laboratory or bulk scale. The first salen ligand and its copper complex were discovered by Combes in 1889.⁷

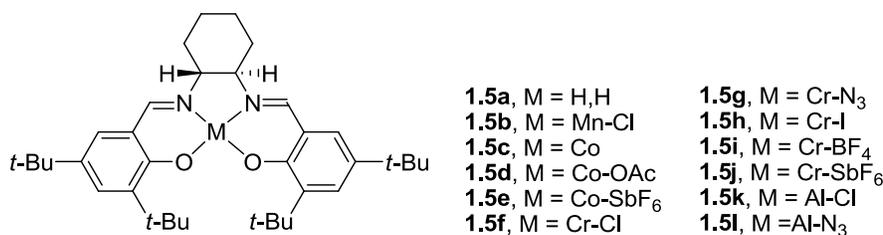


Figure 1-3. Some examples of metal salen complexes.

Salen ligands are capable of coordinating a variety of first and second row transition metals as well as main group elements including Mn, Co, Cr, Al, Ti, V and Ru and have been employed in many asymmetric reactions including aziridinations,¹⁷ oxidations,^{16,8} epoxide ring opening,⁹ hetero Diels-Alder,¹⁰ hydroxylations, cyclopropanations¹¹ and many, many others. A great number of variations to the basic framework utilizing tertiary 1,2-diamines, 1,3- or 1,4-diamines and chiral salicylaldehydes have been reported (Figure 1-4) but the basic structure of **1.5a** shows impressive versatility due to some key features. The steric bulk of the tertiary butyl groups at the 3-3' and 5-5' positions enforce the approaching substrate over the chiral diamine. The *trans*-diaxial hydrogen atoms effectively (and quite remarkably) communicate their stereochemical information with high fidelity.

Due in part to the central position of salen ligands in this research, this section will be further reviewed in terms of the reactions salen ligands have been applied.

Asymmetric epoxidation (AE)

Asymmetric olefin epoxidation was reported as early as 1985 by Kochi using Cr(V)oxo salen complexes whose structures were confirmed by X-ray analysis.¹² It was

later discovered that cationic Mn(V)salen was superior to the Cr(V) species and the Mn(V)oxo salen was invoked as the active catalyst.

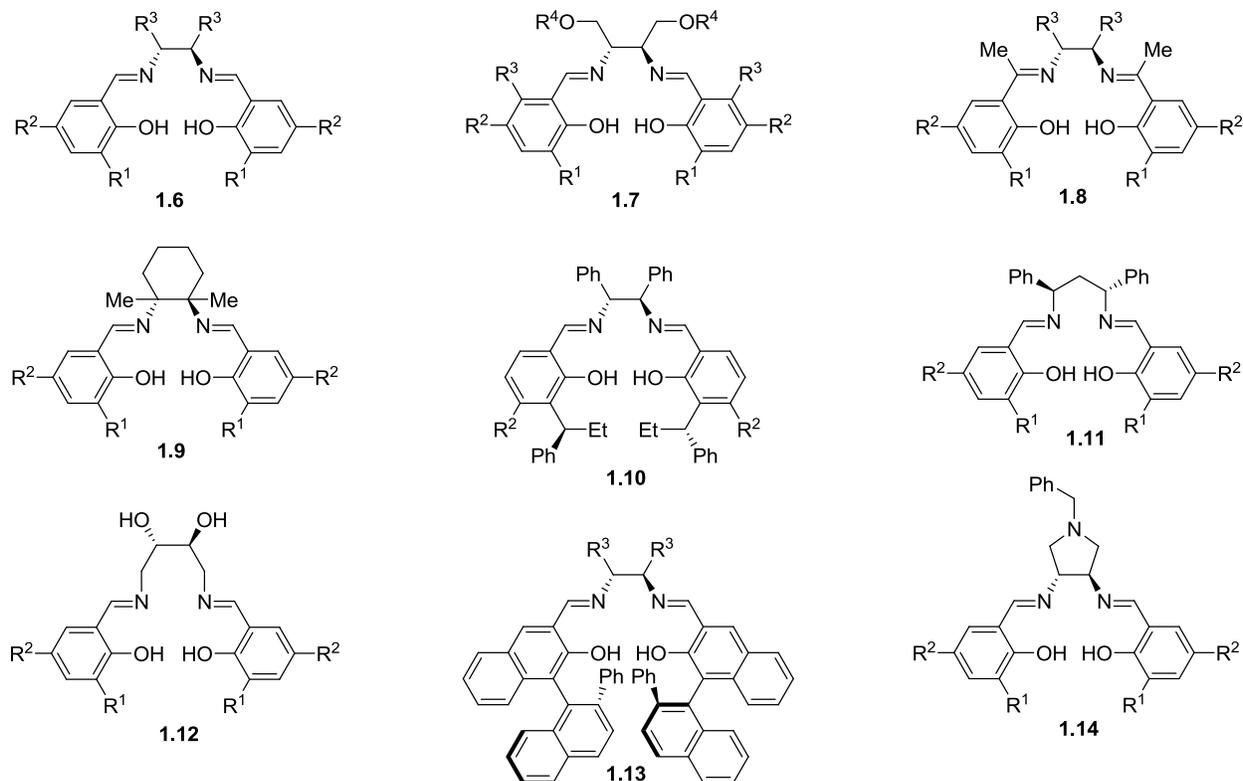
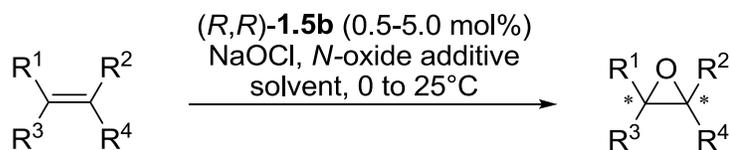


Figure 1-4. Examples of structural variations of the salen ligand framework.

Arguably the most influential seminal work on the application of salen ligands to asymmetric epoxidation has been contributed by Jacobsen^{13, 14} and co-workers and independently in the same year by Katsuki,¹⁵ and co-workers, with their investigation of Mn(III)Cl salen complex **1.5b** for the asymmetric epoxidation of olefins. Other early contributions from Thornton¹⁶ and Burrows¹⁷ should be noted as well. This practical approach uses a Mn(III)Cl salen as a pre-catalyst and a stoichiometric oxidant such as bleach or an organic peracid to generate the active Mn(V)oxo species.



Scheme 1-1. Conditions for asymmetric epoxidation (AE) of conjugated olefins catalyzed by Mn(III)Cl salen complex.

The addition of organic *N*-oxides such as 4-phenylpyridine *N*-oxide or *N*-methylmorpholine *N*-oxide have been shown to dramatically improve efficiency¹⁸. *N*-oxides are believed to act as axial ligands that inhibit formation of the inactive μ -oxo-Mn(IV)dimer. Jacobsen and co-workers demonstrated the importance of these additives by developing salen complexes in which the additive was covalently tethered to the catalyst.¹⁹

Better reactivity is generally observed with electron rich alkenes that lie in conjugation with some other group. High enantiomeric excess can be achieved for *cis*-1,2-disubstituted, tri- and even tetrasubstituted alkenes^{20,21} while lower temperatures are generally need for terminal olefins.²² Interestingly, epoxidation of *trans*-olefins generally suffers from low enantioselectivity using Mn(V)oxo salen catalysts while the corresponding Cr(V)oxo salen catalyst are capable of achieving higher % ee.²³ *Trans*- β -methylstyrene undergoes epoxidation in 71% ee (vs. 24% ee for the corresponding Mn(V)oxo salen complex)²⁴ but reported reactivity is sluggish and the less convenient iodosylbenzene is employed as oxidant. While the Mn(V)oxo salen complex has been proven to be involved in the epoxidation reaction by electrospray mass spectrometric analysis²⁵ the active catalyst is too unstable to be isolated, however the Cr(V)oxo salen catalyst is isolable²⁶ and can be used directly.

Epoxide ring opening reactions

Many asymmetric reactions generate new stereogenic sp^3 carbon atoms by the transformation of prochiral sp^2 centers in the form of C=C, C=O or C=N bonds. In contrast, much less attention has been paid to the generation of new stereogenic sp^3 centers from pre-existing sp^3 centers by asymmetric substitution reactions. This approach can be best applied in the desymmetrization of meso compounds or by kinetic resolution of racemic mixtures. Jacobsen and co-workers previously reported work of the catalytic asymmetric epoxidation of olefins led them to question an extension of the simplified model of enantiofacial discrimination of the olefin approaching the oxo metal center in a side-on manner (Figure 1-5). While the exact mechanism of oxygen transfer is still under debate, as previously mentioned, this transition state model originally proposed by Groves²⁸ is generally accepted. It was proposed that if the transition state of oxygen transfer to olefins was able to discriminate between the prochiral faces of the olefin, then the ground state of coordinated epoxide may provide a chiral environment to direct incoming nucleophiles.

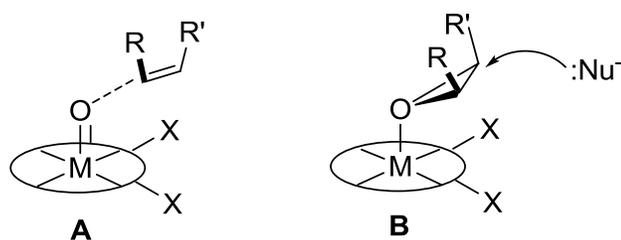


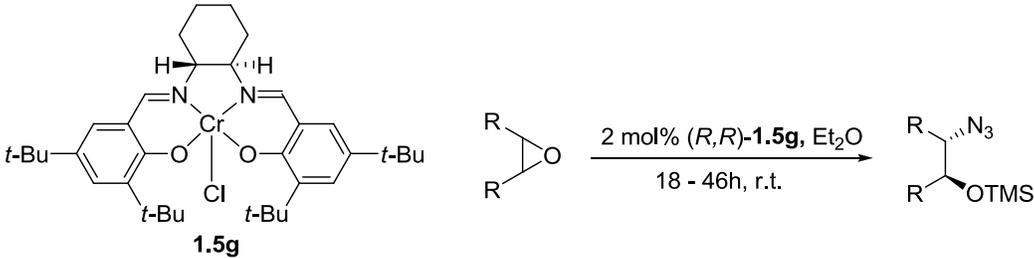
Figure 1-5. Models for olefin epoxidation and epoxide activation by chiral metal salen complexes.

Desymmetrization of meso epoxides

The first asymmetric ring opening (ARO) of meso epoxides catalyzed by metal salen complexes was reported by Jacobsen and co-workers using trimethylsilylazide

(TMSN₃) and Cr(III)Cl salen complex **1.5f**.²⁹ Complex **1.5g** was later revealed as the active catalyst from observation that stoichiometric azide transfer could be accomplished using **1.5g**.⁴¹ Cyclic epoxides provided higher enantioselectivities than acyclic epoxides and selectivity generally decreased with increasing ring size (Table 1-1). Epoxides derived from cyclic olefins containing heteroatoms were well tolerated in terms of selectivity with furan derived epoxide **1.17** giving lower yield, presumably from competing coordination to the metal center with the epoxide oxygen. The synthetic utility in this reaction results from the rapid access to differentially protected 1,2-amino alcohols, a common element in several classes of pharmacologically important compounds such as prostaglandins,³⁰ chitinase inhibitors,³¹ protein kinase inhibitors³² and antitumor antibiotics.³³

Table 1-1. Enantioselective opening of meso epoxides with Cr(III)Cl salen.



1.5g

	1.15	1.16	1.17	1.18	1.19	1.20	1.21
Time (h)	18	28	18	36	16	46	30
Yield (%) ^a	80	80	80	80	90	80	65
ee (%)	88	94	98	95	95	81	82

^a Isolated yield of the corresponding azidoalcohol after hydrolysis.

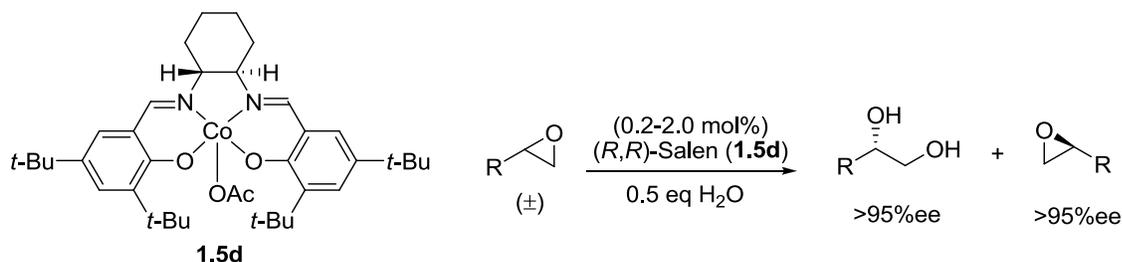
Other nucleophiles have been employed in the desymmetrization reaction including thiols,³⁴ halides including fluoride^{35,36} and even scattered reports of enolate³⁷ and aryllithium³⁸ carbon nucleophiles. While oxygen nucleophiles are to be given

special consideration due to the central role played in the hydrokinetic resolution (HKR) of terminal epoxides, reports of their addition of meso epoxides are limited. Shortly after the report on the addition of azide to meso epoxides, Jacobsen and co-workers also demonstrated the desymmetrization reaction with Co(III)OAc salen catalyst (**1.5d**) using benzoic acid as a nucleophile. Enantioselectivities are best in the case of aryl substituted epoxides but the depressed selectivity in the case of cyclohexene oxide can be improved from 77% ee to 98% ee through a single recrystallization.

Kinetic resolution of terminal epoxides

While not the first asymmetric epoxide opening reaction catalyzed by salen metal complexes reported, the hydrolytic kinetic resolution (HKR) of terminal racemic epoxides might certainly be classified as the most important.

The previous limitations of Mn(V)oxo salen complexes to access enantioenriched terminal epoxides were overcome in the initial report in 1997³⁹ by Jacobsen and co-workers and expanded upon the following year.⁴⁰

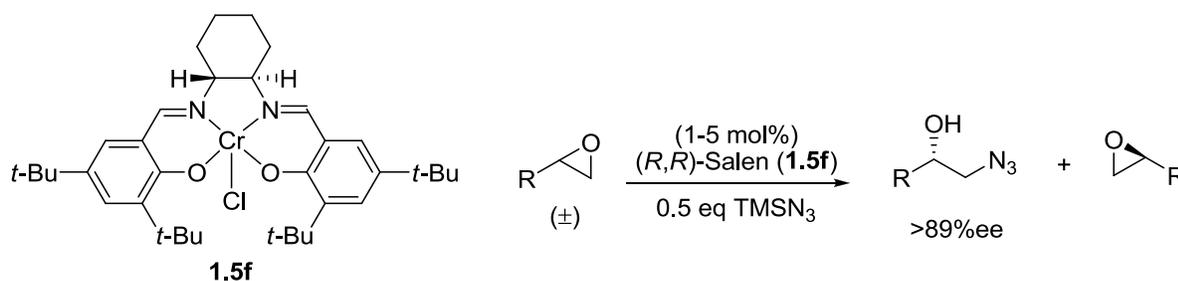


Scheme 1-3. HKR of terminal epoxides with water using Co(III)OAc salen.

In that report, several terminal epoxides derived from allyl halides and ethers undergo resolution with Co(III)OAc salen (**1.5d**) with remarkable selectivity and efficiency (Scheme 1-3). While resolutions can theoretically only achieve a 50% maximum yield, the HKR process is still highly attractive for several practical reasons. When allowed to reach full resolution (50% yield) both the epoxide and the diol can be

obtained in high enantiomeric excess, generally with very low catalyst loadings. The reaction products can be easily isolated by vacuum distillation or extraction. Using water as a nucleophile is safe, convenient and has a low molecular weight. After the reaction products are removed, the catalyst residue has been found to retain its activity many times over.

The introduction of nitrogen nucleophiles in the kinetic resolution of terminal epoxides using salen catalysts was reported shortly after Jacobsen and co-workers seminal publication on the asymmetric ring opening of meso epoxides²⁹ using trimethylsilylazide (TMSN₃) and Cr(III)Cl salen complex **1.5f** (Scheme 1-4).



Scheme 1-4. HKR of terminal epoxides with TMSN₃ using Cr(III)Cl salen.

The synthetic utility of this reaction was rapidly demonstrated in the short synthesis of (*S*)-propranolol, a widely used anti-hypertensive agent, and (*R*)-9-[2-(phosphonomethoxy) propyl]adenine (PMPA), a compound displaying prophylactic activity against simian immunodeficiency virus.

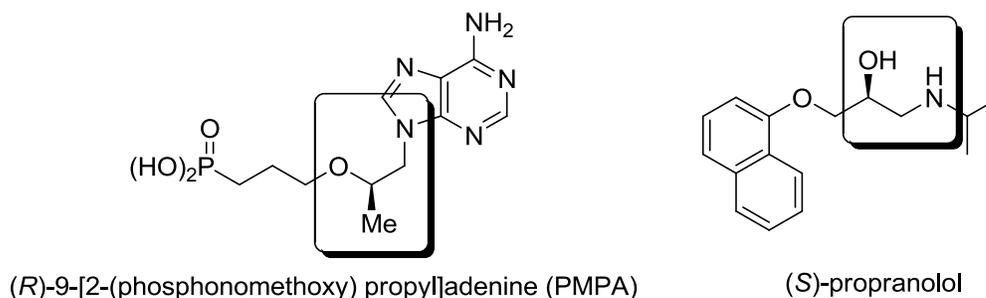


Figure 1-6. Molecules of biological interest synthesized using kinetic resolution.

It was near this time that Jacobsen and co-workers discovered one of the most interesting mechanistic features of this reaction and other ring opening reactions. It was found that a linear correlation existed between k_{obs} and $[\text{catalyst}]^2$ reflecting a second order dependence on catalyst concentration.⁴¹ This provided strong evidence for a bimetallic reaction pathway in which one metal center coordinates and activates the epoxide for attack while another metal center coordinates and delivers the incoming nucleophile. This pathway is also supported by a non-linear relationship between enantiopurity of the catalyst and of the resulting product, further suggesting that two equivalents of catalyst are involved in the stereodifferentiating step. While this bimetallic mechanism is highly intriguing, it creates some significant limitations on how low the catalyst loading can be and on the overall catalyst concentration in solution. Since high enantiomeric excess of epoxide can only be achieved at high conversion (near 50%) in the case of kinetic resolution, the ability to completely turn over substrate becomes very crucial. Excess nucleophile or higher catalyst loadings are often used to overcome these issues but another useful and fascinating method in the case of the HKR reaction, is in the selection of counter ion to the penta-coordinate Co(III) center. It was observed early on that trace amounts of chlorohydrins could be isolated as by-products that resulted from nucleophilic addition of the chloride counter ion from the metal center.

If this addition is rapid, Co(III) can be reduced to Co(II) and considerably slow the reaction. It was found that weakly nucleophilic anions from electron deficient benzoic and arylsulfonic acids could increase the rate of reaction by slowing this unwanted addition. Furthermore, it was found in an elegant study by Jacobsen and co-workers⁴² that in the case of the HKR reaction, the choice of oxidizing acid was extremely crucial

in providing the correct proportion of Co(III)OH and Co(III)X with bound epoxide. The problem of local catalyst concentration would soon be overcome as well.

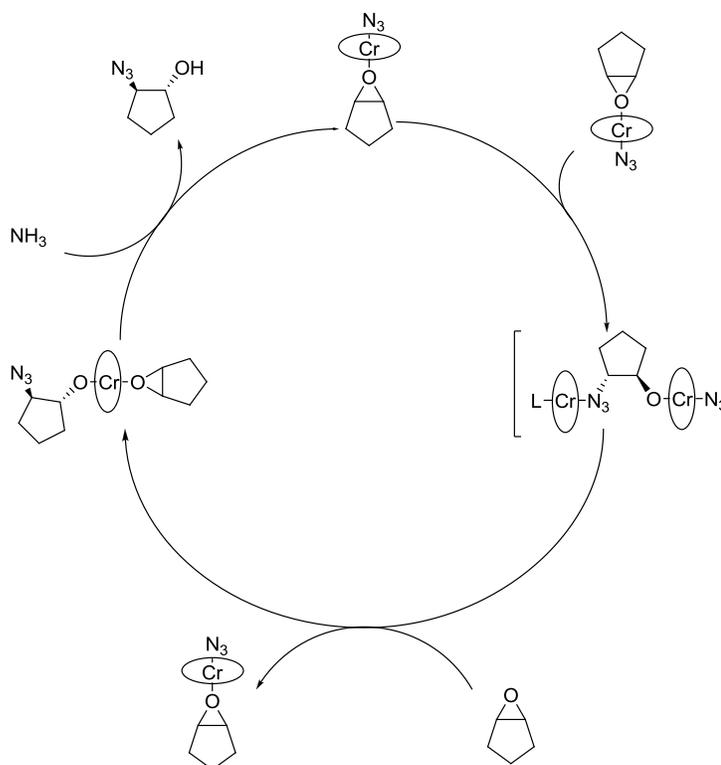


Figure 1-7. Proposed bimetallic mechanism for the asymmetric ring opening of epoxides with Cr(III) salen catalyst.

Multinuclear salen catalyst for epoxide opening

In an effort to combat the entropic problem created by the necessity of two discrete catalysts being involved in the transition state for asymmetric ring opening reactions, considerable efforts have been made to construct bi- or multimetallic catalysts. Jacobsen and co-workers reported that while at lower concentrations, dimeric Cr(III)Cl salen catalysts linked through their diamine backbone displayed rate acceleration in the delivery of azide to cyclopentene oxide versus their analogous monomeric counterparts (Figure 1-8), although the observed enantiomeric excess was less than 10%.⁴³

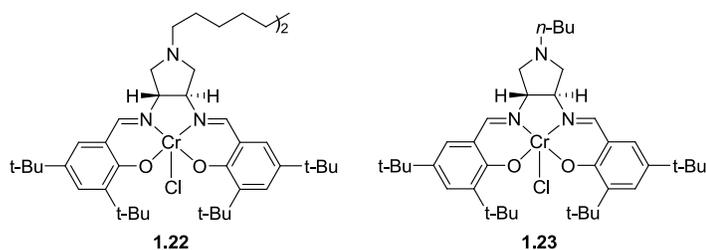


Figure 1-8. Backbone linked dimeric Cr(III)Cl salen and its monomeric analogue.

It was rationalized that two limiting geometries existed for the approach of the two salen metal complexes in solution, either a “head-to-head” or a “head-to-tail” fashion (Figure 1-9). The results from the previously described reaction suggest that while the bimetallic mechanism was in operation using **1.22** a “head-to-head” orientation dramatically eroded stereoselectivity. In response to these results, dimeric salen complexes were developed that were joined through ester linkages of various lengths on the aryl rings. These dimeric catalysts were tested in the ARO reaction of cyclopenteneoxide with HN_3 versus their monomeric analogue. Kinetic studies were carried out measuring initial reaction rates and indicated that dimeric catalysts **1.24a-g** displayed both inter- and intramolecular catalytic behavior where as **1.25** only displayed intermolecular behavior (Figure 1-10).

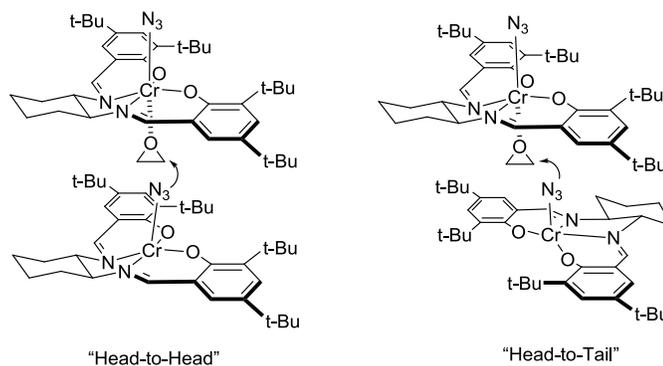
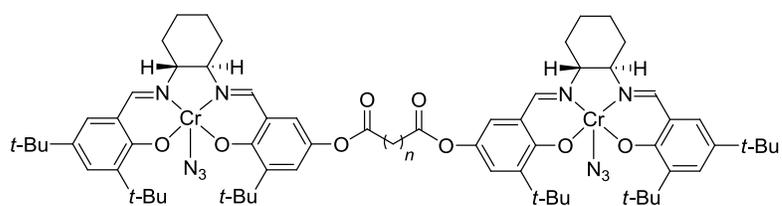
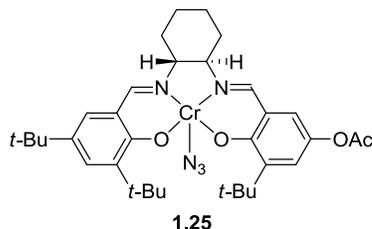


Figure 1-9. Limiting geometries for the transition state of the ARO.



1.24a: n=2, 1.24b: n=4, 1.24c: n=5, 1.24d: n=6, 1.24e: n=7, 1.24f: n=8, 1.24g: n=10,



1.25

Figure 1-10. Aryl linked dimeric Cr(III)Cl salen and their monomeric analogue.

Other multimeric systems were soon to follow including a dendrimeric system developed by Jacobsen and co-workers.⁴⁴ In the preceding years, increasing interest had been devoted to the synthesis and characterization of compounds that displayed unique behavior as a direct consequence of the dendrite architecture.⁴⁵ This series of catalysts were based on the commercially available NH_2 -terminated polyamidoamine (PAMAM) precursors (Figure 1-11). For comparison, analogous monomeric and dimeric catalysts were also prepared and initially evaluated in the HKR of (rac.) vinylcyclohexene oxide.

As expected, at 0.0025 mol% Co(III), the native, unfunctionalized Co(III)I salen (**1.5h**) was effectively unreactive after 40 hours while the dendrimeric catalyst **1.26b** completely resolved (rac.) vinylcyclohexene oxide in only 20 hours giving the resolved epoxide in 98% ee. Rate plots also revealed that dendrimeric catalysts of various orders of branching not only exhibit rate acceleration versus the monomeric catalyst analogue **1.28** but the dimeric catalyst **1.27** as well. While reaction rates on a per molecule basis of catalyst were linear with respect to the order of branching, on a per mole of Co(III) it

was found that catalyst **1.26a** with four Co(III)salen units provided the greatest rate acceleration.

These findings represent an interesting example of cooperative interaction between salen units and also revealed that limitations may exist in terms of the creating favorable interactions and that simply “more is not always better”.

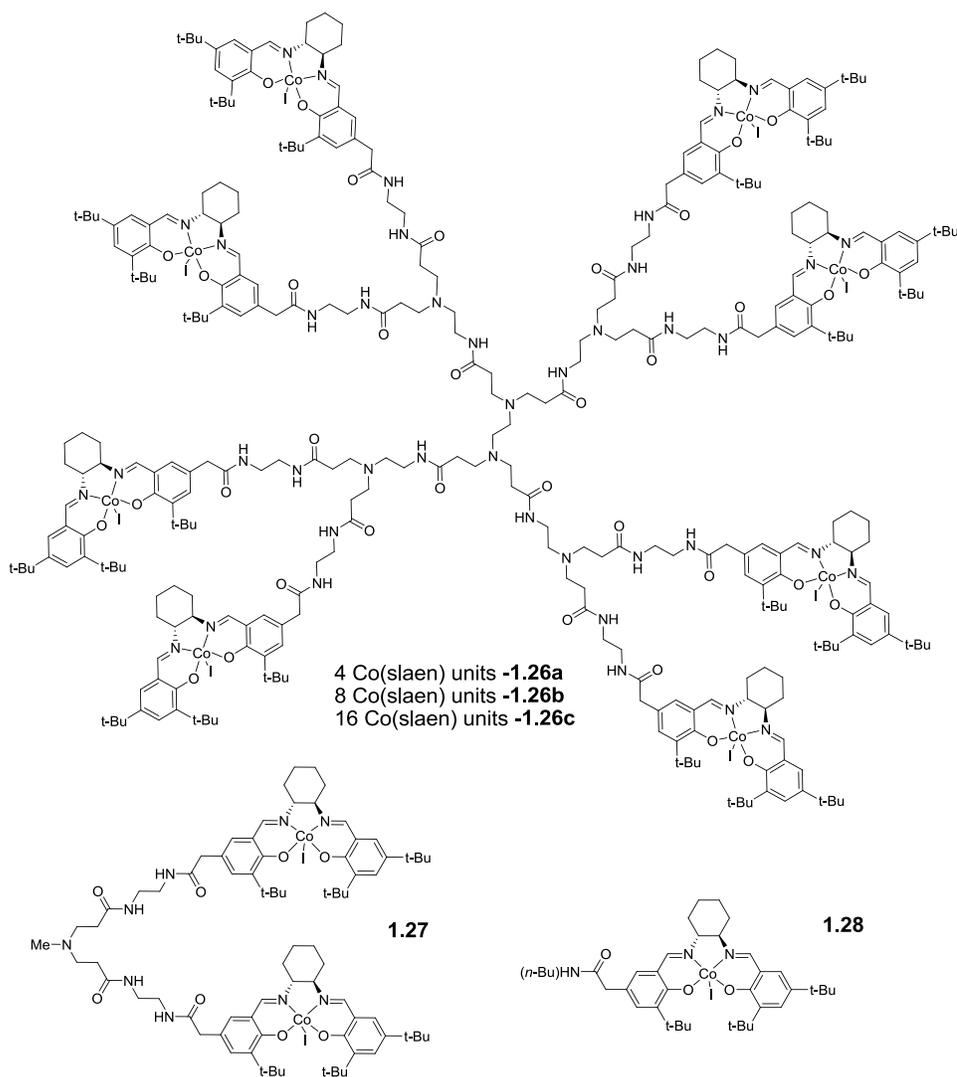
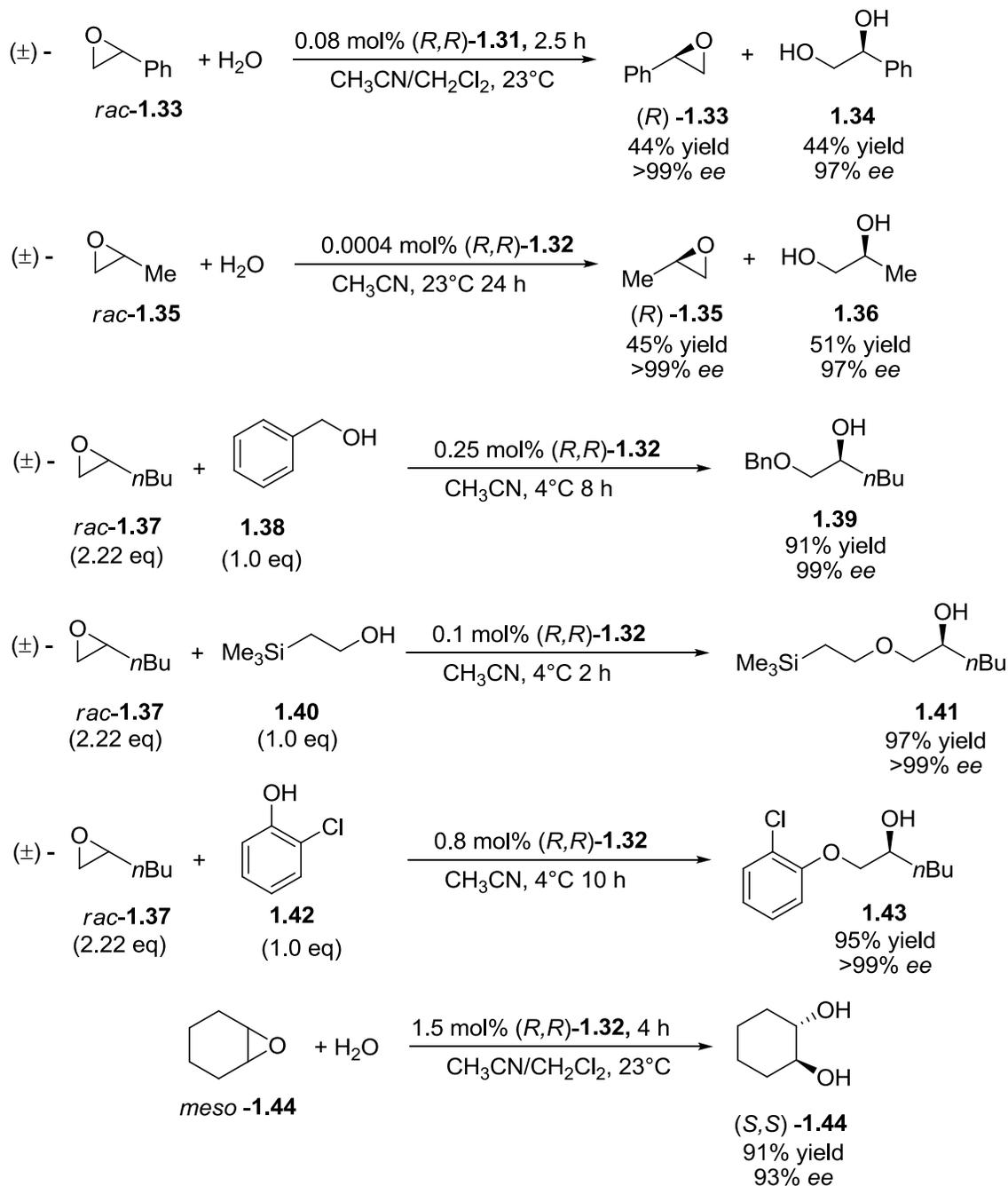


Figure 1-11. Structures of dendrimeric, dimeric and monomeric Co(III)salen.

= 1-5 resulted in more than 10,000 different possible compounds due to the additional stereocenters involved. Removing this group allowed for a much easier synthesis and allowed for isolation of discrete oligomers as a means to gain a better understanding the influence of oligomer size.



Scheme 1-6. Examples of ARO using oligomeric Co(III)salen catalysts.

As an alternate method of electronic tuning, the counter ion was modified and shown to have a positive impact on reactivity and, surprisingly, selectivity when camphorsulfonic acid (**1.31**–CSA=10-camphorsulfonate) and 3-nitrobenzenesulfonic acid (**1.32**–NBS=3-nitrobenzenesulfonate) are used. While the catalysts can effectively be used as mixtures of oligomers where $n=1-3$, evaluation of discrete oligomers revealed that the best results occurred with the trimer when $n=2$.

It was proposed that the trimer possessed the right balance of structural rigidity to minimize nonselective pathways while maintaining enough flexibility to access the optimal transition state. The above contributions from the labs of E. Jacobsen constitute a successful development of covalently linked catalysts based on data that strongly suggested a bimetallic mechanism in epoxide ring opening reactions. While these tethered catalyst show dramatic improvements versus their monomeric counterparts, the development of novel catalysts based on a similar approach is far from over.

In 2006, Weberskirch and co-workers⁴⁸ reported a polymeric Co(III)OAc salen catalyst. These polymeric catalysts were synthesized by covalently linking hydroxyl substituted salen ligands to block co-polymer containing pendant carboxylic acid groups. These block co-polymers were comprised of a hydrophobic and a hydrophilic block with the pendent salen ligands located in the hydrophilic region. These catalysts were designed with the observation that in the HKR reaction the addition of water generally needs to be carefully controlled and at lowered temperatures since the process is exothermic.

The equivalents of water must also be controlled to provide high enantiomeric excesses. These salen containing block co-polymers were designed to create a micellar

environment in which the hydrophilic shell of the micelle provides water solubility while the hydrophobic core creates a higher, local concentration of salen catalyst.

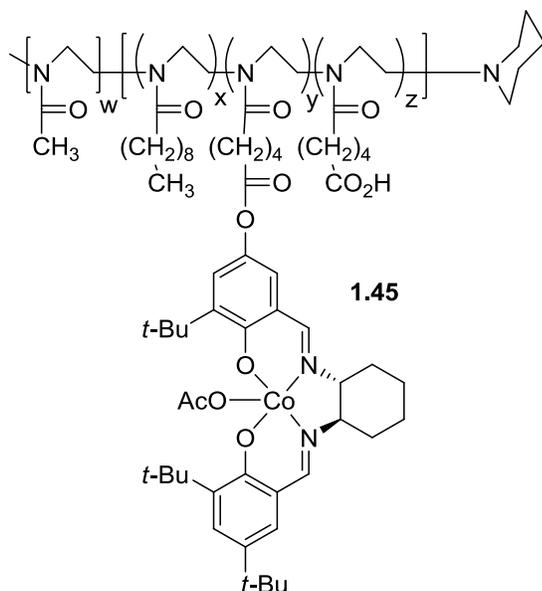
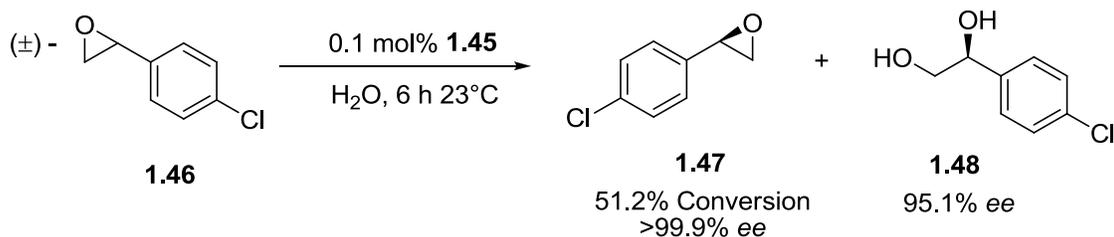


Figure 1-13. Amphiphilic (*R,R*)-macrosalen ligand ($w=41$, $x=4.5$, $y=2.8$, $z=2.3$)

This polymeric catalyst was shown to resolve several aromatic substituted terminal epoxides with exceptionally high % ee at very low catalyst loadings. Furthermore, these reactions can be conducted in water as solvent and the catalyst can be subsequently removed and recycled without appreciable loss of efficiency, for up to 4 cycles. These results demonstrate the first HKR of terminal epoxides catalyzed by Co(III)OAc salen incorporated into amphiphilic block co-polymer carried out in water as a solvent.



Scheme 1-7. Example of (HKR) of terminal epoxides in water in the presence of polymeric catalyst.

In 2007, Weck and co-workers⁴⁹ developed a highly efficient variation of macrocyclic oligomeric Co(II)salen catalysts for the HKR of terminal epoxides (Figure 1-14). These oligomers were constructed using a ring expanding olefin metathesis approach using Grubbs 3rd generation catalyst. These catalysts showed impressive rate enhancements versus their monomeric analogues and in comparison to any previously developed systems for the HKR of terminal epoxides. Resolution of racemic epichlorohydrin could be effected in only 2.5h with greater than 99% ee with only 0.01 mol% catalyst (Scheme 1-8). While no kinetic evidence was provided in order to better understand these new catalysts, they show impressive rate acceleration over previously reported systems over a broad range of substituted terminal epoxides.

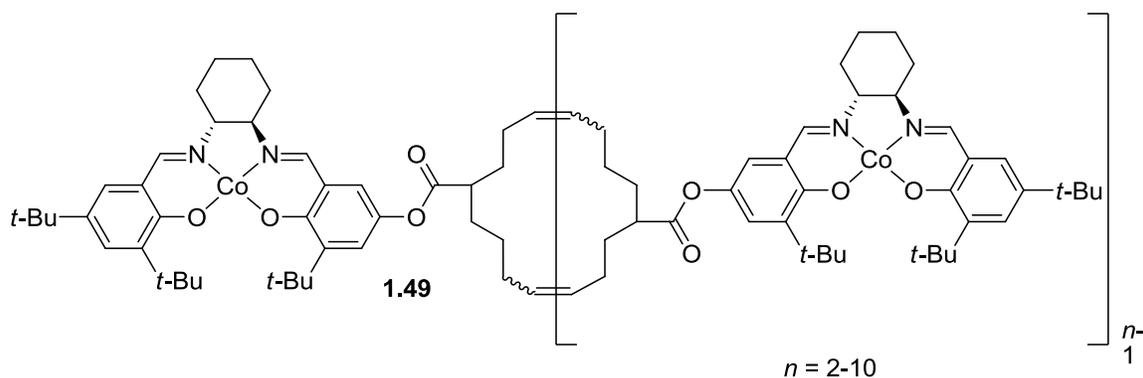
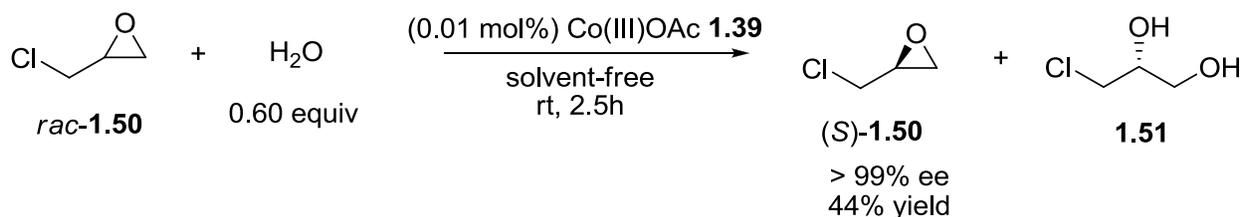


Figure 1-14. Macrocyclic Co(II)salen complexes developed by Weck.

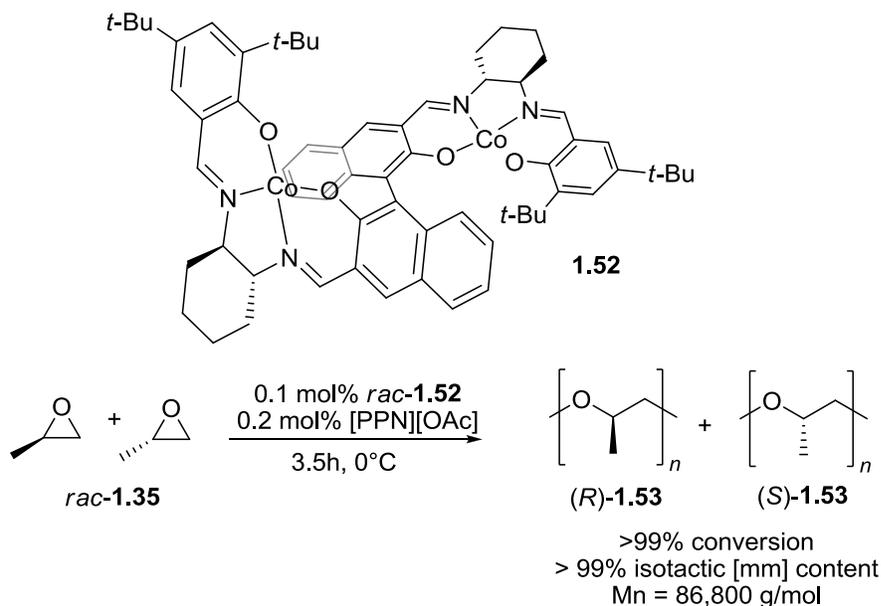


Scheme 1-8. HKR of epichlorohydrin by macrocyclic Co(III)OAc salen.

In 2007, Coates⁵⁰ and co-workers developed a bis-salen dimer based on a chiral BINOL backbone for the polymerization of terminal epoxides. These dimeric catalysts show exceptionally high selectivity factors (s) and near perfect isotacticity for a series of substituted terminal epoxides (Scheme 1-9).

While the polymer enantioselectivities are generally over 99%, the conversions are somewhat low leading to lower enantiopurity in the remaining epoxide. Interestingly, neither the Co(II)salen species **1.52** nor its oxidized form Co(III)Cl-**1.52** showed any catalytic activity alone. The reaction requires bis(triphenylphosphine)iminium acetate (PPN)OAc salt as a co-catalyst. This dependency was also observed in the co-polymerization with epoxides and CO₂ with similar catalysts.⁵¹

While the mechanism is still currently unclear for polymerizations and co-polymerizations of this type, it is believed that the exogenous anion may facilitate the initial ring-opening to begin polymerization.^{52,53}



Scheme 1-9. Bimetallic salen catalyst for enantioselective epoxide polymerization.

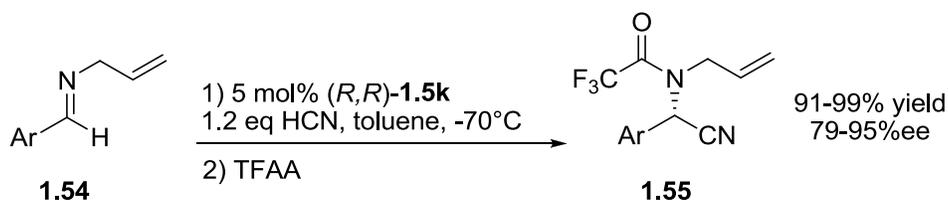
These findings represent the first example of a polymerization catalyst for the kinetic resolution of terminal epoxides. The racemic form of the catalyst polymerizes racemic epoxides to highly isotactic polyethers in quantitative yield and provides a highly interesting application of epoxide opening chemistry by metallosalen catalysts.

Carbonyl addition processes

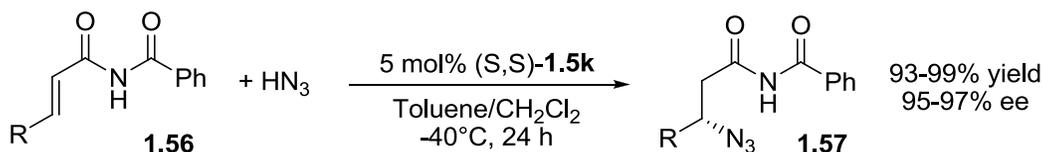
The asymmetric addition of nucleophiles to carbonyl groups is of considerable interest due not only to the variety of newly formed C-Nu bonds that can be generated but in the high synthetic value placed on the chiral alcohols or amines generated from ketones and aldehydes or imines, respectively. Since the construction of stereogenic C-C bonds is central to asymmetric synthesis, the addition of carbon nucleophiles such as HCN to carbonyl groups is of particular interest. The addition of HCN to imines (the Strecker reaction) provides access to optically active α -amino acids and metallosalen catalysts have played a considerable role in this reaction.

Jacobsen and co-workers⁵⁴ screened a series of metal salen complexes for catalysis in the reaction of *N*-allyl benzaldimine with trimethylsilylcyanide. Several (salen)metal complexes were found to catalyze the reaction with varying degrees of conversion and enantioselectivity, and the best results were observed with the Al(III)Cl salen complex **1.5k** (Scheme 1-10). Kinetic analysis demonstrated that this reaction was not second order in the Al(III)Cl catalyst, indicating a bimetallic mechanism was not operating. Jacobsen and co-workers⁵⁵ also described the asymmetric addition of HN_3 to α - β unsaturated imides catalyzed by Al(III)Cl salen **1.5k** giving products easily converted into β -amino acids (Scheme 1-11).

Evans and co-workers⁵⁶ also employed an Al(III)SbF₆ in the asymmetric addition of 5-alkoxyoxazoles to aldehydes.

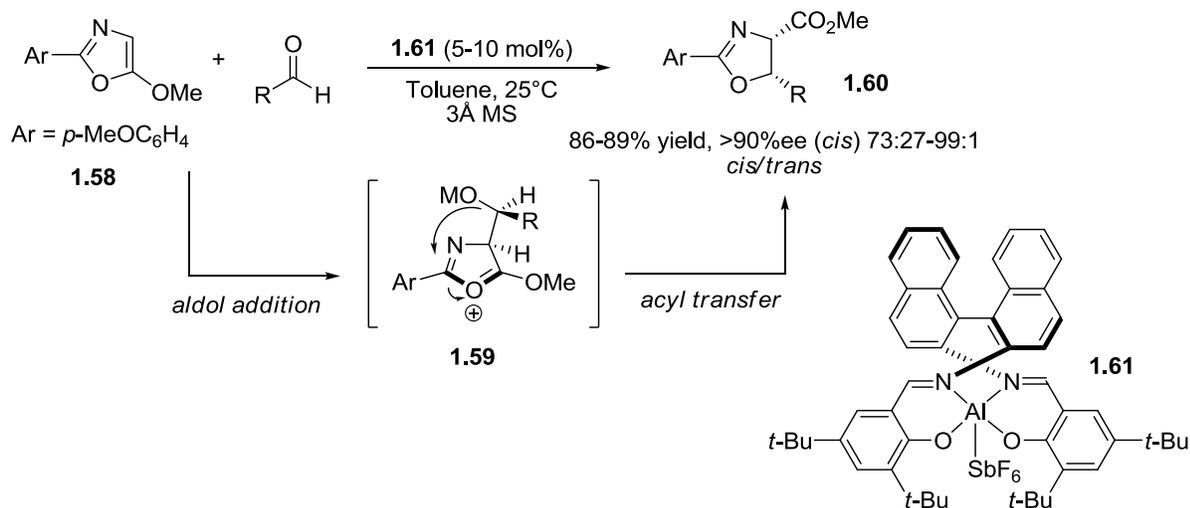


Scheme 1-10. Asymmetric Strecker reaction catalyzed by Al(II)Cl salen complex.



Scheme 1-11. Asymmetric addition of NH₃ to α - β unsaturated imides catalyzed by Al(III)Cl salen.

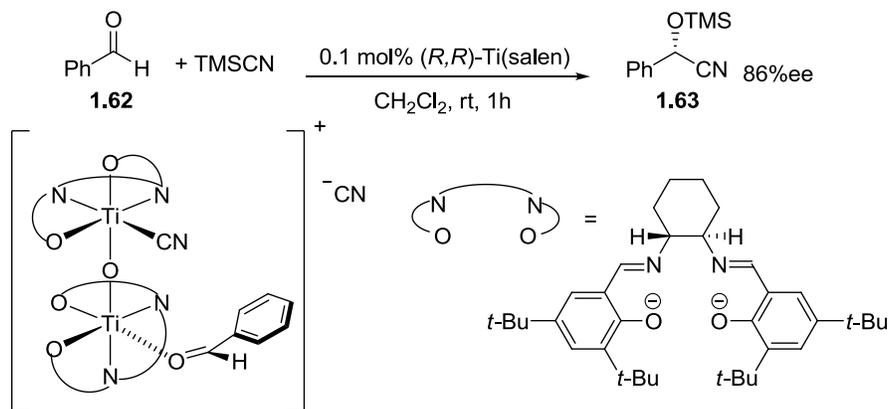
This salen catalyst incorporated a chiral 2,2'-diamino-1,1'-binaphthyl (BINAM) as the chiral backbone (Scheme 1-12). The reaction products were obtained in high yield, diastereo- and enantiomeric excess and could easily be converted in to valuable β -hydroxy- α -amino acid derivatives.



Scheme 1-12. Asymmetric addition 5-alkoxyoxazoles to aldehydes catalyzed by Al(III)SbF₆ salen.

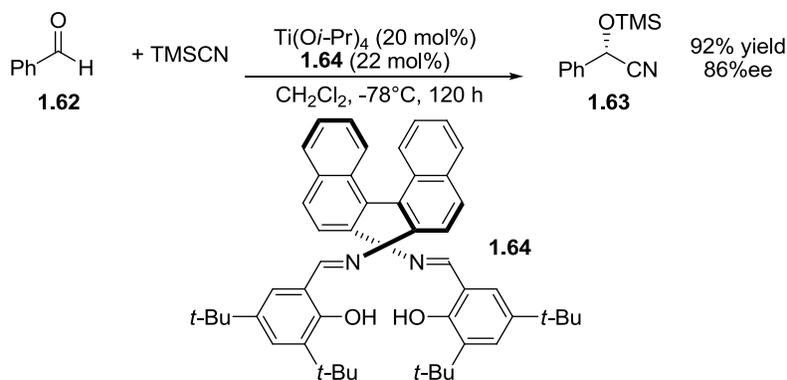
While the reaction products were obtained as the *cis* isomer, they could be equilibrated to the *trans* isomer under basic conditions providing ready access to both diastereomers. Asymmetric addition of TMSCN to aldehydes has been demonstrated by

Belkon⁵⁷ and North using a Ti(IV)Cl₂ complex of salen **1.5a** in quantitative yield and high enantioselectivity. Interestingly, mechanistic analysis of the Ti(IV)Cl₂ salen complex revealed a non-first-order dependency on catalyst concentration and is believed to proceed through a *cis*-β-di-μ-oxo species that allows for the intermolecular transfer of cyanide to the carbonyl substrate.⁵⁸



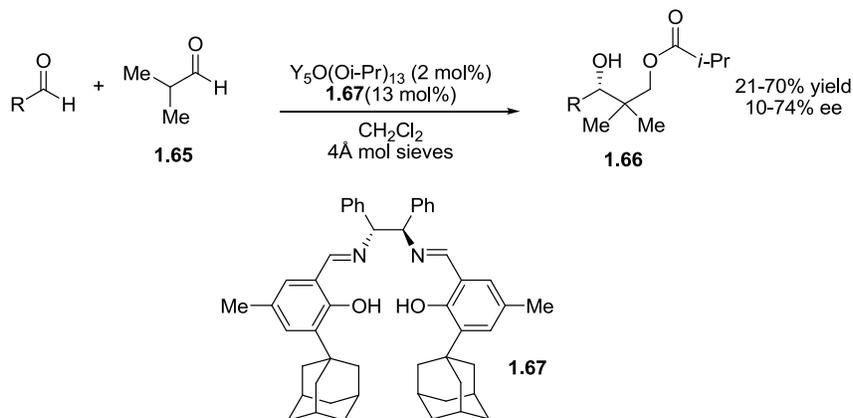
Scheme 1-13. Asymmetric addition of TMSCN to benzaldehydes catalyzed by Ti(IV)salen.

Che and co-workers also found the reaction to be catalyzed in the presence of Ti(O*i*-Pr)₄ and salen ligand **1.64** containing a chiral 2,2'-diamino-1,1'-binaphthyl (BINAM) backbone.⁵⁹ Other examples include the asymmetric aldol-Tischenko reaction catalyzed by Y(III)salen **1.67**.



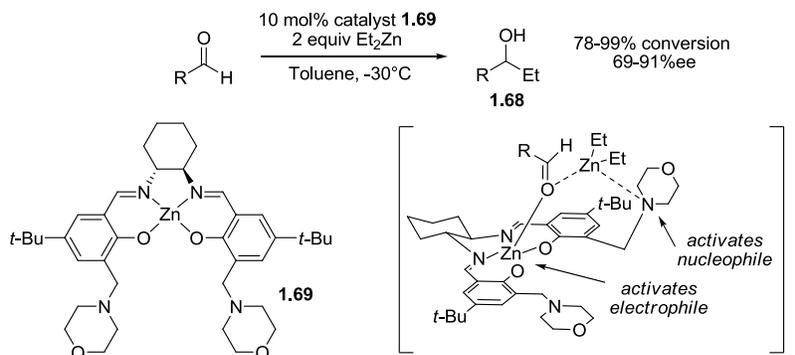
Scheme 1-14. Asymmetric addition of TMSCN to benzaldehydes catalyzed by Ti(IV)BINAM salen.

Kozlowski and co-workers⁶⁰ developed Zn(II) salen catalysts for the asymmetric addition of Et₂Zn to aryl and aliphatic aldehydes. These catalysts were designed to operate via a bimetallic mechanism but not in the traditional manner seen in epoxide opening reactions.



Scheme 1-14. Asymmetric aldol-Tischenko reaction catalyzed by Y(III)salen

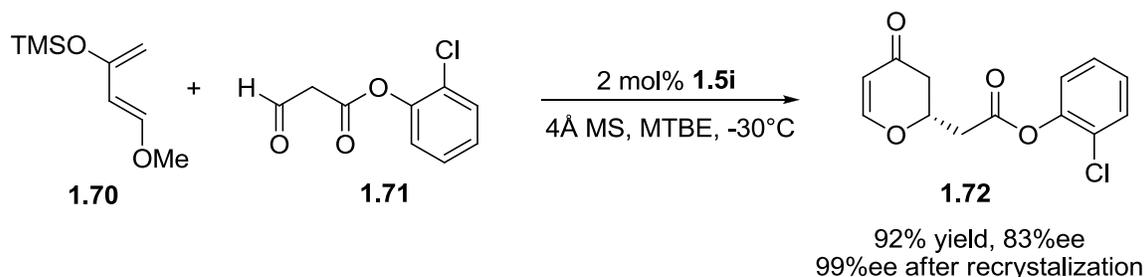
These catalysts contained a Lewis basic functional group at the 3 and 3' position of the aryl rings to aid in the delivery of nucleophile to the electrophile coordinated to the central Lewis acid (Scheme 1-15). It was shown that the pK_a of the corresponding conjugate acid of the basic pendant group correlated to observed enantioselectivity. A pK_a near 6 was found to be optimal while others of higher or lower value displayed lower selectivity.



Scheme 1-15. Asymmetric addition of Et₂Zn to aldehydes catalyzed by bifunctional Zn(II)salen.

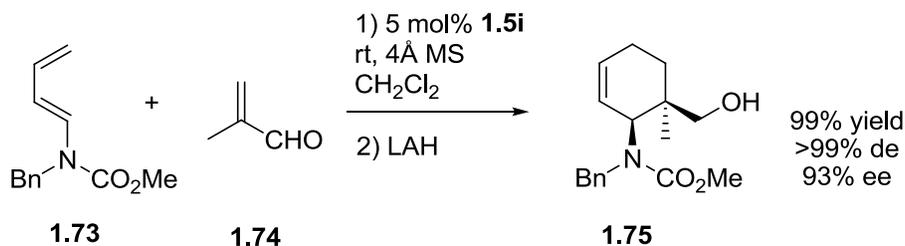
Diels-Alder and Hetero-Diels-Alder

Salen ligands have also been successfully employed in a variety of cycloaddition reactions. Jacobsen and co-workers⁶¹ found that Cr(III)SbF₆ salen catalyst **1.5i** was effective in catalyzing the asymmetric hetero-Diels-Alder reaction between [(2-chlorobenzoyl)oxy]-acetaldehyde and 1-methoxy-3-[(trimethylsilyl)oxy]buta-1,3-diene (Scheme 1-16).



Scheme 1-16. Asymmetric hetero Diels-Alder reaction catalyzed by Cr(III)SbF₆ Salen.

Rawal and co-workers⁶² also demonstrated the efficiency of these Cr(III)salen catalysts in the highly endo-selective Diels-Alder reaction between 1-amino-1,3-butadiene derivatives and substituted acroleins (Scheme 1-17). In these cases, enantioselectivity was generally greater than 90%. Reactivity is dramatically improved when cationic Co(III)SbF₆ salen catalysts are used allowing catalyst loadings as low as 0.05%. Interestingly, when the tertiary butyl groups at the 3 and 3' positions are replaced with trialkylsilyl groups both selectivity and reactivity is improved.

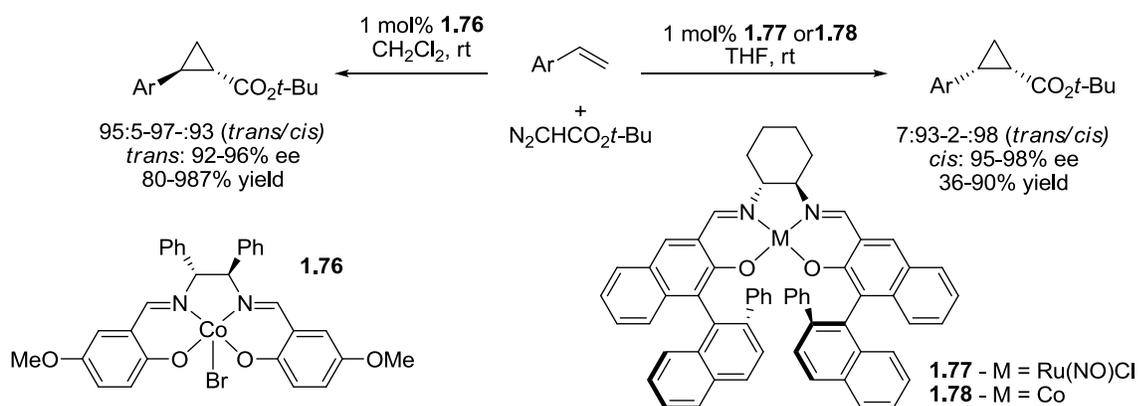


Scheme 1-17. Asymmetric Diels-Alder reaction catalyzed by Cr(III)SbF₆ salen.

Cyclopropanation

While considerable efforts have been devoted to the advancement of new methods of cyclopropanation, arguably the most versatile and useful are the reactions between terminal olefins and diazo compounds leading to *cis* and *trans* diastereomeric products. The diazo compounds are convenient metal-carbenoid precursors in the presence of a suitable metal with loss of molecular nitrogen. Metallosalen-catalyzed asymmetric cyclopropanation was first reported by Otsuka and Nakamura⁶³ using a Co(II)salen complex as catalyst, though enantioselectivity was rather poor (>10% ee). Katsuki and co-workers have demonstrated high *trans*- and enantioselectivity with Co(III)salen complex **1.76** that has no substituent at the 3,3'-positions of the salen ligand (Scheme 1-18).

It was reasoned that olefins may approach the carbenoid species along the Co–O bond axis with an orientation perpendicular to the Co-carbenoid bond. The presence of 3,3'-substituents blocks incoming substrate-approach and -rotation.⁶⁴ Katsuki also demonstrated high *cis* selectivity with Ru(III)salen⁶⁵ (**1.77**) and Co(II)salen⁶⁶ complexes (**1.78**) utilizing second generation salen ligands bearing axially chiral salicylaldehyde derivatives.

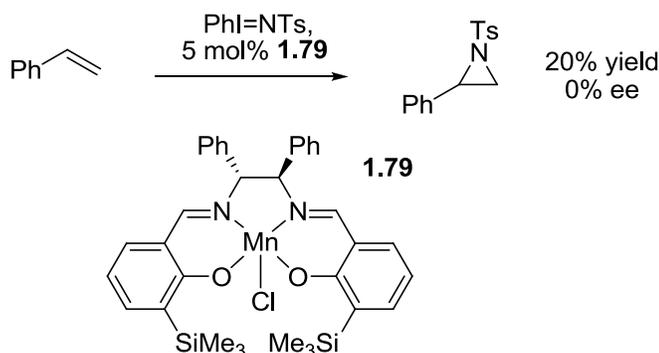


Scheme 1-18. Cyclopropanation of styrene derivatives with Co and Ru salen complexes.

Aziridination

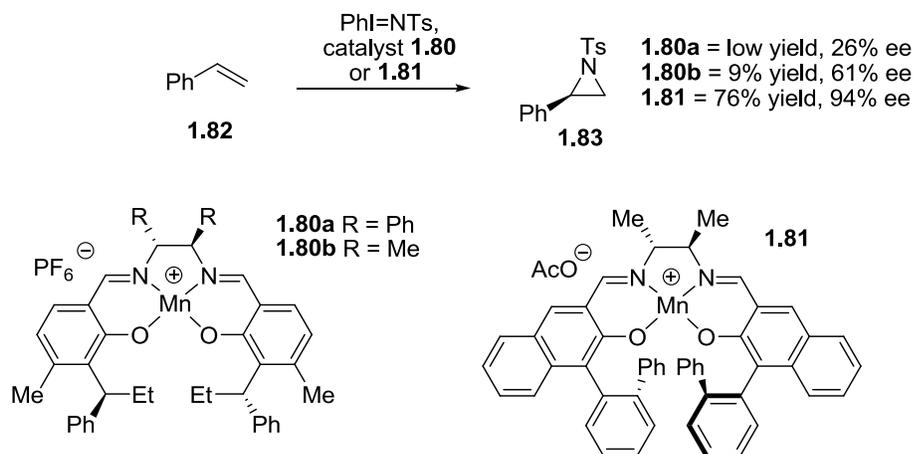
Aziridination through the reaction of olefins with metal nitrenes can be thought of as analogous to epoxidation via oxene transfer. In the same manner that enantioenriched epoxides are of high synthetic value, so are their nitrogen analogues. As such, catalytic methods to access such compounds are of considerable interest.

Burrows and co-workers⁶⁷ first investigated chiral Mn(III)Cl salen complex **1.79** as a catalyst in the aziridination of styrene using tosyliminoiodobenzene as nitrene transfer reagent. The observed yield was low and no asymmetric induction was observed.



Scheme 1-19. First report of aziridination of styrene using Mn(salen) complexes.

Katsuki and co-worker's early examination of aziridination of styrene with Mn(salen) complex **1.80a** was shown to give poor yield and only modest % ee.⁶⁸

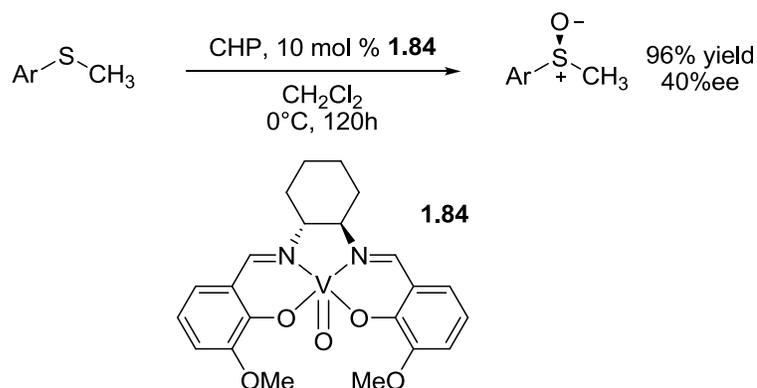


Scheme 1-20. Asymmetric aziridination of styrene with Mn(salen) complexes.

Unlike metal-oxo complexes, the metal bound nitrene contained an additional substituent and less steric demand from the ligand may be required for improved efficiency. Indeed, replacement of the aryl groups for methyl (**1.80b**) along the backbone significantly improved enantioselectivity but conversion was still sluggish. When second generation salen ligand **1.81** was used, a dramatic increase in reactivity was observed.⁶⁹ It was suggested that the rate acceleration was due to “ligand acceleration” in which attractive CH- π interactions between ligand and olefin can facilitate the nitrene transfer. These interactions have been observed in X-ray crystal structures of Mn(salen) complexes.⁷⁰

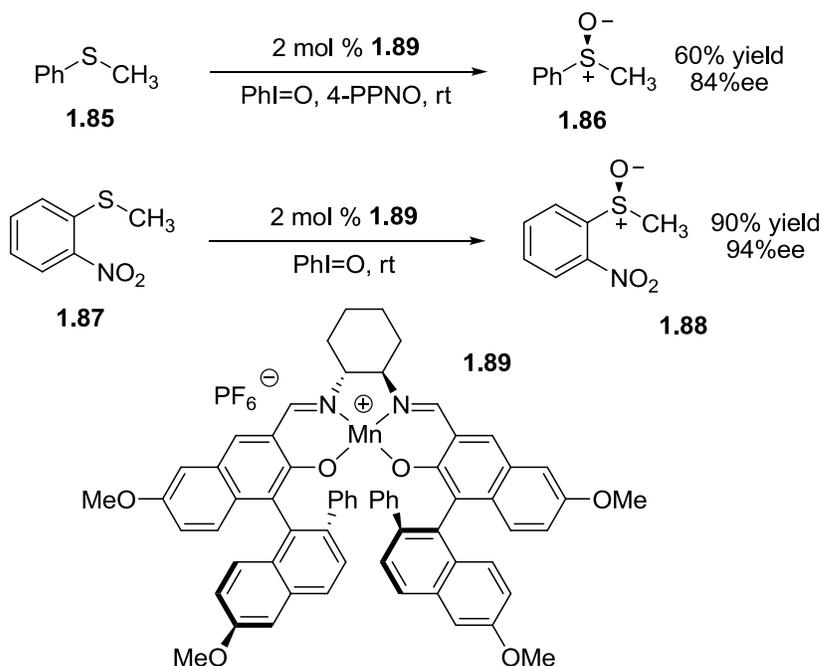
Oxidation of sulfides

Chiral sulfoxides are useful chiral auxiliaries for asymmetric synthesis and catalytic asymmetric sulfoxidation is a straightforward and efficient method for their preparation. Fujita⁷¹ reported the first example of asymmetric sulfide oxidation using V(IV)oxo salen complex **1.84**. This catalyst afforded the enantioselective oxidation of methyl phenyl sulfide with cumene hydroperoxide (CHP) in methylene chloride in high yield albeit modest enantioselectivity.



Scheme 1-21. Asymmetric oxidation of methyl phenyl sulfide with V(IV) oxo salen.

Jacobsen and co-workers⁷² reported similar results using Mn(III)Cl salen **1.5b** to catalyze the oxidation of sulfides using unbuffered hydrogen peroxide as the oxidant. Katsuki and co-workers showed that cationic Mn(III)PF₆ second-generation salen complex **1.89** were found to serve as efficient catalysts for asymmetric sulfoxidation. These reactions did require however, the less-atom efficient iodosylbenzene as the terminal oxidant.

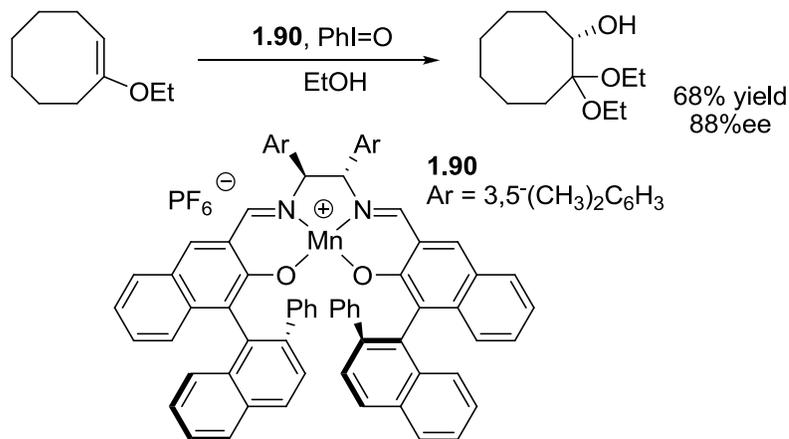


Scheme 1-22. Asymmetric oxidation of methyl phenyl sulfide with cationic Mn(V)PF₆ salen.

Oxidation of enol derivatives

Thornon and co-workers⁷³ reported that Mn(III)Cl salen complex type **1.14** catalyzed the oxidation of silyl enol ethers to give α -hydroxyketones using iodosylbenzene as oxidant and proceed with good to excellent yield (70–94%) and moderate asymmetric induction (14–62%) although good substrates are limited to conjugated enol ethers or esters.

However, Katsuki and co-workers⁷⁴ demonstrated that cationic Mn(III)PF₆ salen complex **1.90** can be successfully applied to the oxidation of simple enol ethers. Reactions of cyclic enol ethers in ethanol proceeded with high enantioselectivity, giving the corresponding α -hydroxy acetals.

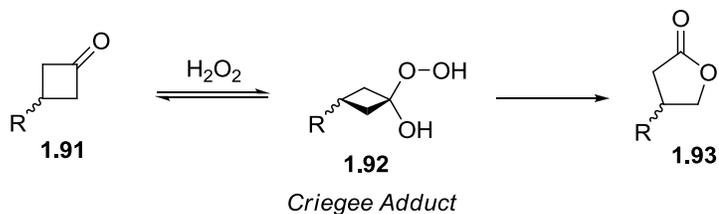


Scheme 1-23. Asymmetric oxidation of cyclic enol ethers with cationic Mn(V)PF₆ salen.

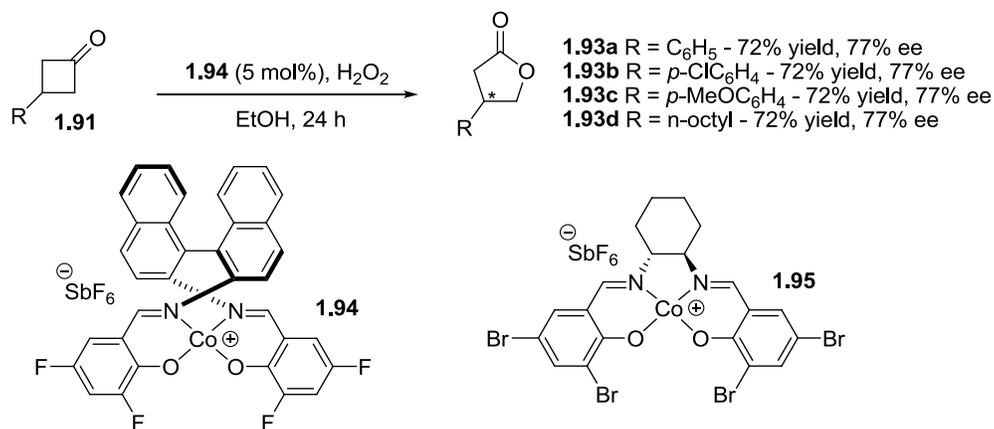
Asymmetric Baeyer–Villiger oxidations

The conversion of carbonyl compounds to esters by the Baeyer–Villiger reaction is widely used in organic synthesis.⁷⁵ This transformation can be performed in an enantioselective manner when the carbonyl compounds are racemic or prochiral.

The first step of this reaction is nucleophilic addition of a peroxy compound to a carbonyl compound giving a Criegee intermediate followed by migration of the α -carbon to the peroxy oxygen atom. This step is rate-determining and migration can occur only when the α -carbon C-O bond and peroxy O-O bond are anti-periplanar to one another.



Scheme 1-24. Baeyer–Villiger oxidation.



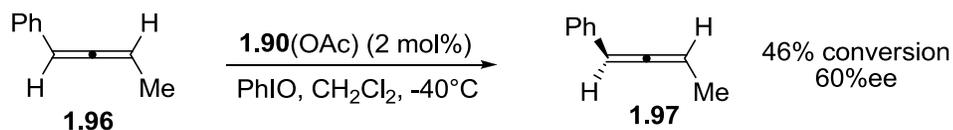
Scheme 1-25. Asymmetric Baeyer–Villiger oxidation catalyzed by cationic Co(salen).

The ability to control this migration would lead to enantioenriched products. While traditional *trans*-Co(salen) complexes like **1.95** bearing the cyclohexanediamine backbone gave racemic product, Katsuki and co-workers demonstrated that Co(salen) complexes of *cis*- β -structure (**1.94**) resulting from the strained binaphthyl backbone resulted in good selectivity in several cases.⁷⁶

Kinetic resolution of racemic allenes

As discussed above, Mn(salen) complexes are efficient catalysts for the enantioselective epoxidation of racemic *cis*-olefins. Katsuki and co-workers had reasoned that these catalysts would also be efficient in the kinetic resolution of racemic olefins under similar conditions.

Epoxidation of racemic 1-alkylindenes were examined but only modest enantiomer differentiation was observed. Interestingly, better enantiomer differentiation was observed in the oxidation of racemic aryl-substituted allenes with Mn(salen)OAc **1.90**.



Scheme 1-26. Kinetic resolution of racemic 1-phenylbuta-1,2-diene.

Asymmetric hydroxylation of C–H bonds

In an early report, Kochi and co-workers⁷⁷ reported that Mn(salen) complexes are capable of catalyzing C–H hydroxylation. Two years later, Nishinaga and co-workers⁷⁸ reported the hydroxylation of styrene using chiral Co(salen) complex to produce 1-phenylethanol in modest yield (30% isolated) and enantiomeric excess (38% ee).

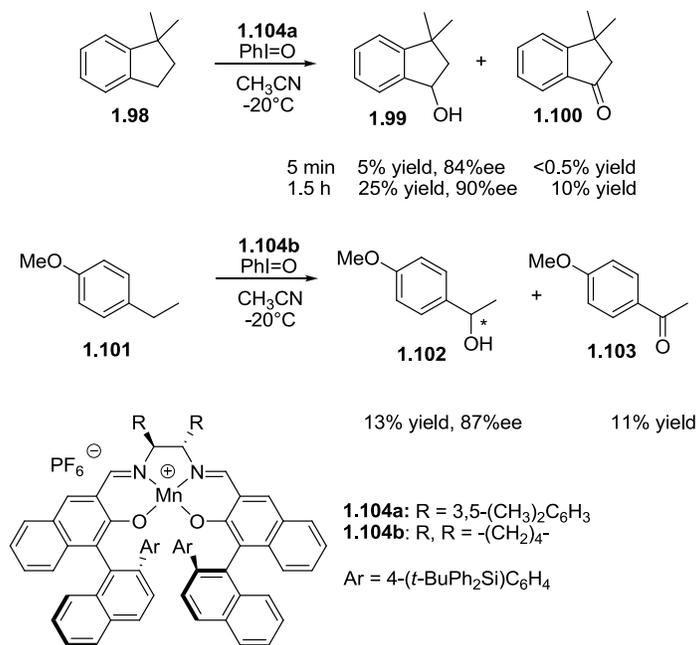
In 1994, Jacobsen and co-workers reported a fascinating kinetic resolution of racemic dihydronaphthalene oxide and related epoxides with Mn(salen) complex.⁷⁹ This resolution was discovered after observing an increasing % ee with decreasing yield toward the end of an asymmetric epoxidation reaction. In the initial findings, the minor epoxide enantiomer was selectively oxidized at the benzylic position to give the *syn*-epoxy alcohol.

Katsuki and co-workers⁸⁰ examined enantioselective benzylic oxidation with second generation Mn(salen) complexes. The ligands **1.104a+b** were designed with the intent of inhibiting radical decay by slowing the rate of dissociating radical intermediate away from the metal center through the incorporation of sterically encumbered silyl groups that hover over the metal center (Scheme 1-27).

Heterocyclic Nitrogen Donor Ligands

2,2-Bipyridine based ligands

Ligands based on 2,2'-bipyridine (BIPY) have been shown to chelate a variety of different metals from across the periodic table. These ligands are generally synthesized via Ni-catalyzed coupling halosubstituted pyridines with pre-installed chiral pendant groups. Bolm and co-workers reported one of the first synthesis of chiral 2,2'-bipyridyl ligands using chiral boranes to obtain the desired alcohols for type **1.105**.⁸¹



Scheme 1-27. Asymmetric benzylic hydroxylation with cationic Mn(salen)s.

Other interesting examples are those whose chirality is based on atropisomers⁸² (**1.106**), on planar chirality (**1.107**) or those relying on a secondary functionalization (**1.108**). These ligands are often employed in reactions such as Cu-catalyzed cyclopropanation,⁸² allylic oxidations,⁸³ Rh-catalyzed hydrosilylations,⁸⁴ and alkylations with R₂Zn.⁸³ C₁-symmetric BIPY ligands have also been developed using similar conditions and for similar applications.

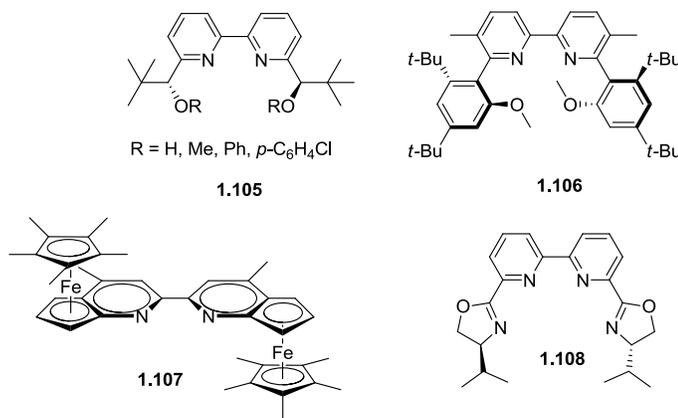


Figure 1-15. Selected examples of chiral 2,2'-bipyridine ligands.

Oxazoline ligands

Oxazoline rings have been the basis of C_2 (**1.109**) and C_1 (**1.110**) symmetric ligands developed largely by Pfaltz and have been thoroughly reviewed.⁸⁵ Aza-bis(oxazolines) (**1.111**) are an interesting variant that allows for further functionalization at the bridging nitrogen. Most often, functionalization at the central nitrogen is in the form of solid supports such as methoxypoly(ethylene glycol) (MeOPEG 5000)⁸⁶ or dendritic structures⁸⁷ in an effort to access recoverable catalysts.

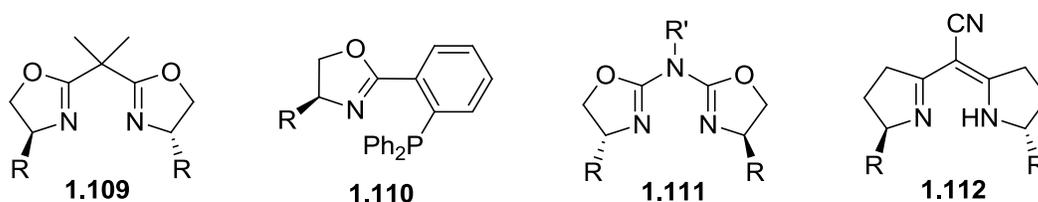
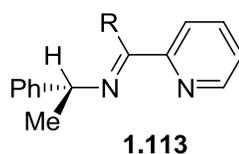


Figure 1-16. Bis-oxazoline and related ligands.

Pyridyloxazoline based ligands

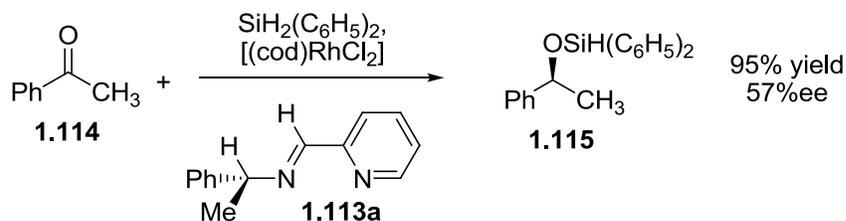
Bridging the gap between bipyridine and diimine ligands are pyridylimine based ligands. These ligands are easily synthesized via Schiff base condensation of chiral amines and either pyridyl- aldehydes or ketones and were independently developed in the labs of Camus,⁸⁸ van Koten⁸⁹ and Brunner.⁹⁰



R = H, Me, Ph

Figure 1-17. Typical pyridylimine type ligand.

Brunner and co-workers⁹⁰ achieved up to 57% ee in the enantioselective hydrosilylation of acetophenone with diphenylsilane using the neutral Rh(I)cod complexes of pyridylimine ligand **1.113a** (R = H) as precatalyst.



Scheme 1-29. Asymmetric hydrosilylation of acetophenone.

The section above reviews just some of the more important types of nitrogen donor ligands with a special emphasis on salen type ligands and some examples of the asymmetric reactions they can affect. The cited examples are in no way a comprehensive review which should be taken as evidence to the breadth and depth of contributions in this area.

Self-Assembling Ligands in Asymmetric Catalysis

Catalysis lies at heart of synthetic chemistry and provides a highly atom economical method for the conversion of basic chemicals into more useful and valuable commodity chemicals. At a time when the careful management of resources has become more important than ever, the use of efficient catalysts to accelerate and control chemical transformations will become increasingly important.

The field of catalysis is often segregated in to one of several categories, homogenous catalysis (including organocatalysis), heterogeneous catalysis and biocatalysis. While these fields have grown and made considerable achievements in the past few decades, the area of supramolecular chemistry has also become quite well established. In contrast, the development of chemistry at the interface between catalysis and supramolecular chemistry⁹¹ has only recently started to gain momentum. Supramolecular catalysis often focuses on either the use of non-covalent interactions for the recognition of substrate molecules or for the self-assembly of more complex

ligand architectures from simple pre-cursors containing functional groups programmed for recognition in solution.

This approach to catalysis is not without its challenges. The prediction of how these interactions occur (and to what extent) is difficult and often highly dependent on intrinsic factors associated with reaction conditions such as solvent polarity, concentration and the reactants or products themselves. However, if these factors can be successfully controlled, highly efficient catalysts that exhibit superior levels of selectivity are possible. In this section, catalysts that use self-assembly in the construction of their ligand architecture will be reviewed.

Self-assembling Catalysts Based on Secondary Metal Coordination

With respect to biocatalysis, enzymes are capable of incredible rate accelerations and often display turn over frequencies (TOF's) that will likely never be matched in a synthetic system. For example, carbonic anhydrase, a metalloprotein whose active site contains a Zn(II) cation, rapidly reacts CO₂ with water to form bicarbonate as a means to regulate physiological pH and to help transport CO₂ out of the body. This transformation is carried out at a rate of 10⁶ reactions/min!⁹² In light of these impressive systems, considerable effort has been placed on mimicking the catalytic environment provided by enzymes. While the exact nature of rate acceleration provided by enzymes is under debate, it is believed that electronic and structural features within the active site stabilize the transition state to an extent that facilitates rapid conversion of the substrate molecules. As a result, much of the efforts focused on supramolecular catalysis are centered on encapsulating reaction partners or the active site itself to increase the local concentration of reactants and/or confer some structural constraints that selectively

favor one reaction product over another. The application of secondary metal coordination as a structural feature of these catalysts has seen considerable use.

Ligands that possess two different metal binding motifs have been widely employed for forming supramolecular bidentate ligands. The major limitation for this approach is the compatibility between the two different ligating groups, which have to coordinate two different metals in the presence of one and other. One metal has to play an exclusively structural role while the other remains catalytically active for the reaction of choice. In many examples, the catalytic metal is played by soft transition metals such as rhodium or palladium, while harder metals such as zinc or titanium play a structural role. *P,N*-ligands are often employed for their respective affinities for soft and hard metals, respectively. A common feature of self-assembled ligands based on this coordinative bonding are three-component systems containing two heterobidentate ligands, non-covalently linked to a metal template (Figure 1-18).

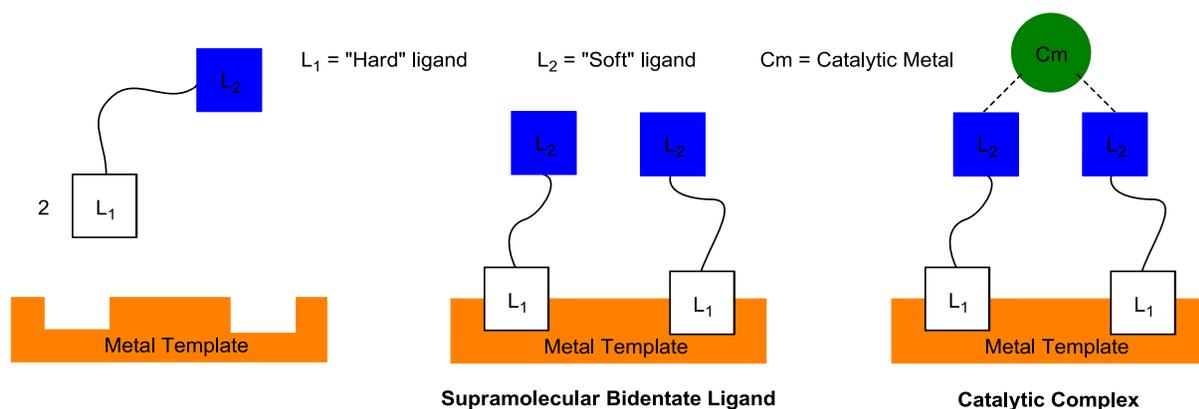
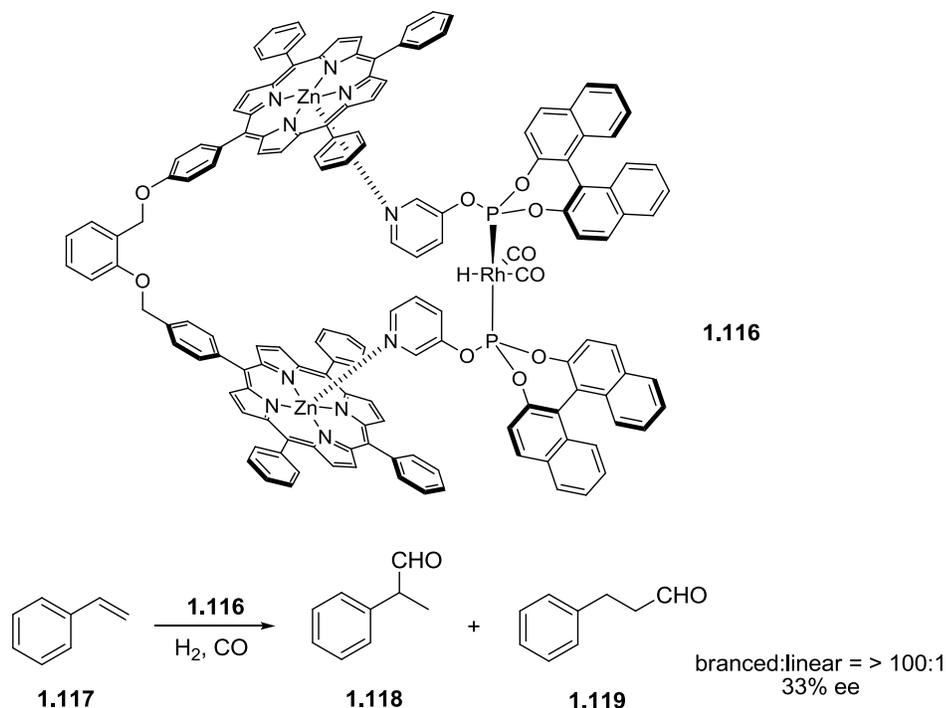


Figure 1-18. Three-component supramolecular bidentate ligands involving a template.

Reek and co-workers reported one of first supramolecular bidentate ligands based on this template approach in 2003.⁹³ Pyridyl phosphite bidentate ligands containing a BINOL chiral backbone were used to support the catalytically active Rh(I) center, while the pyridine nitrogen coordinated to the zinc porphyrin template. This catalyst (**1.116**)

gave only modest enantioselectivity but was highly selective for the branched product in the hydroformylation of styrene.



Scheme 1-30. Heterobidentate ligand on dimeric zinc(II) porphyrin.

Reek and co-workers later reported a template induced supramolecular ligand involving a bis-zinc(II)-salphen template and *P,N*-heterobidentate ligands (**1.120**) similar to those above. This catalyst was reported to give up to 78% ee in the hydroformylation of styrene.⁹⁴

Reek and co-workers also used a combinatorial approach to develop supramolecular bidentate ligands in the absence of a template. Instead, these catalysts relied on the interaction between a free pyridyl phosphine and a chiral phosphite covalently tethered to a zinc porphyrin (**1.120**). A library of the new bidentate ligands were screened in a variety of reactions, including the Rh-catalyzed hydrogenation of

enamide **1.121** which gave the unsaturated amide **1.122** with 100% conversion and 94% ee.⁹⁵

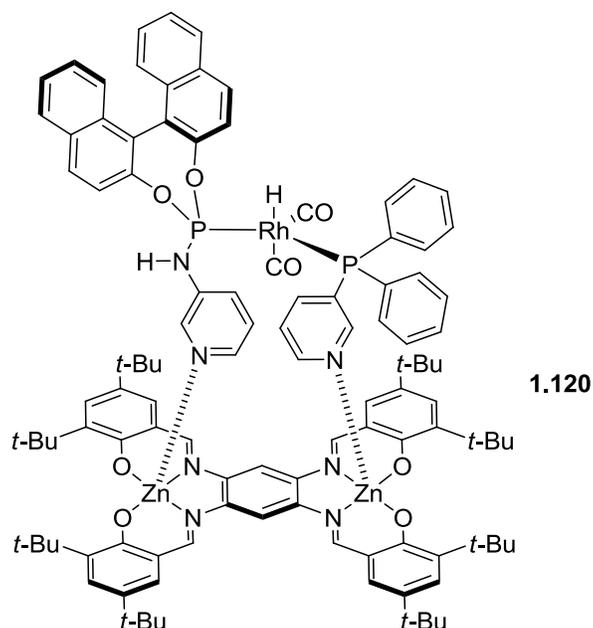
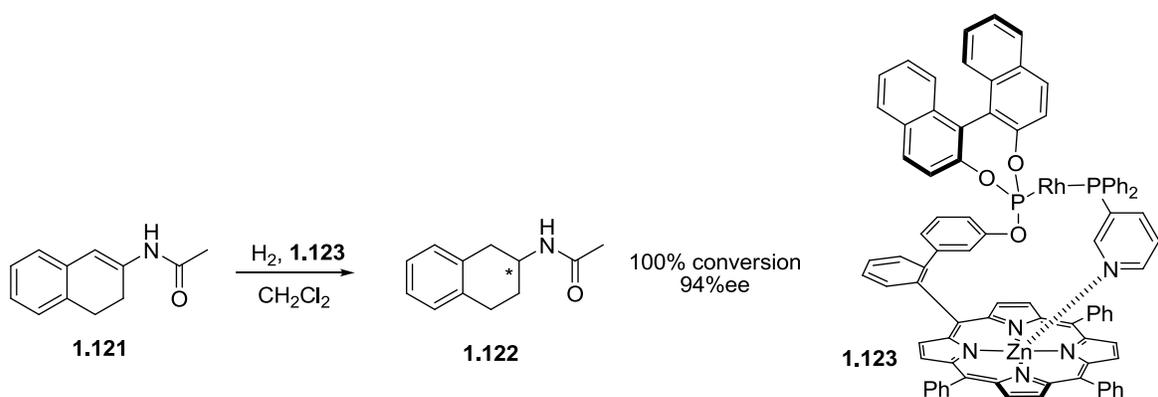
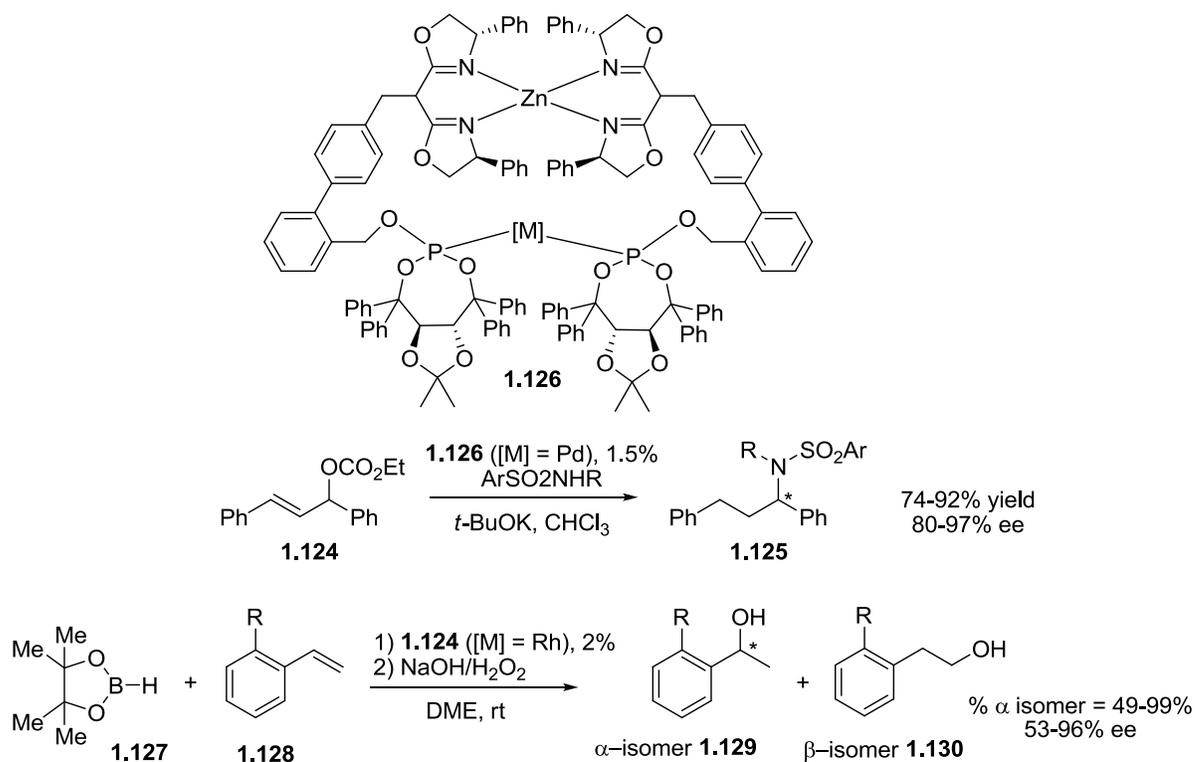


Figure 1-19. Self-assembling heterobidentate ligand on bis-zinc(II)-salphen template.

In 2004, Takacs and co-workers reported an alternative approach to chiral supramolecular bidentate ligands where the structural metal is chelated by modular bis(oxazoline) ligands to form stable tetrahedral zinc(II) complexes(**1.126**).⁹⁶ The differentiating bifunctional ligands contain chiral TADDOL phosphites for binding the second catalytically active metal. The modularity of these supramolecular catalysts allowed for the screening of 50 ligands for various asymmetric reactions. Screening the ligands for the palladium-catalyzed asymmetric allylic amination gave enantioselectivities between 20% and 97% ee.



Scheme 1-31. Rh-catalyzed hydrogenation of enamide.



Scheme 1-31. Supramolecular complex for Pd-catalyzed allylic amination and Rh-catalyzed olefin hydroboration.

The same library was also screened in the Rh-catalyzed asymmetric hydroboration of olefins.⁹⁷ These catalysts showed good to excellent regioselectivity for the branched product and high enantioselectivity (up to 96% ee).

In 2003, Mirkin and co-workers⁹⁸ reported the development of functionalized salen structures capable of binding a secondary metal center through *P,S*, ligation. Unlike previous examples, the “softer” metal here is used as the structural element while the “harder” metal is catalytically active. The development of these catalysts was born from the observation of enzymes whose activity is altered by an allosteric effector. These effectors bind to locations other than the active site causing a conformational change that alters the enzymes activity.⁹⁹ It was reported that even in the “closed” state, **1.131a** displayed a 20-fold rate increase over the analogous monomeric Cr(III)Cl salen (**1.5f**) in the asymmetric addition of TMSN₃ to cyclohexene oxide.

After treatment with bis(triphenylphosphine)iminium chloride (PPNCl) and CO (1 atm) to give the “open” state catalyst (**1.131b**), it gave a 40-fold rate increase over monomer **1.5f**. While enantioselectivity was improved over the monomer (68% vs. 12% ee) at the given concentration, it was lower than what has been previously accomplished with Jacobsen’s oligomeric catalysts.

In the following year, Mirkin¹⁰⁰ reported a “tweezer” complex that, unlike their previously reported macrocyclic salen catalyst, did not contain a site for additional metal chelation on one side (**1.133** and **1.134**). Instead, they were replaced with simple tertiary butyl groups, increasing the complexes solubility to a range of solvents known to yield ring opened products in higher % ee. As predicted, asymmetric ring opening of cyclohexene oxide with TMSN₃ could be achieved in 80% ee from the “closed” state with the Cr(III)Cl salen **1.133a**.

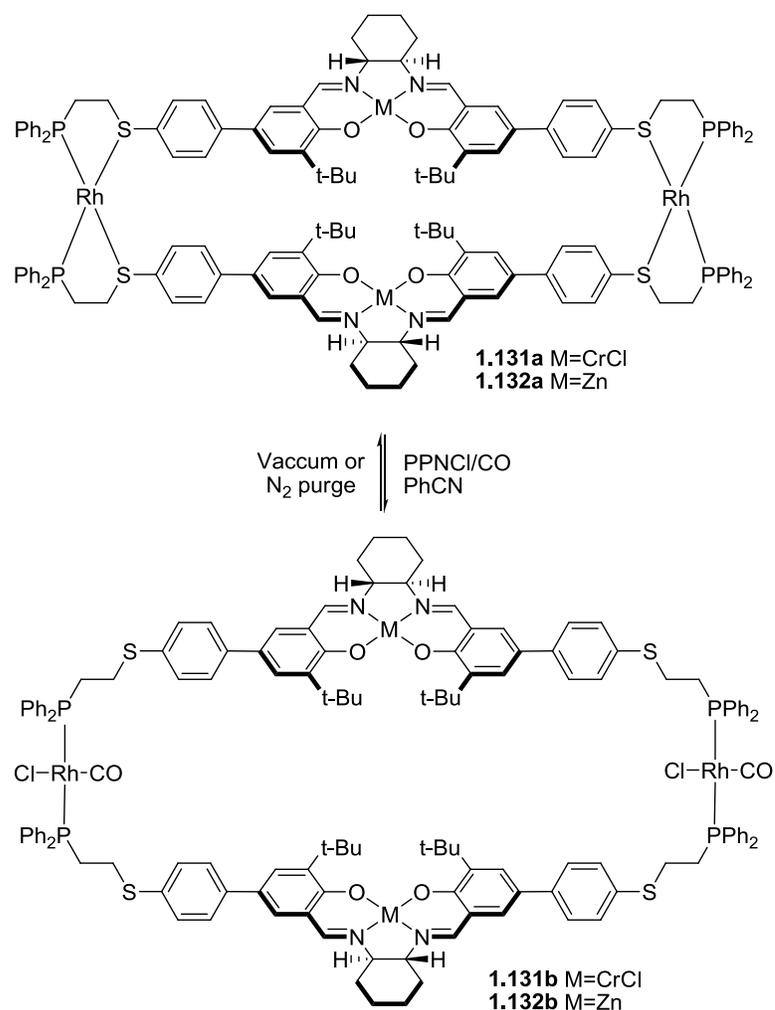


Figure 1-20. Macrocyclic allosteric salen catalyst.

Interestingly, while both outperform the monomeric catalyst **1.5f**, the selectivity difference from the “closed” state (**1.133a**) and “open” states (**1.133b**) is not as dramatic as one might expect. What is dramatic, however, is the difference in reaction rate between the “open” and “closed” states and that these two states can be interconverted *in situ*. These results demonstrate a novel approach to “switchable” supramolecular catalysts controlled by allosteric effectors.

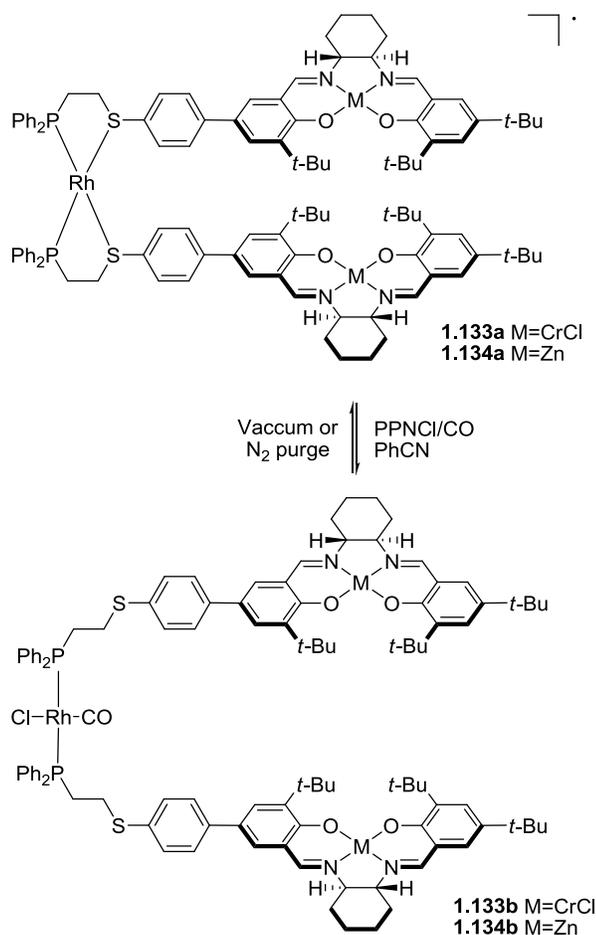
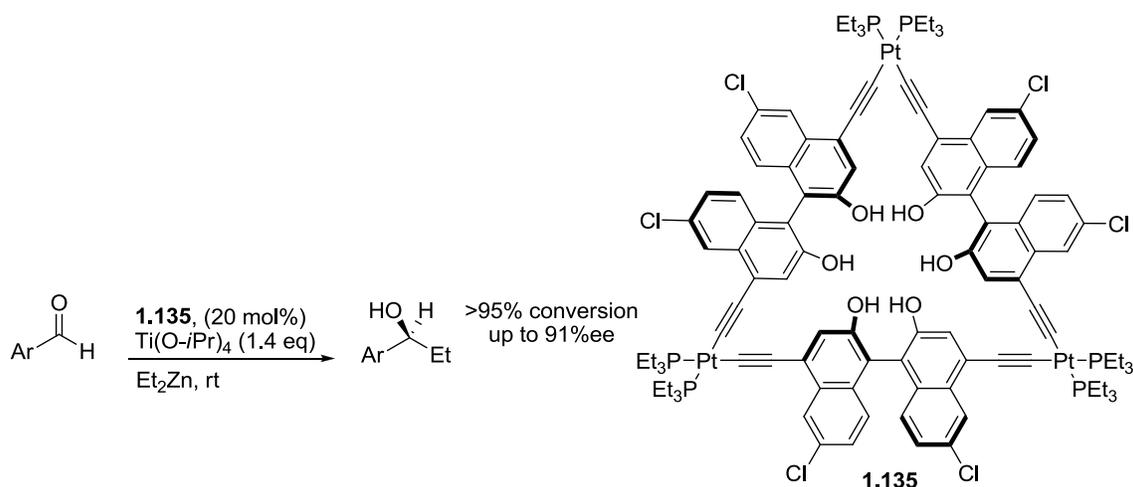


Figure 1-21. Hinged allosteric salen catalyst.

The previously described examples generally rely on two equivalents of a bifunctional ligand, capable of coordinating to both a templating metal as a structural element and a second catalytically active metal. Lin and co-workers¹⁰¹ developed an interesting variation that incorporates three equivalents of bi-functional ligand to create the sides of a triangular supramolecular catalyst creating a chiral, catalytic pocket in the center. In this case, Pt(II) is used as the softer structural metal to form the “corners” of the structure while Ti(*O*-*i*-Pr)₄ acts as the harder Lewis acid, supported by the BINOL oxygens. Trimer **1.135** in the presence of Ti(*O*-*i*-Pr)₄ catalyzes the asymmetric addition of Et₂Zn to several aromatic aldehydes with high conversion and high levels of selectivity.



Scheme 1-32. Asymmetric addition of Et_2Zn to aryl aldehydes.

While the previously discussed examples were focused on the phenomena of ligand templating and/or insulating or encapsulating a catalytic active site, there are still other approaches in which self-assembly is used to create reversible, encapsulating environments or “nanoreactors”.

Raymond and co-workers¹⁰² have developed the chiral tetrahedral $[\text{M}_4\text{L}_6]^{-12}$ coordination cage consisting of four metal ions and six bis-bidentate catechol amide ligands. Four metal ions are situated at the corners of the tetrahedron and the ligands create the edges of the tetrahedron. The chelation by three bidentate ligands renders the metal atoms chiral (Δ or Λ), and the coupling between the metals through those ligands results in exclusive formation of the homochiral assemblies $\Delta, \Delta, \Delta, \Delta$ and $\Lambda, \Lambda, \Lambda, \Lambda$. A guest template molecule (such as NR_4^+ where R = Me, Et, Pr) is needed during the assembly process to achieve the desired stoichiometry with a tetrahedral shaped cage. The negatively charged tetrahedral cage is soluble in water and other polar solvents. The anionic character of the cage allows for the encapsulation of

monocationic guests such as alkylammonium ions and cationic organometallic complexes.

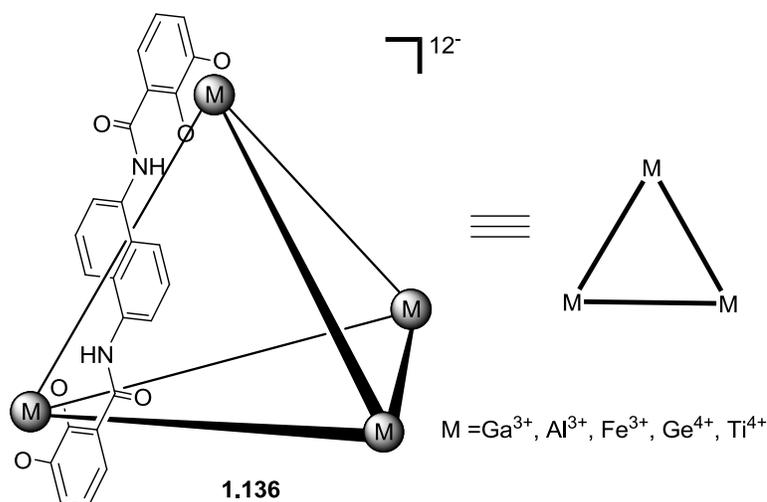
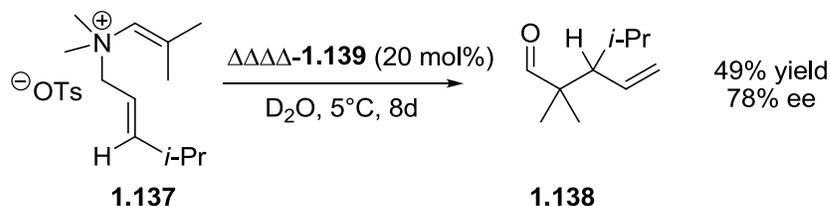


Figure 1-22. Tetrahedral coordination cage.

Many self-assembled, cage-type capsules have been developed to create either concentrated local environments and/or impart some structural constraints on encapsulated substrate molecules for enhanced selectivity. One of the more common challenges in these systems is product inhibition. In these cases, the product molecule is better stabilized within the capsule than the substrate molecules themselves. This problem often requires stoichiometric amounts of these structures. While still able to impart selectivity to certain reactions, these cannot truly be defined as catalysts.

In 2009, Raymond and co-workers¹⁰³ reported the use of their developed supramolecular cage in the catalytic asymmetric aza-Cope rearrangement of enammonium substrates. In this remarkable example, the chiral but racemic mixture of $\Delta\Delta\Delta$ -**1.139** and $\Lambda\Lambda\Lambda$ - **1.139** was first separated using ion exchange chromatography. Due to its anionic nature, enammonium cations are suitable molecules for encapsulation and once inside the capsule, a reactive conformation is enforced. The

cavity itself bears no other sites for coordination or reactive functional groups. As it may be expected, this encapsulation approach is highly substrate specific, giving low to modest yield and enantioselectivity in several cases. At reduced temperatures and elongated reaction times enammonium **1.137** was rearranged then hydrolyzed to aldehyde **1.138** in moderate yield and good enantioselectivity.



Scheme 1-33. Asymmetric aza-Cope rearrangement.

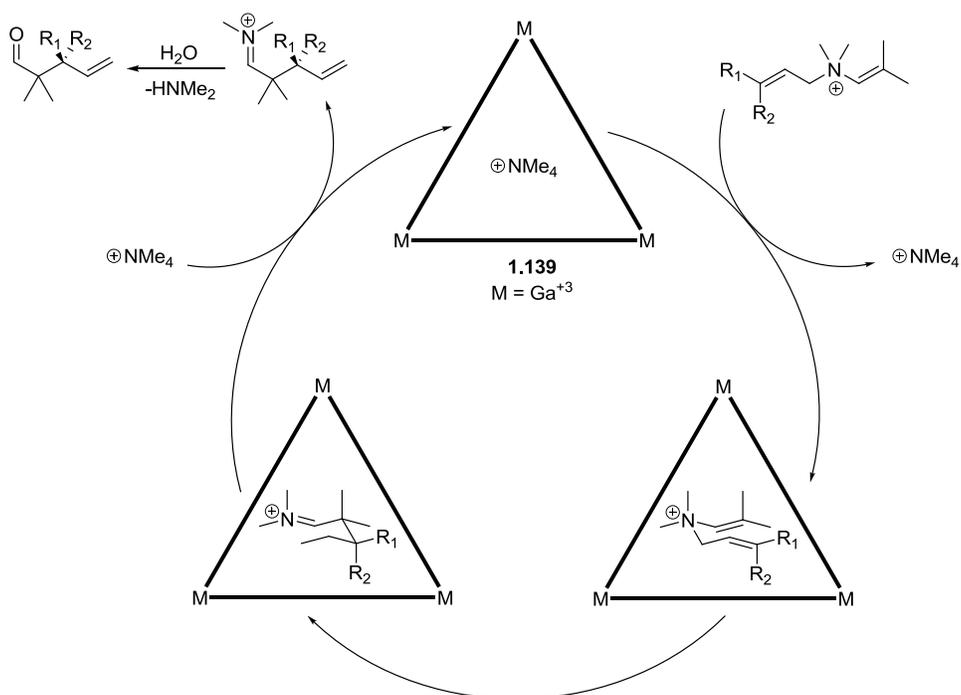


Figure 1-23. Aza-Cope rearrangement within a supramolecular cage.

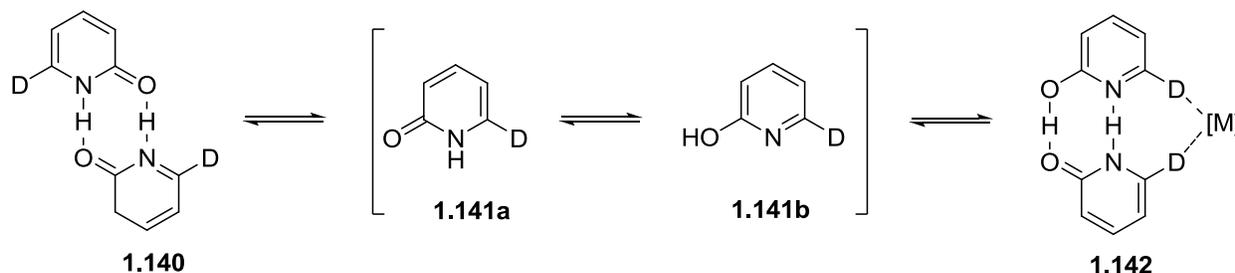
The examples described in this section are only a few of the more important developments in coordination driven self-assembly as applied to asymmetric catalysis.

Equally important are those developments in ligand self-assembly driven by hydrogen bonding.

Self-Assembling Catalysts Based on Hydrogen-Bonding

The use of hydrogen bonds for the construction of supramolecular ligands is a highly practical approach. The functional groups capable of hydrogen bonding such as amides, ureas and guanidines are attractive since they tend to be stable and easy to install. The hydrogen bonds themselves are self-repairing, controllable and/or reversible in the reaction medium and can often co-exist with other interactions.

The first example of ligands designed specifically for self-assembly through hydrogen bonds to form bidentate ligands was reported by Breit and Seiche in 2003.¹⁰⁴ The 2-pyridone (**1.141a**)/2-hydroxypyridine (**1.141b**) tautomer system was employed as a dynamic scaffold (Scheme 1-34). The parent system (where D = H) is known to dimerize in aprotic solvents to form predominantly the symmetrical pyridone dimer **1.140**. However, if “D” is a donor atom capable of binding to a metal center, such as phosphine, the equilibrium can be shifted towards the mixed hydroxypyridine/pyridone dimer **1.142**.



Scheme 1-34. Tautomer system of 2-pyridone/2-hydroxypyridine.

Börner, Breit and co-workers later reported the synthesis of several derivatives of these tautomeric pyridones bearing a chiral phosphine (Figure 1-24).^{105,106,107} The self-

assembled rhodium complexes were employed for catalyzing the enantioselective hydrogenation of several prochiral olefins with high enantioselectivity (up to 99% ee). All of the ligands capable of self-assembly were found to be superior to *O*-alkylated analogues, demonstrating the benefit of self-assembly.

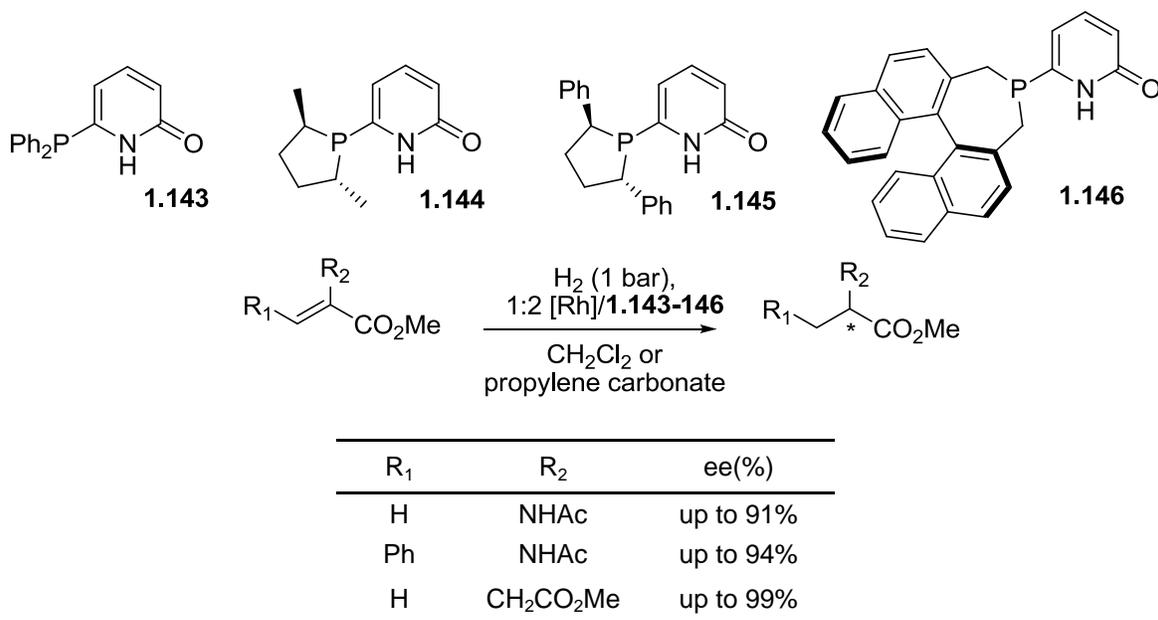
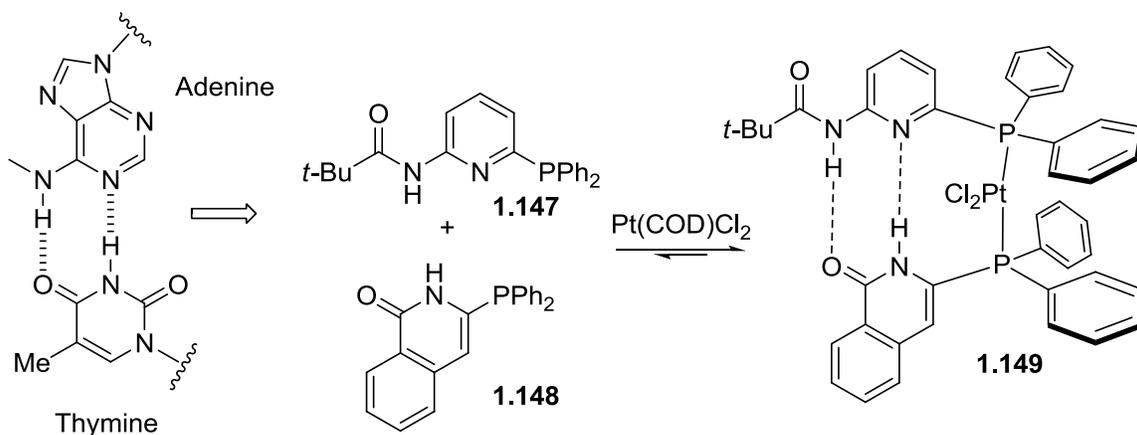


Figure 1-24. Self-assembling pyridine based ligands for the Rh-catalyzed hydrogenation of olefins.

Using 2-pyridone as a scaffold has its limitations. The complexes generated can only be homodimers as a result from the equilibrium between **1.141a** and **1.141b**. If two different ligating functionalities were to be introduced to the 2-pyridone unit, a mixture of homo- and heterodimers would be formed.

Reminiscent of the hydrogen bonding network of nucleobase pairs in DNA, Breit and co-workers selected an A–T base-pair model, relying on the aminopyridine **1.147** and isoquinolone **1.148** to create the heterodimeric ligand assembly seen in Scheme 1-35.¹⁰⁸ When phosphine ligands based on this platform were mixed in the presence of a Pt(II) salt, the *cis*-heterodimeric platinum complex **1.149** was formed exclusively. The X-

ray structure of **1.149** showed the expected Watson–Crick type two-point binding interactions of A and T in DNA.



Scheme 1-35. Heterocomplexes formed by aminopyridine/isoquinolone interaction.

The major advantage of these heterodimeric complexes is the ability to structurally modify both the 2-aminopyridine and the 2-pyridone subunits to generate large combinatorial libraries for the rapid screening and identification of optimal pairs for a selected reaction. For example, a Rh(I) complex was found supported by 2-aminopyridine **1.153c** and 2-pyridone **1.154c** that catalyzed the hydroformylation of terminal alkenes (Figure 1-25) with outstanding activity ($\text{TOF} = 8643 \text{ h}^{-1}$) and regioselectivity (linear:branched= 96:4).

Later, Breit and co-workers¹⁰⁹ reported that the self-assembly strategy relying on aminopyridine/isoquinolone interactions was also effective for the enantioselective Rh-catalyzed hydrogenation of prochiral olefins.

Several chiral *P*-ligands bearing either the aminopyridine or the isoquinolone moiety were synthesized and combined to form Rh-heterocomplexes that gave high enantioselectivity in the hydrogenation of acetamidoacrylate with a remarkable catalyst loading of only 0.01 mol% (Scheme 1-36).

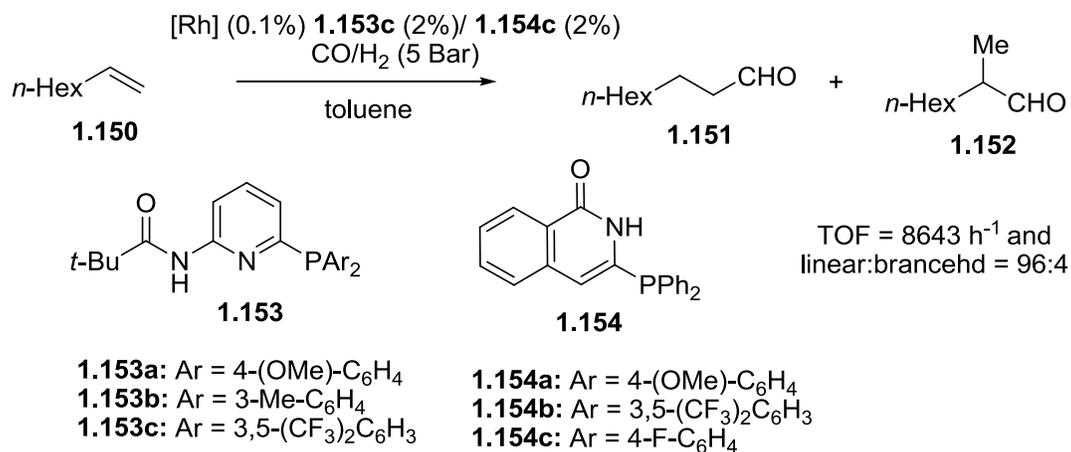
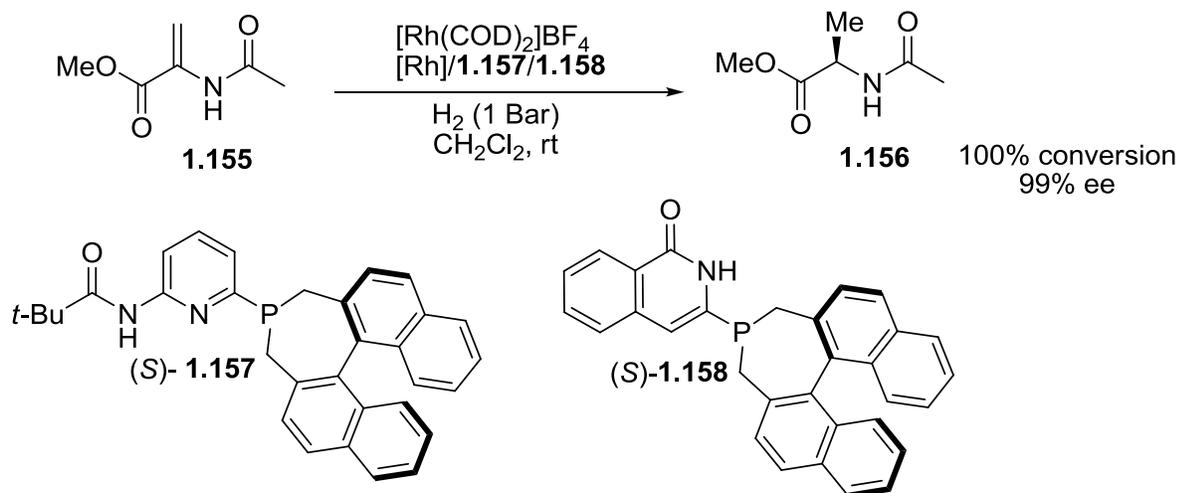
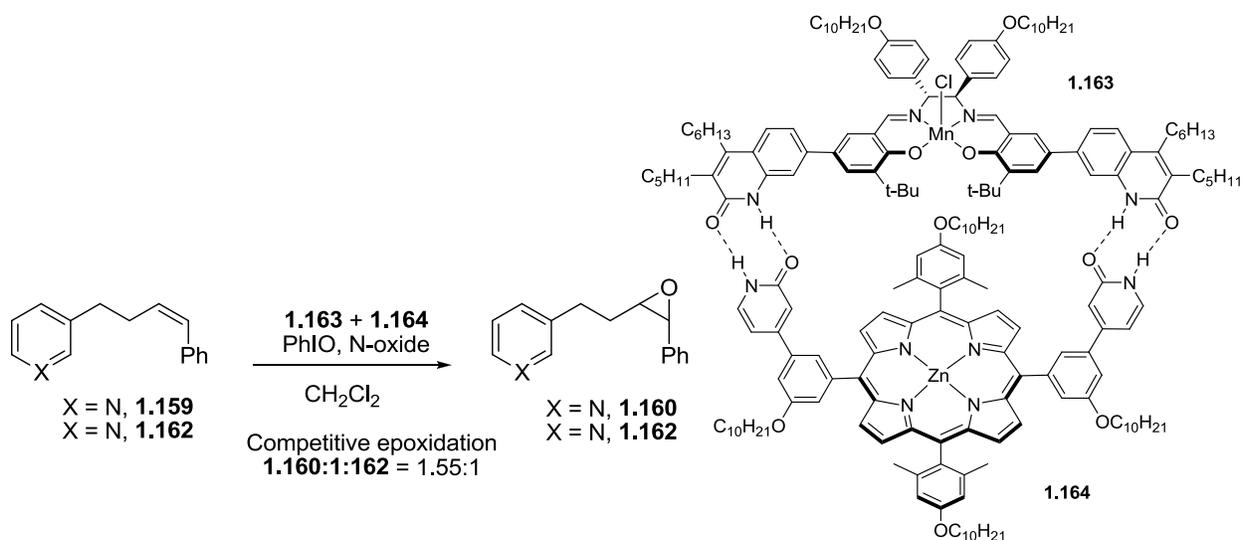


Figure 1-25. Regioselective hydroformylation of 1-octene using hetero combinations.



Scheme 1-36. Rhodium catalyzed hydrogenation of acetamidoacrylate.

Wärnmark and co-workers¹¹⁰ reported a unique heterobimetallic supramolecular catalyst containing a manganese salen subunit paired with a zinc porphyrin subunit, hydrogen bonded by complementary 2-pyridone/isoquinolone groups. This system was designed with the intent to selectively recognize nitrogen containing olefins by the zinc porphyrin subunit for catalytic epoxidation. While the difference in selectivity was not great, it was still noticeable in competition experiments.

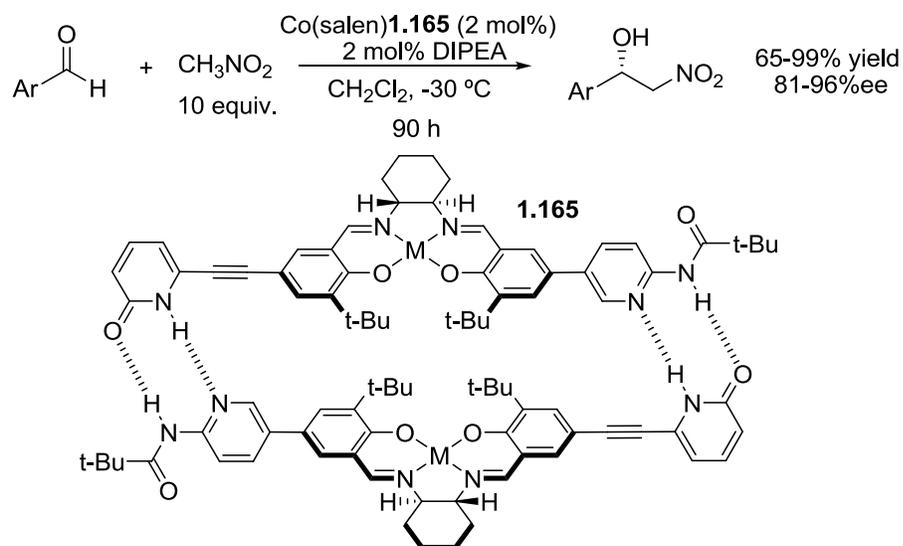


Scheme 1-37. Catalytic epoxidation by self-assembling heterobimetallic system.

Exploiting the 2-aminopyridine/2-pyridone type interactions, Hong and co-workers¹¹¹ developed Co(II)salen catalysts functionalized with nucleobase mimics also designed to self-assemble in solution.

Yamada¹¹² and the Skarzewski¹¹³ had previously reported the use of simple salen ligands for the asymmetric Henry reaction in the presence of base. It was reasoned that this reaction may provide a good model system for these new self-assembling catalysts.

The newly developed catalysts were in fact found to catalyze the asymmetric nitroaldol (Henry) reaction between substituted benzaldehydes and nitromethane in excellent yield and enantioselectivity. Evidence for self-assembly was also provided by similar ¹H-NMR experiments that allowed for the calculation of a dimerization constant estimated as $53 \pm 21 \text{ M}^{-1}$ by using nonlinear curve fitting methods. Single crystals suitable for X-ray diffraction were grown from the Ni(II) complex of **1.165** and clearly show a well organized dimer formed from the two-point hydrogen bonding between the aminopyridine and pyridone functional groups.



Scheme 1-38. Asymmetric nitro-aldol (Henry) reaction catalyzed by self-assembling Co(II)salen.

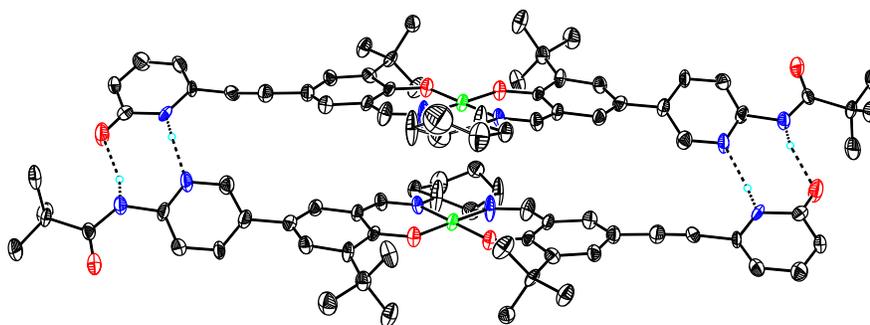
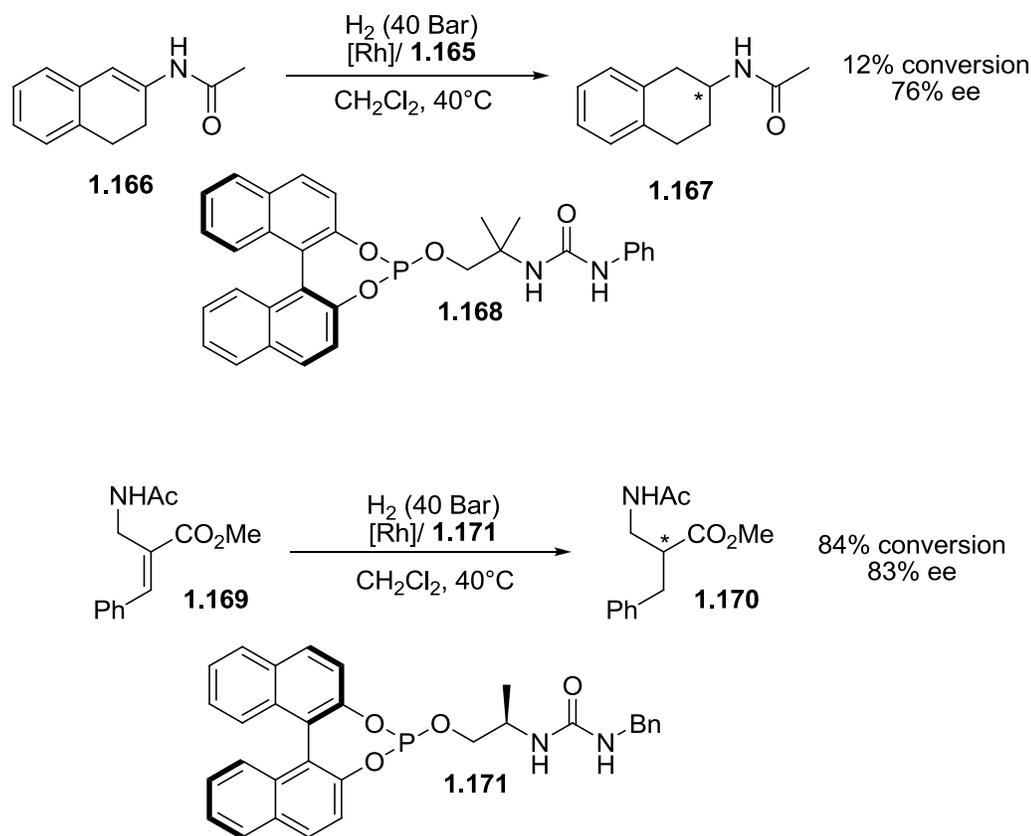


Figure 1-26. X-ray crystal structure of Ni(II)salen showing dimeric structure.

Reek and co-workers developed a new class of chiral urea-functionalized phosphite¹¹⁴ (**1.168**) and phosphoramidite¹¹⁵ ligands (**1.171**), called UREAphos, capable of self-assembly in the presence of a rhodium precursor to give the supramolecular homocomplexes. These catalysts relied on the self-complementary hydrogen-bonding between urea functional groups. Rhodium complexes of UREAphos ligands were screened in the enantioselective hydrogenation of traditional substrates, giving high

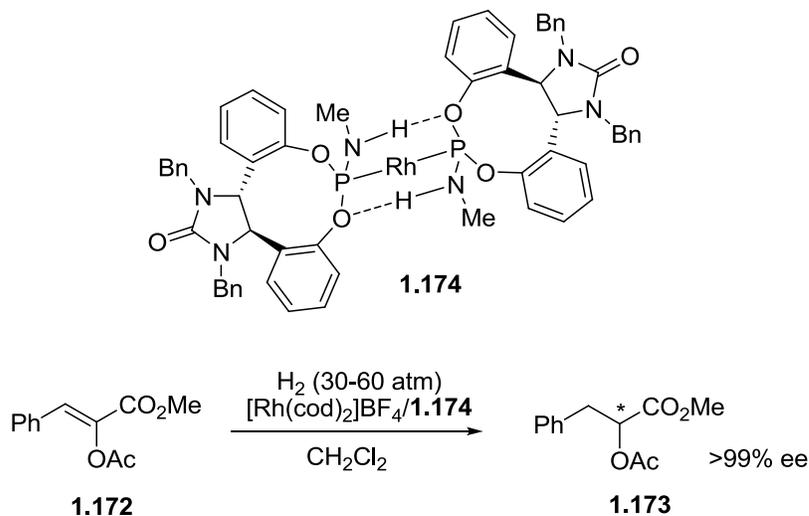
conversion and % ee while other, more challenging, industrially relevant olefins such as **1.166** and **1.169** gave lower conversions but in good % ee (Scheme 1-39).



Scheme 1-39. Structure and application of selected UREAphos ligands.

In 2006, Ding and co-workers¹¹⁶ reported a new class of phosphoramidite ligands (DpenPhos, **1.174**) for the enantioselective hydrogenation of several α,β -unsaturated esters (Scheme 1-40). Interestingly, when the phosphoramidite nitrogen is tertiary, and thus lacking a hydrogen bond donor group, it becomes totally inactive. This observation emphasizes the role that hydrogen bonding plays for these systems. DFT calculations carried out on the Rh-complex of a simplified structural mimic of **1.174** allowed some insight to the structure of the pre-catalytic complex featuring two hydrogen bonds between the adjacent phosphoramidite ligands.

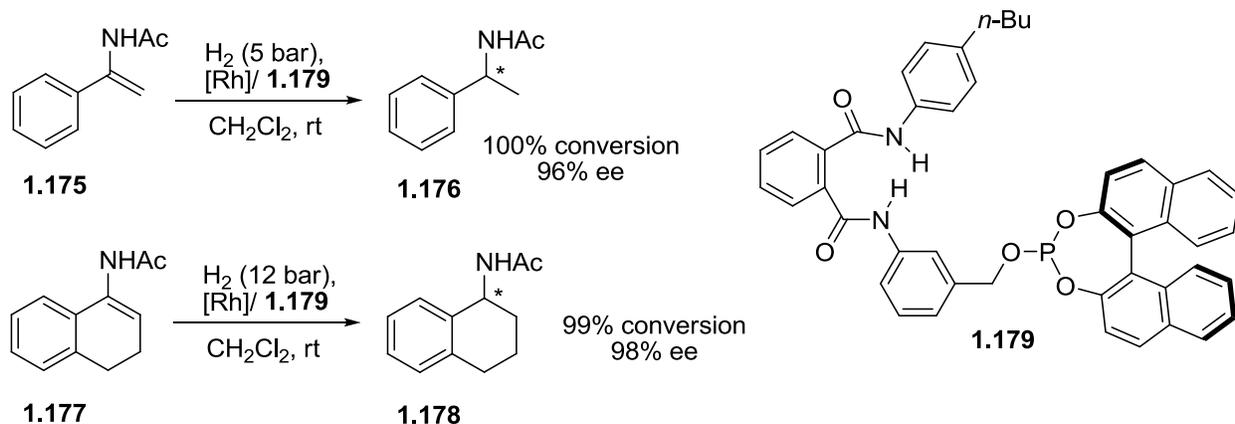
Gennari, Piarulli and co-workers¹¹⁷ reported a new class of ligands capable of self-assembling by means of self-complementary amide hydrogen bonds. These ligands (PhthalaPhos) owe their chirality to a BINOL-derived phosphite backbone possessing a phthalic acid bis-amide moiety which can act as both hydrogen bond donor and acceptor.



Scheme 1-40. Hydrogen-bonded phosphoramidite ligands applied in the [Rh] catalyzed asymmetric hydrogenation.

A library of ligands were prepared whose rhodium complexes showed good enantioselectivity and high conversion in the asymmetric hydrogenation of commonly employed olefins such as *N*-(1-phenylvinyl)acetamide **1.175** (up to 99% ee). Outstanding levels of enantioselectivity and conversion were also observed in the hydrogenation of challenging substrates (Scheme 1-41) such as the cyclic enamide **1.177** (up to 96% ee). Spectroscopic (NMR, IR and HRMS) studies were carried out on a representative PhthalaPhos ligand and on its Rh-complex. Interestingly, while no intramolecular hydrogen bonds were detected in the free ligand, the NH_A group is intramolecularly hydrogen-bonded in the metal complex. Computational studies

including conformational analysis followed by DFT optimization of the most stable structures, gave insight into the nature of the pre-catalytic complex $[\text{Rh}(\text{L})_2(\text{cod})]^+$ and was found to be consistent with the spectroscopic data (Figure 1-27).



Scheme 1-41. Example of a PhthalaPhos ligand and the application to the asymmetric hydrogenation of olefins.

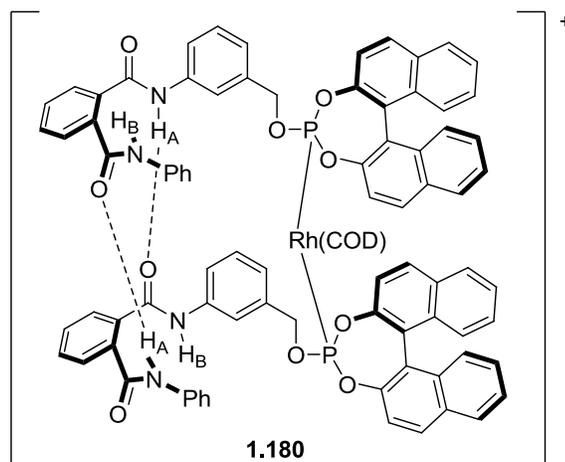
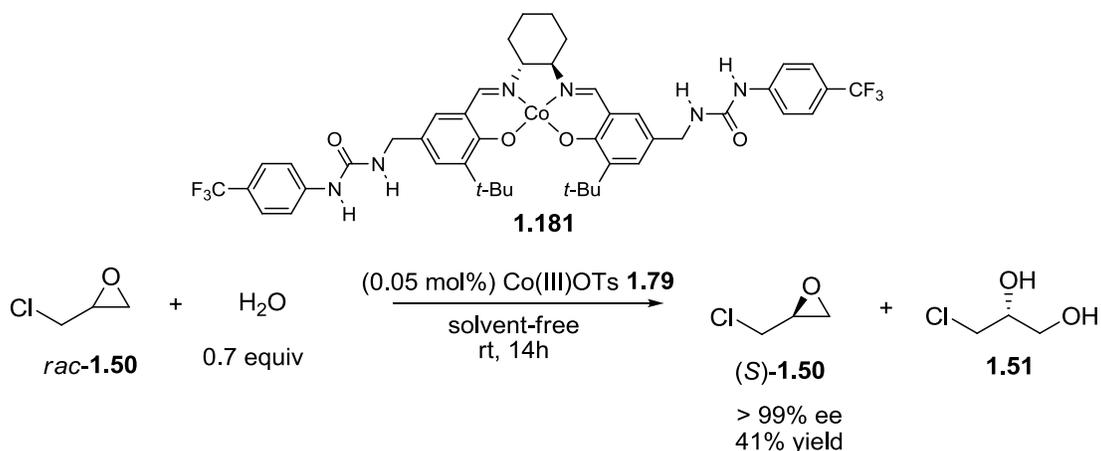


Figure 1-27. PhthalaPhos ligands: structure of the pre-catalytic complex $[\text{Rh}(\text{L})_2(\text{cod})]^+$ Hong and co-workers¹¹⁸ recently developed bis-urea functionalized salen catalysts that are capable of self-assembly in solution to form multimetallic systems from simple monomeric species. Various substitutions to the terminal aryl group of the urea function

were synthesized in an attempt to find a catalyst with superior rate acceleration. Salen catalyst **1.181** was shown to be highly efficient in the HKR reaction with terminal epoxides with a reaction rate more than 13 times faster relative to the parent monomeric Co(III)OTs salen catalyst.

This self-assembling catalyst showed an impressive substrate scope (11 examples) showing greater than 98% ee and good conversions with catalyst loadings as low as 0.03 mol%.



Scheme 1-42. Selected example of HKR reactions using self-assembling catalyst.

Evidence of self-assembly was provided in a variety of forms. Changes in the stretching frequencies of urea protons involved in H-bonding were measured with IR. Stretching frequencies associated with “free” N-H bonds disappeared with increasing catalyst concentration; while frequencies associated with hydrogen bonded N-H groups appeared. A similar effect could be observed with increasing catalyst concentration using ¹H-NMR, and X-ray crystal packing also clearly showed the interaction of urea functional groups.

Indirect methods were also used to support the concept of self-assembly, such as determination of the reaction order in terms of catalyst and observed rate deceleration

when the urea nitrogens are methylated, thus removing the ability to self-assemble. The development and success of these catalysts demonstrate the utility of self-assembly as a viable alternative to covalently tethered multimetallic systems.

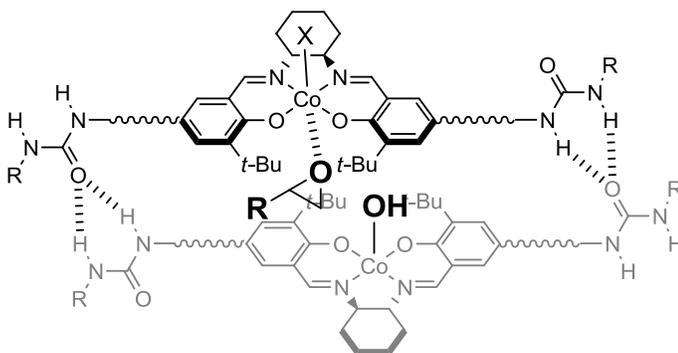


Figure 1-28. Proposed mechanism of self-assembly to enforce bimetallic cooperation.

This section highlights some of the more important developments in ligand-ligand interactions driven by hydrogen bonding for use in asymmetric catalysis. These contributions demonstrate the utility of this strategy toward achieving better, more efficient catalysts for a variety of practical applications.

CHAPTER 2 NEW *N,N*-LIGANDS FOR ASYMMETRIC CATALYSIS

Asymmetric Nitro-Aldol Reaction

Background

The nitroaldol (Henry) reaction constitutes an important C-C bond formation that yields β -nitroalcohols from carbonyl compounds and nitroalkanes. The β -nitroalcohols produced contain at least one newly formed stereogenic center and are valuable intermediates in the construction of synthetically important building blocks.^{119,120,121,122} The value of these reaction products has prompted the development of a number of successful asymmetric variants including organocatalysts^{123,124,125,126} and numerous Lewis acid catalysts employing metals such as lanthanides,^{127,128,129,130} Cr(III),^{131,132,133} Co(II),^{134,135,136,137} Zn(II),^{138,139,140,141} Cu(I),^{142,143,144,145,146,147} and Cu(II).^{148,149,150,151,152,153,154,155,156,157,158,159,160,161,162,163} Of the Lewis acids described, copper, in particular, has found considerable attention due in part to its availability, low toxicity and ease in handling. The Cu metal center is often supported by nitrogen-based chiral ligands bearing amine,^{142,146,147,148,149,150,151,152,153,154,155,156} imine (or pyridine),^{145,157,158} oxazoline,^{144,159,163} oxazolidine,^{143,162} or imidazoline^{160,161} moieties.

Recently, we developed synthetic routes to isoquinoline-based chiral diaminocarbenes via Bischler–Napieralski cyclization and several chiral diimines such as compounds **2.1**¹⁶⁴ and **2.3**¹⁶⁵ were prepared as precursors to those carbenes (Figure 2-1). The literature precedence of imine-containing ligands used in the asymmetric Henry reaction, as well as our experience in this reaction^{134,144} led us to question whether the isoquinoline-based imine ligands (**2.1** and **2.3**) could be effective in the

enantioselective Henry reaction. Reported here are the applications of isoquinoline-based chiral diimines in the Cu(II)-catalyzed asymmetric Henry reaction.

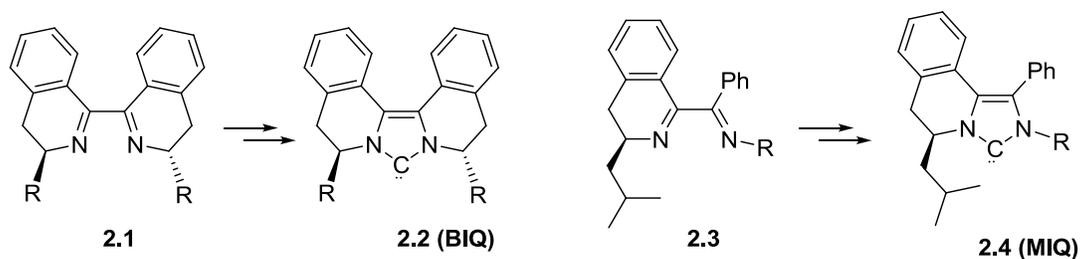


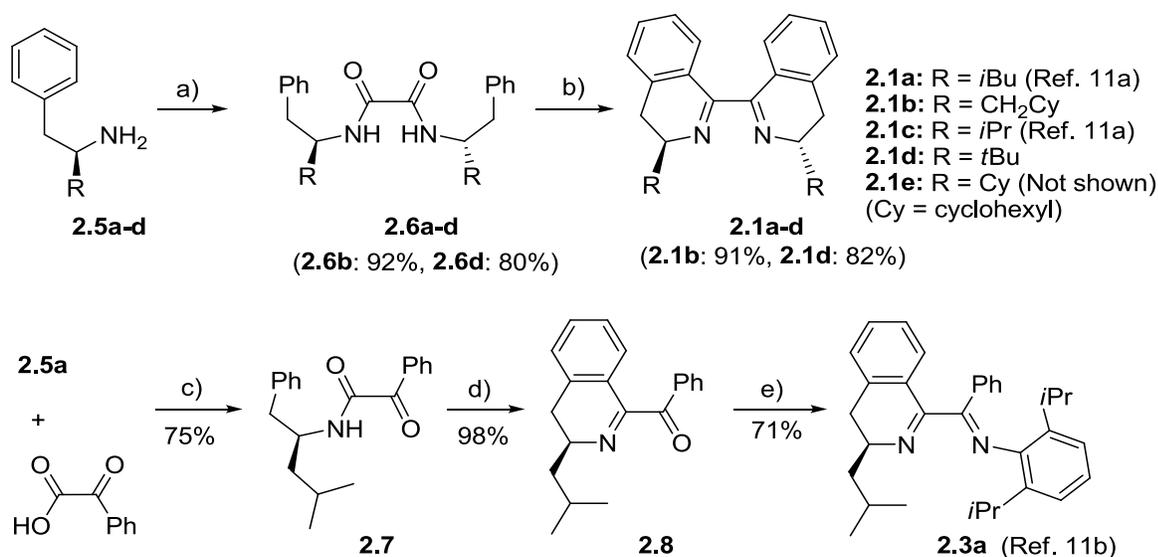
Figure 2-1. Isoquinoline-based chiral carbene ligands.

Results and Discussion

Scheme 2-1 summarizes a concise synthesis of various isoquinoline-based diimines (**2.1** and **2.3**) from the phenethylamine precursors (**2.5a-d**). C₂-symmetric diimines (**2.1a-d**)¹⁶⁴ as well as a C₁-symmetric diimine (**2.3a**)¹⁶⁵ were prepared by the procedures previously reported by our group.

The isoquinoline-based diimine ligands were evaluated in the copper catalyzed Henry reaction of nitromethane and 4-nitrobenzaldehyde (Table 2-1). C₂-symmetric, *i*-Bu substituted diimine (**2.1a**) gave higher enantioselectivity than structurally related C₁-symmetric diimine (**2.3a**) (entry 2 vs. entry 1). When the R group in C₂-symmetric diimines was varied, more sterically demanding substituents resulted in lower enantioselectivity and longer reaction time (*i*-Bu ~ CH₂Cy > *i*-Pr >> *t*-Bu, entries 2-5). Thus, the best result was obtained using the C₂-symmetric diimine with the *i*-Bu substituent (**2.1a**), affording nitroaldol product **2.10a** in 89% yield and 77% ee after 24h.

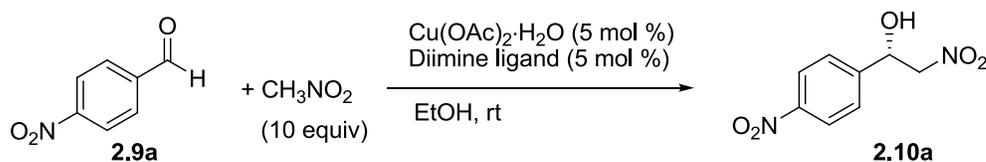
Attempts were made to further optimize the reaction conditions by changing the Lewis acidic metal and the solvent (Table 2-2).



Scheme 2-1. Synthesis of isoquinoline-containing chiral imine ligands.

Reagents and conditions: a) oxalyl chloride, Et₃N, THF, 0°C to rt, 12h. b) PCl₅, Zn(OTf)₂, toluene, 85 °C, 12h. c) EDC, HOBT, rt, 12h. d) Tf₂O, DMAP, toluene, 90°C, 8 h. e) 2,6-diisopropylaniline, TiCl₄, Et₃N, toluene, rt, 12h.

Table 2-1. Nitro-aldol ligand survey



entry ^a	ligand	time (h)	yield(%) ^b	ee (%) ^c
1	2.3a (R = <i>i</i> Bu)	48	84	11
2	2.1a (R = <i>i</i> Bu)	24	89	77
3	2.1b (R = CH ₂ Cy)	24	90	75
4	2.1c (R = <i>i</i> Pr)	48	90	65
5	2.1d (R = <i>t</i> Bu)	48	48	5

^a All reactions were performed on a 0.5 mmol scale at a 0.4 M concentration. Reactions were run at room temperature in a screw-capped vial for the indicated time. ^b Values are isolated yields after

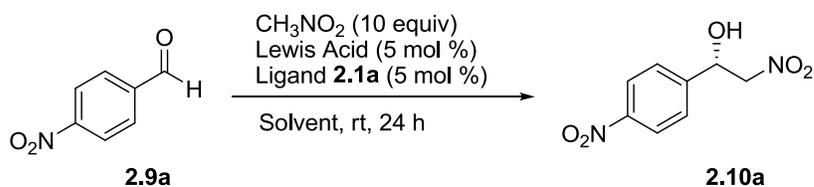
chromatographic purification. ^c Enantiomeric excess was determined by HPLC using Chiralpak[®] IB column.

Replacing Cu(OAc)₂ with other divalent metal acetates such as Ni(OAc)₂ or Zn(OAc)₂ resulted in lower enantioselectivity (entry 1 vs. entries 2-3).

Protic solvents (EtOH or *i*-PrOH) proved to be better than aprotic solvents (THF or CH₂Cl₂), giving higher yield and % ee (entries 1 & 4 vs. entries 5-6).

These results led us to retain our originally selected conditions (entry 1) as optimal. We then sought to explore the scope of the reaction (Table 2-3). In general, high enantiomeric excess (75-93% ee) was observed at room temperature with various substrates.

Table 2-2. Optimization of reaction conditions



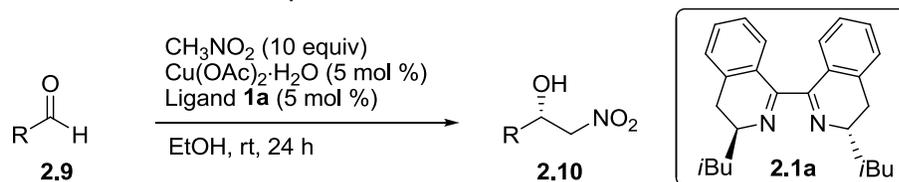
entry ^a	Lewis acid	solvent	yield (%) ^b	ee (%) ^c
1	Cu(OAc) ₂ ·H ₂ O	EtOH	89	77
2	Ni(OAc) ₂ ·4H ₂ O	EtOH	91	30
3	Zn(OAc) ₂ ·2H ₂ O	EtOH	64	0
4	Cu(OAc) ₂ ·H ₂ O	<i>i</i> PrOH	84	72
5	Cu(OAc) ₂ ·H ₂ O	THF	59	40
6	Cu(OAc) ₂ ·H ₂ O	CH ₂ Cl ₂	38	54

^a All reactions were performed on a 0.5 mmol scale at a 0.4 M concentration. Reactions were run at room temperature in a screw-capped vial. ^b Values are isolated yields after chromatographic purification. ^c Enantiomeric excess was determined by HPLC using Chiralpak[®] IB or Whelk-O[®]1 columns.

While yields were depressed in some cases, additional reaction time was not found to improve those yields. It was observed, however, that increasing the catalyst loading to 10 mol% could improve the yield without loss of selectivity (entry 2). Ortho, meta and para substituted benzaldehydes gave uniformly good enantiomeric excess

(77-93% ee, entries 3-11). It is interesting to note that the substrate scope is not limited to benzaldehydes, as cinnamaldehyde was an effective substrate, affording nitro-aldol product **2.10k** in 75% ee (entry 12).

Table 2-3. Nitroaldol substrate scope



entry ^a	R	product	yield (%) ^b	ee (%) ^c
1	Ph	2.10b	55	91
2 ^d	Ph	2.10b	80	90
3	2-MeO-C ₆ H ₄	2.10c	57	77
4	2-Cl-C ₆ H ₄	2.10d	87	90
5	2-F-C ₆ H ₄	2.10e	52	93
6	3-F-C ₆ H ₄	2.10f	51	91
7	4-F-C ₆ H ₄	2.10g	59	90
8	4-Cl-C ₆ H ₄	2.10h	78	88
9	4-NO ₂ -C ₆ H ₄	2.10a	89	77
10	4-Ph-C ₆ H ₄	2.10i	78	81
11	1-Naphthyl	2.10j	68	87
12	PhCH=CH	2.10k	50	75

^a All reactions were performed on a 0.5 mmol scale at a 0.4 M concentration. Reactions were run at room temperature in a screw-capped vial. ^b Values are isolated yields after chromatographic purification. ^c Enantiomeric excess was determined by HPLC using Chiralpak[®] IB or Whelk-O[®]1 columns. ^d 10.0 mol % of $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ and 10.0 mol % of ligand **2.1a** were used.

The X-ray structure of **2.1a-PdCl₂** shed some light on unique structural features of the isoquinoline-based C₂-symmetric diimines. The *i*-Bu substituent takes the axial position on the six-membered azacycle that is folded into a boat-like conformation. In addition, helical (or axial) chirality seems to exist owing to the severe steric repulsion

between two phenyl rings. **2.1a-PdCl₂** shows *P* helicity (or axial chirality) as well as *S* stereogenic centers.

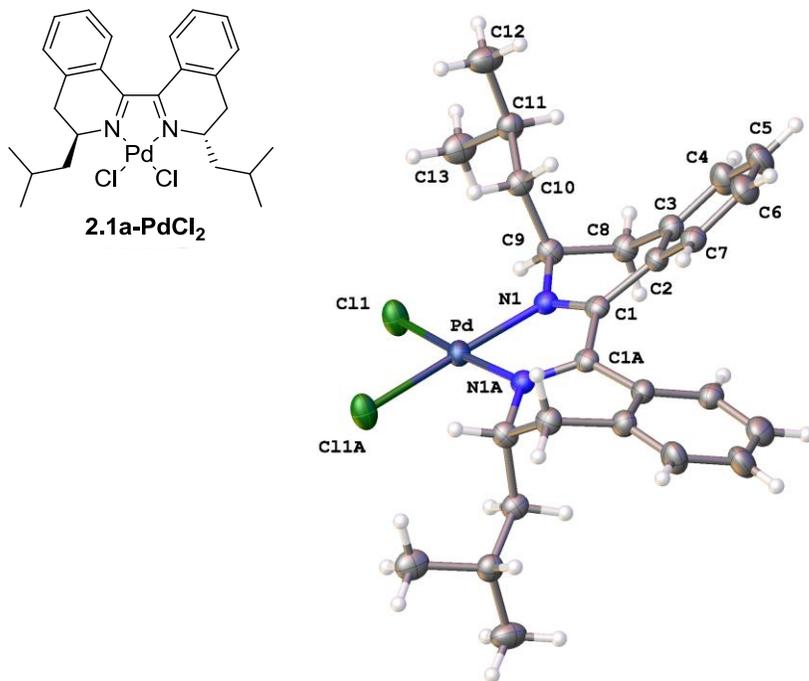


Figure 2-2. X-ray structure of **2.1a-PdCl₂**.

Thermal ellipsoids are drawn at the 50% probability level. Selected bond lengths (Å), angles (°), and torsion angles (°): Pd–N1: 2.0095(18), N1–C1: 1.302 (3), N1–Pd–N1A: 79.32(7), N1–C1–C1A: 113.9(2), Pd–N1–C1–C1A: 11.1(2), C2–C1–C1A–C2A: -25.1(3).

1,2-Boronic Acid Addition

Background

Organoboron reagents are very attractive amongst other organometallic reagents for their low toxicity, functional group tolerance and stability towards air and moisture.^{166,167,168,169} The addition of aryl organoboron reagents to aldehydes has received considerable attention as a powerful C-C bond forming reaction and provides access to diaryl alcohols, a structural motif found in compounds with reported activity as antimuscarinics,¹⁷⁰ antidepressants,¹⁷¹ and endothelin antagonists.¹⁷² While examples

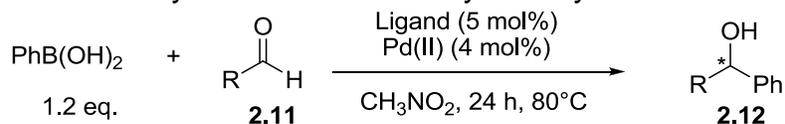
of Rh(I) catalyzed addition of organoboron reagents to aldehydes are known,^{173,174,175,176,177,178} less attention has been paid to the Pd(II) catalyzed transformation.^{179,180,181,182}

It has been shown that cationic Pd(II) complexes of 2,2'-bipyridine (BIPY) catalyzed the 1,2-addition of aryl boronic acids to aryl aldehydes.¹⁸³ Seeing our ligand family as relatives to BIPY, we wished to survey our BIQ ligands in this reaction.

Results and Discussion

In general, yields are low to moderate and selectivity's were poor for several differently substituted BIQ ligands. More sterically congested ligands (entry 2 vs. entry 1) resulted in significantly lower yields.

Table 2-4. 1,2-Addition of aryl boronic acids to aryl aldehydes



Entry ^a	Ligand	R	Product	Pd(II)	Yield (%) ^b	ee(%) ^c
1	2.1a	<i>p</i> -NO ₂ C ₆ H ₅	2.12a	Pd(OAc) ₂	76	15
2	2.1e	<i>p</i> -NO ₂ C ₆ H ₅	2.12a	Pd(OAc) ₂	33	13
3	2.1b	<i>p</i> -NO ₂ C ₆ H ₅	2.12a	Pd(OAc) ₂	63	10
4	2.1d	<i>p</i> -NO ₂ C ₆ H ₅	2.12a	Pd(OAc) ₂	n.r. ^d	-
5	2.1a	<i>p</i> -NO ₂ C ₆ H ₅	2.12a	Pd(CF ₃ CO ₂) ₂	61	15
6	2.1a	<i>p</i> -NO ₂ C ₆ H ₅	2.12a	Pd(CH ₃ CN) ₄ (BF ₄) ₂	52	7
7	2.1a	1- Naphthyl	2.12b	Pd(OAc) ₂	37	0
8	2.1a	2- Naphthyl	2.12c	Pd(OAc) ₂	31	0

^a All reactions were performed on a 0.3 mmol scale at a 1.0 M concentration. ^b Values are isolated yields after chromatographic purification. ^c Enantiomeric excess was determined by HPLC using Chiralpak[®] IB column. ^d n.r. = No reaction

Pd(II) sources with more weakly coordinating counter ions were used in hope of providing a more accessible palladium center to increase activity, however, we found the opposite to be true (entries 5 and 6). More sterically demanding naphthaldehydes (entries 7 and 8) were found to be much more sluggish and resulted in a complete erosion of stereoselectivity.

Summary

In summary, a series of chiral isoquinoline-based imine ligands are conveniently prepared through Bischler-Napieralski cyclization. *i*-Bu-substituted, C₂-symmetric diimine ligand **2.1a** is effective in Cu(II)-catalyzed enantioselective Henry reactions between nitromethane and various aldehydes (12 examples), showing 50-89% yield and 75-93% ee. The application of these ligands in the Pd(II) catalyzed 1,2-addition of phenyl boronic acid to substituted benzaldehydes suffered from sluggish reactivity, low selectivity and a narrow range of substrates. The development of these ligands mark a significant addition to the diverse range of chelating *N,N*-donor ligands for asymmetric catalysis. Their relative ease of synthesis, structural modularity and unique structural features make them a valuable addition to the tools available for a variety of important asymmetric transformations.

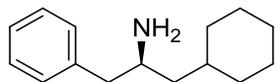
Experimental

All reactions were conducted in flame-dried glassware under an inert atmosphere of dry argon unless otherwise specified. THF, CH₂Cl₂, CH₃CN and Et₂O were passed through two packed columns of neutral alumina under positive pressure of argon prior to use. All other chemicals used were commercially available and were used as received without further purification. NMR spectra were recorded using an FT-NMR machine, operating at 300 MHz for ¹H NMR and at 75.4 MHz for ¹³C NMR. All chemical shifts for

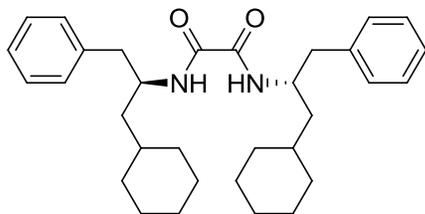
^1H and ^{13}C NMR spectroscopy were referenced to Me_4Si (δ 0.0 ppm) for ^1H and ^{13}C or residual signals from (CDCl_3) (δ 7.24 ppm) for ^1H and (δ 77.23) for ^{13}C . High resolution mass spectra were recorded on a DIP-CI-MS spectrometer, an APCI-TOF spectrometer, an ESI-TOF spectrometer, or a TOF-LC/MS spectrometer. Specific optical rotations were obtained on a JASCO P-2000 Series Polarimeter (wavelength = 589 nm). Enantiomeric ratios were determined by chiral HPLC analysis (Shimadzu) using Chiralpak[®] IB and (S,S) Whelk-O[®]1 columns or by Chiral GCMS analysis (Shimadzu) using an Astec CHIRALDEX[™] column (G-TA) with helium as the carrier gas. Substituted benzaldehydes were purchased from Sigma-Aldrich and used without further purification. Known compounds have been identified by comparison of spectral data (^1H NMR and ^{13}C NMR) with those previously reported.

Synthesis and Characterization of Reported MIQ and BIQ Ligands

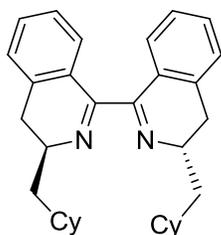
(S)-1-Cyclohexyl-3-phenylpropan-2-amine (2.5b). Synthesis of (S)-*N*-(1-cyclohexyl-3-phenylpropan-2-yl)-4-methylbenzenesulfonamide. To a suspension of CuI (0.276 g, 1.45 mmol) in THF (5.0 mL), PhMgCl solution (2.0 M in THF, 4.8 mL, 9.6 mmol) was slowly added at -30°C . After 30 min stirring at -30°C , (S)-2-(Cyclohexylmethyl)-1-toluenesulfonylaziridine (1.42 g, 4.84 mmol) was added. The reaction temperature was slowly increased to room temperature for 3 h. The reaction was cautiously quenched by a saturated aqueous NH_4Cl solution (20 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic mixture was dried over anhydrous MgSO_4 , filtered, and concentrated under reduced pressure. The residue was filtered through a column of silica gel with EtOAc as an eluent to afford the sulfonamide.¹⁶⁴



(S)-1-Cyclohexyl-3-phenylpropan-2-amine (2.5b). To a suspension of Li (0.50 g, 72 mmol) in THF (30 mL) under argon, naphthalene (50 mg, 0.39 mmol) was added at room temperature. After 30 min, the solution turned dark blue. (*S*)-*N*-(1-cyclohexyl-3-phenylpropan-2-yl)-4-methylbenzenesulfonamide was added at -78°C, and the reaction temperature was slowly warmed to room temperature. After 12h, the solution was transferred through a canula to another flask to remove the remaining Li. The solution was quenched by a saturated aqueous NH₄Cl solution (50 mL) and rinsed with water (100 mL). To the organic solution was added 1 M HCl aqueous solution (15 mL), and the organic layer was discarded. To the acidic aqueous solution was added 20% NaOH aqueous solution (20 mL). The aqueous layer was extracted by Et₂O (3 x 20 mL) and was dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure to afford the phenethylamine (0.600 g, 2.76 mmol, 57% yield). $[\alpha]_D^{23} = 9.7$ (c 0.27, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 7.39–7.02 (m, 5H), 3.10 (br. s, 1H), 2.78 (dd, J = 4.3, 13.3 Hz, 1H), 2.41 (dd, J = 8.8, 13.5 Hz, 1H), 1.89–0.71 (m, 13H); ¹³C NMR (75 MHz, CDCl₃) δ 140.0, 129.5, 128.6, 126.3, 49.9, 45.9, 45.5, 34.7, 34.4, 33.2, 26.9, 26.6, 26.5. HRMS (ESI) calcd for C₁₅H₂₃N (M+H)⁺ : 218.1903; found: 218.1906.



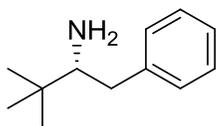
***N,N'*-Bis((*S,S*)-1-cyclohexyl-3-phenylpropan-2-yl)oxalamide (2.6b)** To a cooled, magnetically stirred solution of (*S*)-1-cyclohexyl-3-phenylpropan-2-amine (**2.5b**) (90.2 mg, 0.415 mmol) and triethylamine (65 μ L, 0.46 mmol) in THF (5.0 mL) under argon, oxalyl chloride (17.6 μ L, 0.202 mmol) was added dropwise at 0°C. The reaction mixture was allowed to warm to room temperature and was then stirred for 12h. The reaction mixture was cooled to 0 °C before quenching with water (10 mL). The mixture was extracted with CHCl₃ (3 x 15 mL). The combined organic extracts were dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 3:1 chloroform/hexane) to afford the oxalamide (90.1 mg, 0.184 mmol, 92% yield) [α]_D²³ = -21.9 (c 0.29, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 7.33–7.10 (m, 12H), 4.32–4.11 (m, 2H), 2.78 (d, J = 6.4 Hz, 4H), 1.89–1.49 (m, 12H), 1.43–1.05 (m, 11H), 1.01–0.63 (m, 4H); ¹³C NMR (75 MHz, CDCl₃) δ 159.4, 137.7, 129.6, 128.6, 126.7, 48.7, 41.9, 41.6, 34.5, 34.0, 32.8, 26.7, 26.4, 26.3. HRMS (ESI) calcd for C₃₂H₄₄N₂O₂ (M+Na)⁺: 511.3295; found: 511.3308.



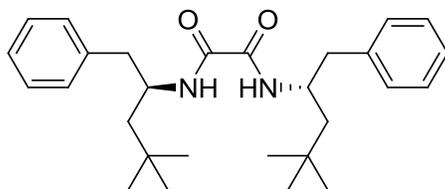
(*S,S*)-3,3'-Bis(cyclohexylmethyl)-3,3',4,4'-tetrahydro-1,1'-biisoquinoline

(2.1b) To a solution of *N,N*-Bis((*S*)-1-cyclohexyl-3-phenylpropan-2-yl)oxalamide (**2.6b**) (0.450 g, 0.921 mmol) in toluene (45 mL) under nitrogen was added Zn(OTf)₂ (1.00 g, 2.76 mmol) and PCl₅ (1.15 g, 5.52 mmol). The reaction mixture was heated at 85°C for 12h and then was cooled to room temperature before quenching with a 30% aqueous

NH₄OH solution (20 mL). The mixture was extracted with EtOAc (3 x 30 mL). The combined organic extracts were dried over MgSO₄, filtered, and concentrated under reduced pressure. Purification of the crude product by flash column chromatography (silica gel, 5:1 hexanes/EtOAc) afforded the bisoquinoline (0.380 g, 0.839 mmol, 91% yield) $[\alpha]_D^{23} = -12.9$ (c 0.37, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 7.44–7.04 (m, 8H), 3.98–3.75 (m, 2H), 2.93 (dd, J = 5.6, 15.8 Hz, 2H), 2.64 (dd, J = 11.1, 15.8 Hz, 2H), 1.98–1.48 (m, 16H), 1.38–1.06 (m, 6H), 1.06–0.75 (m, 4H); ¹³C NMR (75 MHz, CDCl₃) δ 164.0, 137.5, 131.1, 128.6, 128.0, 127.1, 126.9, 54.5, 43.5, 34.6, 34.1, 33.3, 31.6, 26.9, 26.6. HRMS (ESI) calcd for C₃₂H₄₀N₂ (M+H)⁺: 453.3264; found: 453.3286.

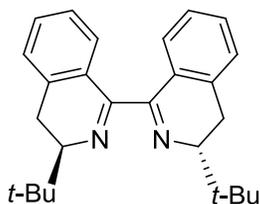


(R)-3,3-Dimethyl-1-phenylbutan-2-amine (2.5d) 93%. $[\alpha]_D^{22} = 48.6$ (c 0.88, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 7.35–7.27 (m, 2H), 7.25–7.18 (m, 3H), 2.98 (dd, J = 2.3, 13.3 Hz, 1H), 2.69 (dd, J = 2.4, 10.9 Hz, 1H), 2.21 (dd, J = 11.0, 13.3 Hz, 1H), 1.00 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 141.3, 129.4, 128.7, 126.3, 62.3, 39.0, 34.5, 26.6. HRMS (ESI) calcd for C₁₂H₁₉N (M+H)⁺: 178.1590; found: 178.1582.



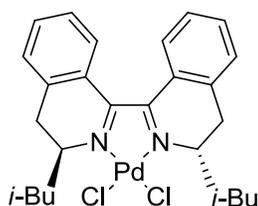
N,N'-Bis((R)-3,3-dimethyl-1-phenylbutan-2-yl)oxalamide (2.6d) 80%. $[\alpha]_D^{22} = 36.3$ (c 0.54, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 7.21–7.00 (m, 12H), 3.86 (td, J = 2.8, 11.0 Hz, 2H), 3.01 (dd, J = 2.8, 14.2 Hz, 2H), 2.36 (dd, J = 11.3, 14.2 Hz, 2H), 0.97 (s,

18H); ^{13}C NMR (75 MHz, CDCl_3) δ 159.5, 138.8, 129.0, 128.5, 126.4, 60.1, 36.6, 35.1, 26.7. HRMS (ESI) calcd for $\text{C}_{26}\text{H}_{36}\text{N}_2\text{O}_2$ ($\text{M}+\text{Na}$) $^+$: 431.2669; found: 431.2671.



(3R,3'R)-3,3'-Di-tert-butyl-3,3',4,4'-tetrahydro-1,1'-biisoquinoline (2.1d) 82%.

$[\alpha]_{\text{D}}^{22} = 204.8$ (c 0.62, CHCl_3); ^1H NMR (300 MHz, CDCl_3) δ 7.49 (d, $J = 7.9$ Hz, 2H), 7.35–7.27 (m, 2H), 7.24–7.11 (m, 4H), 3.23 (dd, $J = 5.0, 15.1$ Hz, 2H), 2.86–2.56 (m, 4H), 1.09 (s, 18 H); ^{13}C NMR (75 MHz, CDCl_3) δ 163.2, 139.1, 130.5, 128.9, 127.7, 127.5, 126.5, 66.4, 34.3, 27.1, 26.9. HRMS (ESI) calcd for $\text{C}_{26}\text{H}_{32}\text{N}_2$ ($\text{M}+\text{H}$) $^+$: 373.2638; found: 373.2639.



Dichloro[(3S,3'S)-3,3'-diisobutyl-3,3',4,4'-tetrahydro-1,1'-biisoquinoline]-palladium(II) (2.1a-PdCl₂) To a solution of 1a (0.205 g, 0.550 mmol) in toluene (3 mL), $\text{PdCl}_2(\text{CH}_3\text{CN})_2$ (0.130 g, 0.500 mmol) was added, and the solution was stirred at room temperature for 12 h. The precipitated product was filtered and washed with hexanes (20 mL). (0.271 g, 98.6%) $[\alpha]_{\text{D}}^{23} = -702.5$ (c 0.43, CHCl_3); ^1H NMR (300 MHz, CDCl_3) δ 7.55 (m, 2H), 7.34 (d, $J = 7.4$ Hz, 2H), 7.13 (m, 2H), 6.86 (d, $J = 7.6$ Hz, 2H), 5.04–4.86 (m, 2H), 3.26–3.06 (m, 2H), 3.04–2.84 (m, 2H), 2.11–1.87 (m, 2H), 1.67–1.40 (m, 2H), 1.00 (d, $J = 6.8$ Hz, 6H), 0.91–0.80 (m, 2H), 0.78 (d, $J = 6.5$ Hz, 6H); ^{13}C NMR (75 MHz,

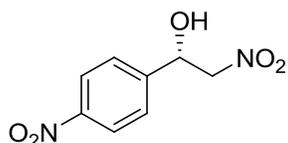
CDCl_3) δ 170.9, 135.7, 134.4, 129.4, 129.2, 126.8, 126.7, 56.4, 35.1, 29.3, 25.9, 24.2.

Anal. calcd for $\text{C}_{26}\text{H}_{32}\text{Cl}_2\text{N}_2\text{Pd}$: C, 56.79; H, 5.87; N, 5.09. found: C, 57.00; H, 6.00; N, 5.01.

General Procedure for Enantioselective Henry Reaction

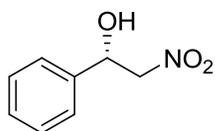
To a 3.0 mL screw cap vial, a magnetic stir bar and ligand (0.025 mmol) were added followed by absolute EtOH (1.25 mL). After the ligand was fully dissolved, $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (4.99 mg, 0.025 mmol) was then added and allowed to stir at room temperature for 1 h. CH_3NO_2 was then added (0.27 mL, 5.0 mmol) followed by aldehyde (0.50 mmol) and allowed to stir for the indicated time. The reaction mixture was purified by flash column chromatography on silica gel and the enantiomeric ratios were determined by chiral HPLC analysis (Shimadzu) using Chiralpak[®] IB and (S,S) Whelk-O[®]1 columns.

Characterization of Nitroaldol Adducts

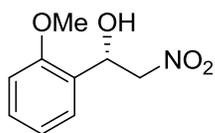


(S)-2-Nitro-1-(4-nitrophenyl)ethanol (2.10a) ^1H NMR (300 MHz, CDCl_3) δ 8.10-8.44 (m, 2 H), 7.62 (d, $J = 8.2$ Hz, 2 H), 5.53-5.76 (m, 1 H), 4.47-4.71 (m, 2 H), 3.17-3.47 (m, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 148.3, 145.3, 127.2, 124.4, 80.9, 70.2.

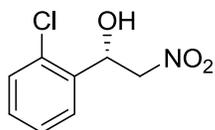
Enantiomeric excess was determined by HPLC with a Chiralpak[®] IB column (85 : 15 hexanes : isopropanol, 1.0 mL/min, 254 nm); t_R (minor) = 12.87 min., t_R (major) = 14.47 min; 77% ee. Configuration assignment: absolute configuration of major isomer was determined to be (S) by comparison of the retention time with literature data.^{134,144}



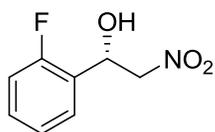
(S)-2-Nitro-1-phenylethanol (2.10b) ^1H NMR (300 MHz, CDCl_3) δ 7.34-7.43 (m, 5H), 5.42 (dd, $J = 9.3, 1.8$ Hz, 1H), 4.59 (ddd, $J = 13.2, 9.6, 0.9$ Hz, 1H), 4.49 (ddd, $J = 13.5, 3.0, 0.9$ Hz, 1H), 2.91 (s, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 138.8, 29.7, 129.6, 126.6, 81.9, 71.6; HRMS (DART) calcd for $\text{C}_8\text{H}_{13}\text{N}_2\text{O}_3$ $[\text{M}+\text{NH}_4]^+$: 185.0921. Found 185.0918. Enantiomeric excess was determined by HPLC with a Chiralpak[®] IB column (85 : 15 hexanes : isopropanol, 0.8 mL/min, 215 nm); t_{R} (minor) = 8.94 min, t_{R} (major) = 9.82 min; 91% ee. Configuration assignment: absolute configuration of major isomer was determined to be (S) by comparison of the retention time with literature data.^{134, 144}



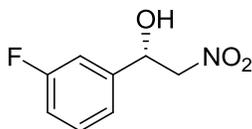
(S)-1-(2-Methoxyphenyl)-2-nitroethanol (2.10c) ^1H NMR (300 MHz, CDCl_3) δ ppm 7.27-7.36 (m, 2 H), 6.86-6.96 (m, 2 H), 5.40 (d, $J = 9.6$ Hz, 1 H), 4.60 (dd, $J = 12.7, 9.1$ Hz, 1 H), 4.47 (dd, $J = 13.3, 3.1$ Hz, 1 H), 3.80 (s, 3 H), 2.80 (d, $J = 2.3$ Hz, 1 H); ^{13}C NMR (75 MHz, CDCl_3) δ 160.3, 130.4, 127.5, 114.6, 81.5, 70.9, 55.6; HRMS (DART) calcd for $\text{C}_9\text{H}_{10}\text{NO}_4$ $[\text{M}-\text{H}]^+$: 196.0615. Found 196.0608. Enantiomeric excess was determined by HPLC with a Chiralpak[®] IB column (85 : 15 hexanes : isopropanol, 0.8 mL/min, 215 nm); t_{R} (minor) = 8.64 min; t_{R} (major) = 9.32 min; 77% ee. Configuration assignment: absolute configuration of major isomer was determined to be (S) by comparison of the retention time with literature data.^{134,144}



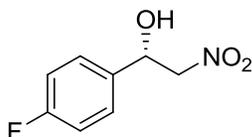
(S)-1-(2-Chlorophenyl)-2-nitroethanol (2.10d) ^1H NMR (300 MHz, CDCl_3) δ 7.65 (d, $J = 6.8$ Hz, 1 H), 7.23-7.41 (m, 3 H), 5.83 (td, $J = 9.3, 2.5$ Hz, 1 H), 4.66 (dd, $J = 13.6, 2.5$ Hz, 1 H), 4.44 (dd, $J = 13.3, 9.3$ Hz, 1 H), 3.24 (br s, 1 H); ^{13}C NMR (75 MHz, CDCl_3) δ 135.8, 131.7, 130.2, 129.9, 127.8, 79.6, 68.1; HRMS (GC-Cl) m/z calcd for $\text{C}_8\text{H}_8\text{ClNO}_3$ $[\text{M}]^+$: 201.0193. Found: 201.0208. Enantiomeric excess was determined by HPLC with a (S,S) Whelk-O[®]1 column (95 : 5 hexanes : isopropanol, 1.0 mL/min, 215 nm); t_R (minor) = 8.53 min; t_R (major) = 9.39 min; 90% ee. Configuration assignment: absolute configuration of major isomer was determined to be (S) by comparison of the retention time with literature data.^{134,144}



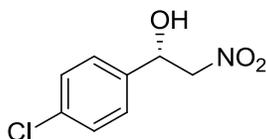
(S)-1-(2-Fluorophenyl)-2-nitroethanol (2.10e) ^1H NMR (300 MHz, CDCl_3) δ ppm 7.54 (td, $J = 7.6, 1.8$ Hz, 1 H), 7.28- 7.42 (m, 1 H), 7.15-7.25 (m, 1 H), 7.01-7.15 (m, 1 H), 5.64-5.79 (m, 1 H), 4.50-4.68 (m, 2 H), 3.26 (br s, 1 H); ^{13}C NMR (75 MHz, CDCl_3) δ ppm 159.6 (d, $J_{\text{CF}} = 246.2$ Hz), 130.7 (d, $J_{\text{CF}} = 8.3$ Hz), 127.8 (d, $J_{\text{CF}} = 3.7$ Hz), 125.1 (d, $J_{\text{CF}} = 3.4$ Hz), 116.7 (d, $J_{\text{CF}} = 21.5$ Hz), 116.0 (d, $J_{\text{CF}} = 21.2$ Hz), 80.0 (d, $J_{\text{CF}} = 2.0$ Hz), 65.7 (d, $J_{\text{CF}} = 2.9$ Hz); HRMS (DART) m/z calcd for $\text{C}_8\text{H}_7\text{FNO}_3$ $[\text{M}-\text{H}]^+$: 184.0415. Found 184.0411. Enantiomeric excess was determined by HPLC with a (S,S) Whelk-O[®]1 column (95 : 5 hexanes : isopropanol, 0.8 mL/min, 215 nm); t_R (major) = 10.6 min; t_R (minor) = 11.5 min; 93% ee. Configuration assignment: absolute configuration of major isomer was determined to be (S) by comparison of the retention time with literature data.^{134,144}



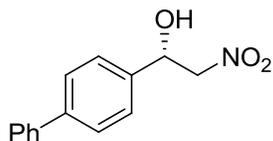
(S)-1-(3-Fluorophenyl)-2-nitroethanol (2.10f) ^1H NMR (300MHz, CDCl_3) δ 7.29–7.45 (m, 1H), 7.10–7.21 (m, 2H), 7.04 (td, $J = 8.4, 2.5$ Hz, 1H), 5.46 (dd, $J = 8.8, 3.4$ Hz, 1H), 4.43–4.64 (m, 2H), 3.11 ppm (s, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 163.3 (d, $J_{\text{CF}} = 246.0$ Hz), 140.8 (d, $J_{\text{CF}} = 6.8$ Hz), 130.9 (d, $J_{\text{CF}} = 8.3$ Hz), 121.7 (d, $J_{\text{CF}} = 3.0$ Hz), 116.1 (d, $J_{\text{CF}} = 21.0$ Hz), 113.3 (d, $J_{\text{CF}} = 22.5$ Hz), 81.2, 70.5 (d, $J_{\text{CF}} = 1.5$ Hz); HRMS (DART) calcd for $\text{C}_8\text{H}_9\text{FN}_2\text{O}_3$ $[\text{M}+\text{NH}_4]^+$: 203.0826, found: 203.0809, $[\alpha]_D^{22} = 26.8$ (c 0.26, CH_2Cl_2); Enantiomeric excess was determined by HPLC with a Chiralpak[®] IB column (85 : 15 hexanes : isopropanol, 1.0 mL/min, 215 nm); t_R (minor) = 6.84 min; t_R (major) = 7.42 min; 91% ee; Configuration assignment: absolute configuration of major isomer was determined to be (S) by analogy of the retention time with other products.



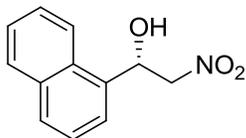
(S)-1-(4-Fluorophenyl)-2-nitroethanol (2.10g) ^1H NMR (300 MHz, CDCl_3) δ 7.31–7.49 (m, 2 H), 7.00–7.20 (m, 2 H), 5.45 (d, $J = 9.1$ Hz, 1 H), 4.58 (dd, $J = 13.5, 9.4$ Hz, 1 H), 4.49 (dd, $J = 13.2, 3.5$ Hz, 1 H), 2.94 (d, $J = 3.8$ Hz, 1 H); ^{13}C NMR (75 MHz, CDCl_3) δ 163.1 (d, $J_{\text{CF}} = 246.8$ Hz), 134.1, 128.0 (d, $J_{\text{CF}} = 8.2$ Hz), 116.2 (d, $J_{\text{CF}} = 21.8$ Hz), 81.3, 70.5; HRMS (DART) calcd for $\text{C}_8\text{H}_7\text{FNO}_3$ $[\text{M}-\text{H}]^+$: 184.0415. Found 184.0413. Enantiomeric excess was determined by HPLC with a Chiralpak[®] IB column (90 : 10 hexanes : isopropanol, 1.0 mL/min, 215 nm); t_R (minor) = 9.11 min; t_R (major) = 9.97 min; 90% ee. Configuration assignment: absolute configuration of major isomer was determined to be (S) by comparison of the retention time with literature data.^{134,144}



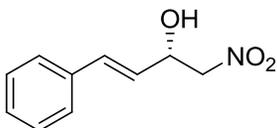
(S)-1-(4-Chlorophenyl)-2-nitroethanol (2.10h) ^1H NMR (300MHz, CDCl_3): δ 7.27-7.47 (m, 4 H), 5.44 (dd, $J = 9.1, 3.5$ Hz, 1 H), 4.42-4.67 (m, 2 H), 2.99 ppm (s, 1 H); ^{13}C NMR (75 MHz, CDCl_3) δ 136.8, 135.1, 129.5, 127.6, 81.2, 70.5; HRMS (DART) Calcd. for $\text{C}_8\text{H}_{12}\text{ClN}_2\text{O}_3[\text{M}+\text{NH}_4]^+$: 219.0531, Found: 219.0527; Enantiomeric excess was determined by HPLC with a Chiralpak[®] IB column (85 : 15 hexanes : isopropanol, 1.0 mL/min, 254 nm); t_{R} (minor) = 7.38 min; t_{R} (major) = 8.15 min; 88% ee. Configuration assignment: absolute configuration of major isomer was determined to be (S) by with literature data. ^{144,151,152}



(S)-1-(Biphenyl-4-yl)-2-nitroethanol (2.10i) ^1H NMR (500 MHz, CDCl_3) δ 7.57-7.69 (m, 4 H), 7.44-7.55 (m, 4 H), 7.38 7.42 (m, 1 H), 5.55 (d, $J = 9.5$ Hz, 1 H), 4.52-4.75 (m, 2 H), 2.86 ppm (br s, 1 H); ^{13}C NMR (75 MHz, CDCl_3) δ 142.3, 140.5, 137.2, 129.1, 128.0, 127.9, 127.4, 126.7, 81.4, 71.1; HRMS (DART) Calcd. For $\text{C}_{14}\text{H}_{17}\text{N}_2\text{O}_3[\text{M}+\text{NH}_4]^+$: 261.1234, Found: 261.1225; Enantiomeric excess was determined by HPLC with a (S,S) Whelk-O[®]1 column (85 : 15 hexanes : isopropanol, 1.0 mL/min, 215 nm); t_{R} (minor) = 8.53 min; t_{R} (major) = 10.51 min; 81% ee. Configuration assignment: absolute configuration of major isomer was determined to be (S) by comparison with literature data. ^{144, 151, 152}



(S)-1-(Naphthalen-1-yl)-2-nitroethanol (2.10j) ^1H 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 $\text{C}_{12}\text{H}_{10}\text{NO}_3$ $[\text{M}-\text{H}]^+$: 216.0666, Found: 216.0658; Enantiomeric excess was determined by HPLC with a Chiralpak[®] IB column (85 : 15 hexanes : isopropanol, 1.0 mL/min, 215 nm); t_{R} (minor) = 8.15 min; t_{R} (major) = 10.7 min; 87% ee. Configuration assignment: absolute configuration of major isomer was determined to be (S) by comparison of the retention time with literature data.¹³⁴



(S,E)-1-Nitro-4-phenylbut-3-en-2-ol (2.10k) ^1H NMR (500 MHz, CDCl_3) δ 7.25-7.47 (m, 5 H), 6.83 (d, $J = 15.9$ Hz, 1 H), 6.13-6.22 (m, 1 H), 5.04-5.15 (m, 1 H), 4.50-4.62 (m, 2 H), 2.65 ppm (d, $J = 4.5$ Hz, 1 H); ^{13}C NMR (126 MHz, CDCl_3) δ 135.8, 134.0, 129.0, 128.8, 127.0, 125.1, 80.1, 69.9; HRMS (DART) calcd for $\text{C}_{10}\text{H}_{15}\text{N}_2\text{O}_3$ $[\text{M}+\text{NH}_4]^+$: 211.1077. Found 211.1077. Enantiomeric excess was determined by HPLC with a Chiralpak[®] IB column (85 : 15 hexanes : isopropanol, 0.8 mL/min, 215 nm); t_{R} (minor) = 18.56 min; t_{R} (major) = 17.16 min; 75% ee. Configuration assignment: absolute configuration of major isomer was determined to be (S) by comparison with literature data.¹³⁸

Crystal Structure Analysis of 2.1a-PdCl₂

Data were collected at 173 K on a Siemens SMART PLATFORM equipped with a CCD area detector and a graphite monochromator utilizing MoK α radiation ($\lambda = 0.71073$ Å). Cell parameters were refined using up to 8192 reflections. A full sphere of data (1850 frames) was collected using the ω -scan method (0.3° frame width). The first 50 frames were re-measured at the end of data collection to monitor instrument and crystal stability (maximum correction on I was < 1 %). Absorption corrections by integration were applied based on measured indexed crystal faces. The structure was solved by the Direct Methods in SHELXTL6,¹⁸⁴ and refined using full-matrix least squares. The non-H atoms were treated anisotropically, whereas the hydrogen atoms were calculated in ideal positions and were riding on their respective carbon atoms. The asymmetric unit consists of a half complex (located on a two-fold rotation symmetry element) and a dichloromethane molecule. A total of 168 parameters were refined in the final cycle of refinement using 3615 reflections with $I > 2\sigma(I)$ to yield R1 and wR2 of 2.48% and 6.40%, respectively. These data can be obtained free of charge from the Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif (CCDC 812994). The thermal ellipsoid drawing (Figure 2-2) was produced using OLEX2.¹⁸⁵

Table 2-5. Crystal data and structure refinement for 1a-PdCl₂.

Identification code	2.1a-PdCl ₂
Empirical formula	C ₂₈ H ₃₆ Cl ₆ N ₂ Pd
Formula weight	719.69
Temperature	173(2) K
Wavelength	0.71073 Å
Crystal system	Tetragonal
Space group	P41212

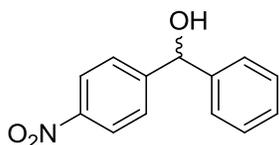
Table 2-5 continued.

Unit cell dimensions	a = 12.8898(3) Å	$\alpha = 90^\circ$
	b = 12.8898(3) Å	$\beta = 90^\circ$
	c = 19.4625(9) Å	$\gamma = 90^\circ$
Volume	3233.63(18) Å ³	
Z	4	
Density (calculated)	1.478 Mg/m ³	
Absorption coefficient	1.090 mm ⁻¹	
F(000)	1464	
Crystal size	0.32 x 0.32 x 0.26 mm ³	
θ range for data collection	1.89 to 27.49°	
Index ranges	-16 ≤ h ≤ 14, -8 ≤ k ≤ 16, -25 ≤ l ≤ 20	
Reflections collected	18011	
Independent reflections	3722 [R(int) = 0.0591]	
Completeness to $\theta = 27.49^\circ$	100.0 %	
Absorption correction	Integration	
Max. and min. transmission	0.7995 and 0.7030	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	3722 / 0 / 168	
Goodness-of-fit on F ²	1.078	
Final R indices [$I > 2\sigma(I)$]	R1 = 0.0248, wR2 = 0.0640 [3615]	
R indices (all data)	R1 = 0.0259, wR2 = 0.0646	
Absolute structure parameter	-0.03(3)	
Largest diff. peak and hole	0.447 and -0.533 e·Å ⁻³	

General Procedure for Enantioselective 1,2-Addition of Phenylboronic Acid

In a thick walled high pressure tube, the Pd(II) precursor was dissolved in CH₃NO₂. Diimine ligand was then added and allowed to stir at room temperature for 30 min. Phenylboronic acid was then added and the mixture was stirred for another 30 min.

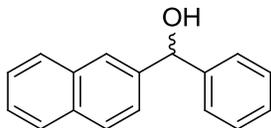
The substituted benzaldehyde was then added and the mixture heated to 80°C with stirring for 24 h. The reaction mixture was then cooled to room temperature and purified by flash column chromatography on silica gel. The enantiomeric ratios were determined by chiral HPLC analysis (Shimadzu) using Chiralpak® IB column.



(4-Nitrophenyl)phenylmethanol (2.12a) ^1H NMR (300 MHz, CDCl_3) δ 2.43 (bs, 1H), 5.92 (s, 1H), 7.30-7.36 (m, 5H), 7.58 (d, $J=8.8\text{Hz}$, 2H), 8.19 ($J=8.8\text{ Hz}$, 2H). ^{13}C NMR (75 MHz, CDCl_3) δ 75.4, 123.7, 126.6, 127.0, 128.4, 129.0, 142.7, 142.8, 150.8; Enantiomeric excess was determined by HPLC with a Chiralpak® IA column (90 : 10 hexanes : isopropanol, 0.5 mL/min, 254 nm); t_{R} (major) = 11.3 min; t_{R} (minor) = 12.3 min; 15% ee.



Naphthalen-1-yl(phenyl)methanol (2.12b) ^1H NMR (300 MHz, CDCl_3) δ 2.50 (bs, 1H), 6.35 (s, 1H), 7.17-7.42 (m, 8H), 7.53 (d, $J=7.2\text{ Hz}$, 1H), 7.75 (d, $J=9.6\text{ Hz}$, 1H), 7.80 (d, $J=7.2\text{ Hz}$, 1H), 7.95 (d, $J=9.6\text{ Hz}$, 1H). ^{13}C NMR (75 MHz, CDCl_3) δ 73.8, 124.3, 124.9, 125.7, 125.9, 126.4, 127.4, 127.9, 128.8, 128.9, 129.1, 131.0, 134.2, 139.1, 143.4.



Naphthalen-2-yl(phenyl)methanol (2.12c) ^1H NMR (300 MHz, CDCl_3) δ 2.54 (bs, 1H), 6.04 (s, 1H), 7.29-7.56 (m, 8H), 7.66 (m, 1H), 7.83-7.93 (m, 3H). ^{13}C NMR (75 MHz, CDCl_3) δ 76.6, 125.1, 125.3, 126.2, 126.5, 127.0, 127.9, 128.3, 128.6, 128.8, 132.9, 133.2, 133.3, 141.1, 143.6

CHAPTER 3 NEW SELF-ASSEMBLING LIGANDS FOR ASYMMETRIC CATALYSIS

Meso-epoxide opening

Background

The asymmetric ring opening of meso epoxides is a highly valuable reaction that affords two new contiguous chiral centers. The wide variety of nucleophilic species that can be employed in this ring opening include sulfur, nitrogen, carbon, halide and oxygen and offer access to a multitude of ring opened products that serve as important synthetic building blocks.^{186,187,188} It has been well established that catalytic hydrolysis of terminal epoxides by Co(salen) complexes shows a second order dependence on catalyst concentration.^{189,190} The desymmetrization of meso epoxides with TMSN₃ by Cr(salen) complex also shows the same dependence¹⁹¹ and it is commonly believed that this kinetic phenomenon is general to metal-salen catalyzed epoxide opening. In the proposed bimetallic mechanism, it is believed that one metal center acts as a Lewis acid to activate the epoxide, while the other serves as counter-ion to the nucleophile. Both metals must also orient the reaction partners in the correct spatial alignment to afford the desired product in high enantioselectivity.¹⁹² In response to these mechanistic insights, there has been significant interest in the development of catalysts that place multiple metal centers in close proximity to one another. A common design element to some previously reported and highly successful systems for the hydrolytic kinetic resolution (HKR) of terminal epoxides focus on incorporating chiral ligands into macromolecular scaffolds such as dimers,^{193,194} oligomers,^{195,196,197} polymers,^{198, 199, 200, 201, 202, 203, 204} dendrites,²⁰⁵ colloids²⁰⁶ and capsules.^{207,208} through covalent bonds. While many of these systems afford ring opened products in high yield and

enantioselectivity, we envisioned a more modular system that could bring multiple metal centers in close proximity through non-covalent hydrogen bonds. In this way, simple monomeric units can be synthesized that contain sites for hydrogen bonding, that in solution will self-assemble to form more structurally complex aggregates in order to organize the requisite metal centers. This approach allows for the rapid structural tailoring of monomeric units in terms of sterics and electronics, to suite the reaction conditions or the manner in which we wish self-assembly to occur.

We have previously reported two generations of catalysts based on this concept. The first generation catalyst (**1.165**) relied on hydrogen bonding between an amino-pyridine and 2-pyridone on the periphery of an existing chiral salen ligand.²⁰⁹ The design was intended to mimic the hydrogen bonding pattern between the nucleobases adenine and thymine, to form a well defined dimeric structure. The second generation (**1.181**) replaced the existing H-bonding motif with urea and offered much more flexibility in terms of steric and electronic tuning.²¹⁰ The installation of the urea motif also created a much more dynamic picture in terms of self-assembly due to the self-complementary nature of the urea hydrogen bond. The directional hydrogen bonding pattern of the urea functional group allows for the possibility of much higher order aggregates, even infinite two dimensional and three dimensional arrays. Because of their unique hydrogen bonding, ureas have been extensively employed as hydrogen bond donor/acceptors in the construction of varied supramolecular structures such as enantiodifferentiating organogels,²¹¹ hydrogels,²¹² optoelectronics,²¹³ artificial micelles²¹⁴ and ion channels.²¹⁵

The reported bis-urea salen catalyst was found to kinetically resolve a broad scope of terminal epoxides in high yield and excellent % ee at very low catalyst loadings with considerable rate acceleration versus monomeric salen catalyst. As expected, kinetic data revealed a second order dependence on catalyst concentration. Other, both direct and in-direct data, strongly suggested that hydrogen bonding was responsible for the observed rate acceleration. Intrigued by both the flexibility and capability of urea as a hydrogen bonding scaffold, we wished to see what effect would be had by repositioning the urea groups toward the center of the catalyst structure, essentially turning the most recent design “in-side-out” (Figure 3-1).

We proposed that by centralizing the two urea groups we could increase the self-assembly strength and suppress the possibility of a staggered self-assembly that could arise in bis-urea salen **1.181**. In addition to its application in the resolution of terminal epoxides, our previously reported bis-urea Co(salen) also catalyzed the asymmetric hydrolysis of cyclohexene oxide. While outperforming the monomeric salen catalyst, we felt there existed room for improvement and saw this notoriously challenging reaction as a fitting target for our newly conceived design. Herein we wish to report a novel bis-urea functionalized, bis-Co(salen) catalyst for the desymmetrization of meso epoxides.

Results and Discussion

Catalyst Preparation. Similar to our previous design, the CH₂ spacer was used to connect the peripheral Co(salen) units to the *N,N*-disubstituted bis-urea core. In order to study the influence of different linking units, several bis-Co(salen) complexes were prepared. These complexes can be prepared in as few as six steps from inexpensive, commercially available materials. Prior to the catalytic reactions, the Co(II) pre-catalysts (**3.8a–g**) were oxidized to the active Co(III) species (**3.8a–g**.OTs) by using 1.0

equivalent (per equiv. of cobalt) of *p*-TsOH (*p*-Ts=*p*-toluenesulfonyl) in the open air. Bis-urea dialdehydes **3.6a-g** were conveniently prepared by the reaction of azide **3.4** with the corresponding isocyanates under catalytic hydrogenation conditions.²¹⁶ The unsymmetrical salen ligands were prepared using a standard protocol²¹⁷ where the chiral diamine **3.7** is first mono protected as the hydrochloride salt followed by condensation with 3,5-di-*tert*-butyl-2-hydroxybenzaldehyde.

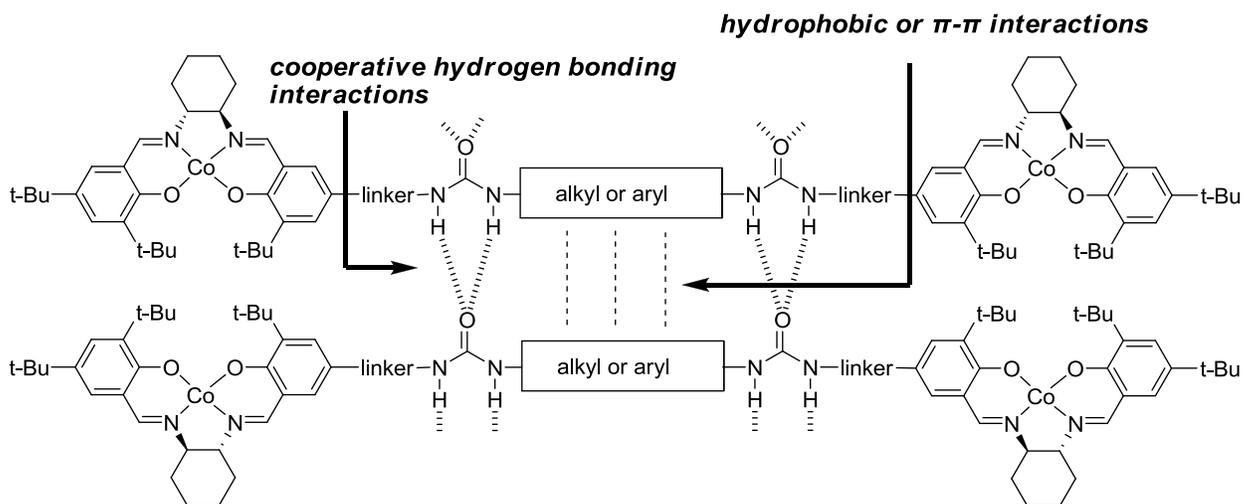
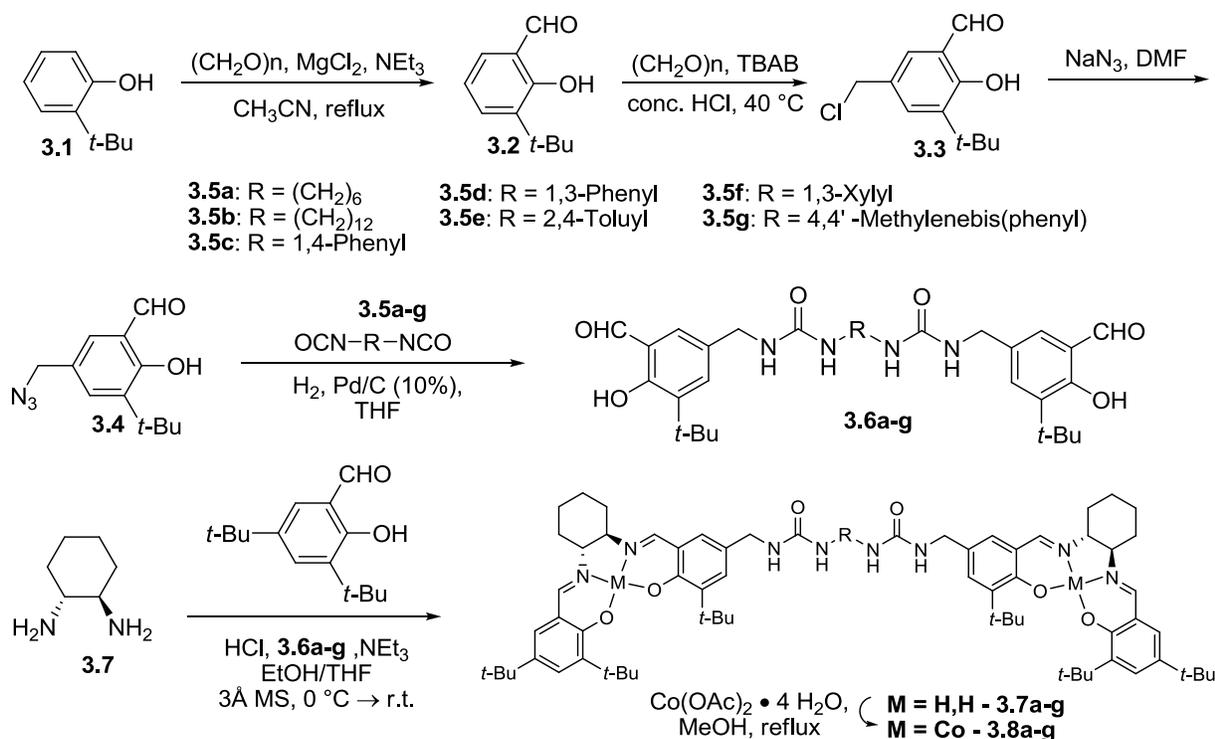


Figure 3-1. Newly designed "in-side-out" bis-urea (bis-salen) catalyst.

After the first condensation, the free amine was liberated under basic conditions in the presence of bis-urea dialdehydes **3.6a-g** and 3 Å MS to afford the desired bis-salen ligands. Although care was taken to remove adventitious water from the reaction, some disproportionation of the monoamine intermediate was still observed, giving the simple, symmetrical salen as by-product. Finally, Co(II) complexes **3.8a-g** were prepared from the reaction of $\text{Co}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$ with the corresponding bis-salen ligands in refluxing MeOH under an argon atmosphere (Scheme 3-1).



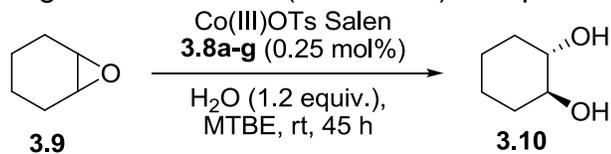
Scheme 3-1. Synthesis of bis-urea functionalized bis-salen catalyst

We first sought to identify the optimal spacing unit for the bis-urea moiety (Table 3-1). The initial reaction conditions chosen were based on those previously reported in our group for the hydrolysis of cyclohexene oxide.²¹⁸ The chosen spacing units consisted of alkyl, aryl and combinations thereof. While alkyl chains of both C₆ and C₁₂ gave encouraging enantioselectivities, the yields were somewhat disappointing. The same trend was also observed for more flexible aryl spacers bearing methylene groups (entries 6 and 7). Interestingly, the 1,4-disubstituted aryl spacer (entry 3) also gave a similar result while 1,3-disubstituted aryl spacers (entries 4 and 5) were considerably improved in terms of both yield and selectivity and complex **3.8e** (entry 5) was selected for further optimization.

It was determined early on that bis-urea catalyst **3.8e** was already significantly more efficient than the corresponding monomeric catalyst (**1.5c**•OTs: 9% yield & 45%

ee) and slightly more efficient than our second generation bis-urea catalyst **1.179** (63% yield & 75% ee) (Scheme 3-2).

Table 3-1. Survey of spacing unit on bis-urea(bis-salens) for epoxide hydrolysis.

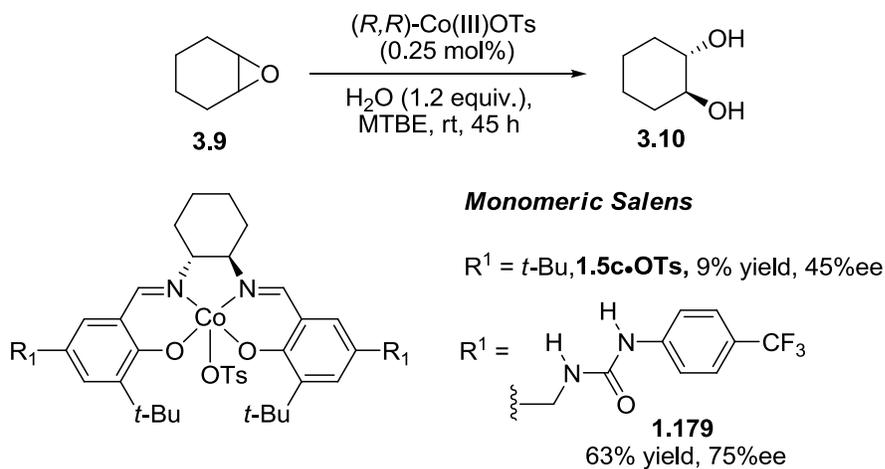


Entry ^a	R	Complex	yield(%) ^b	ee(%) ^c
1	-(CH ₂) ₆ -	3.8a	38	72
2	-(CH ₂) ₁₂ -	3.8b	43	76
3		3.8c	45	71
4		3.8d	69	81
5		3.8e	70	84
6		3.8f	38	74
7		3.8g	31	76

^a All reactions were performed on a 0.5 mmol scale at a 5.0 M concentration. Reactions were run at room temperature in a screw-capped vial. ^b Values are isolated yields after chromatographic purification. ^c Enantiomeric excess was determined by GCMS using a Supelco G-TA column.

We were intrigued to find that the self-assembling properties of the bis-urea structural core of our newly designed catalyst had been extensively studied by Bouteiller and co-workers.^{219,220,221} Bouteiller had proposed that an equilibrium exists between three self-assembling morphologies that included monomer, a “thin-filament” or ladder type structure and a “thick-filament” or tubular type structure. It was also demonstrated that the direction in which the equilibrium lies between these structures could be shifted by the variation of conditions such as temperature, concentration and solvent. Since the nature in which self-assembly occurs could have a profound effect on the outcome of

the targeted ring opening reaction, we were eager to see if any similarities could be drawn between these two related systems.



Scheme 3-2. Comparison vs. monomeric salen for epoxide hydrolysis.

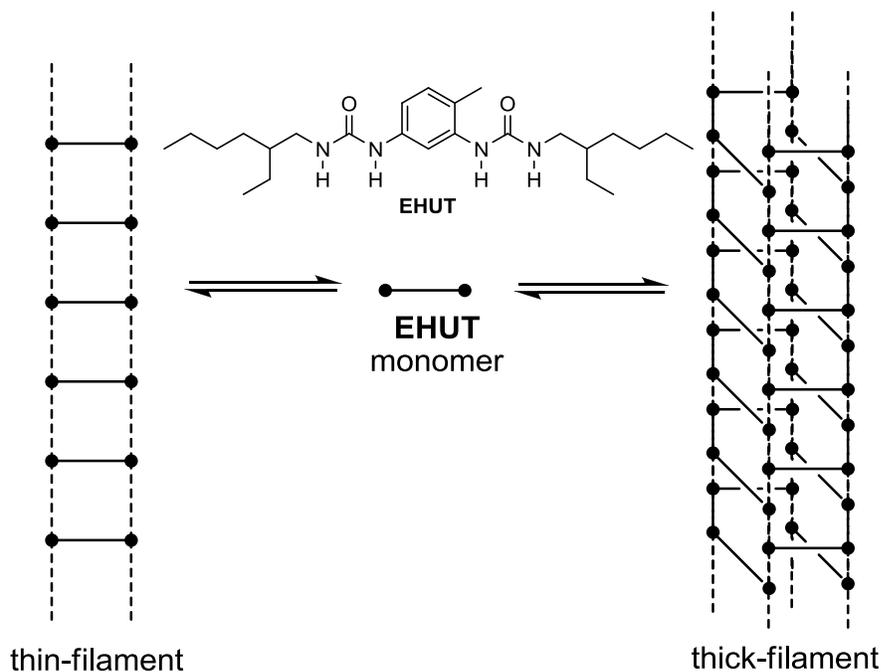


Figure 3-2. Proposed equilibrium of EHUT described by Bouteiller.

The choice of solvent was expected to play a significant role in both catalysis and self-assembly and we felt it was important to observe those effects for a variety of

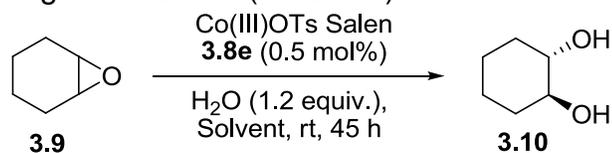
solvent types (Table 3-2). Bouteiller had determined that at ambient temperature, non-polar solvents favored the thick-filament structure while chlorinated solvents favored the thin-filament structure.^{219,220} We reasoned that the thin-filament structure would place the metal centers at the appropriate distance while the thick-filament structures would elongate the metal-metal distance, disfavoring a rapid or highly selective pathway for asymmetric ring opening. Both the catalyst mol% and reaction concentration were increased slightly in a desire to improve the reaction yield in the given time frame while screening various solvents.

Chlorinated solvents gave significantly lower yields but maintained an acceptable level of enantioselectivity. Coordinating solvents generally gave good yields and selectivities with the exception of CH₃CN, although there was a notable decrease in selectivity when using MTBE under the newly chosen conditions. Surprisingly, aliphatic hydrocarbon solvents gave higher yields but lower ee, while aromatic hydrocarbon solvents provided a balance between good yield and selectivity.

We were intrigued by both the efficiency in non-polar solvents and the decrease in selectivity in the case of MTBE under the more concentrated reaction conditions. To determine the extent the role of concentration played, toluene and benzene were selected to further study the effect of reaction and catalyst concentration.

In the cases where toluene or benzene was used, similar trends were observed in each with respect to catalyst concentration (Figure 3-3). In both solvents, the effect of lowering catalyst concentration resulted in lower substrate turnover while the enantioselectivities remained consistently high.

Table 3-2. Solvent screening with bis-urea(bis-salen).



Entry ^a	Solvent	yield(%) ^b	ee(%) ^c
1	CHCl ₃	24	78
2	CH ₂ Cl ₂	24	71
3	Et ₂ O	85	74
4	THF	74	65
5	CH ₃ CN	41	56
6	MTBE	76	70
7	None	53	63
8	Cyclohexane	68	81
9	Hexanes	85	69
10	Heptane	81	67
11	Benzene	84	83
12	Toluene	71	87
13	Xylenes	81	83
14	Mesitylene	77	83

^a All reactions were performed on a 0.5 mmol scale at a 5.0 M concentration. Reactions were run at room temperature in a screw-capped vial. ^b Values are isolated yields after chromatographic purification. ^c Enantiomeric excess was determined by GCMS using a Supelco G-TA column.

It has been observed that in ring opening reactions catalyzed by monomeric salen complexes, decreasing catalyst loading is directly proportional to decreasing enantioselectivity.⁴⁷ These observations are consistent with a competition between a second order, bimetallic pathway and a less selective monometallic pathway. In contrast, if our self-assembled system behaved as if it were covalently linked, we would expect product ee to be independent of catalyst concentration as the highly selectively intermolecular pathway is enforced.

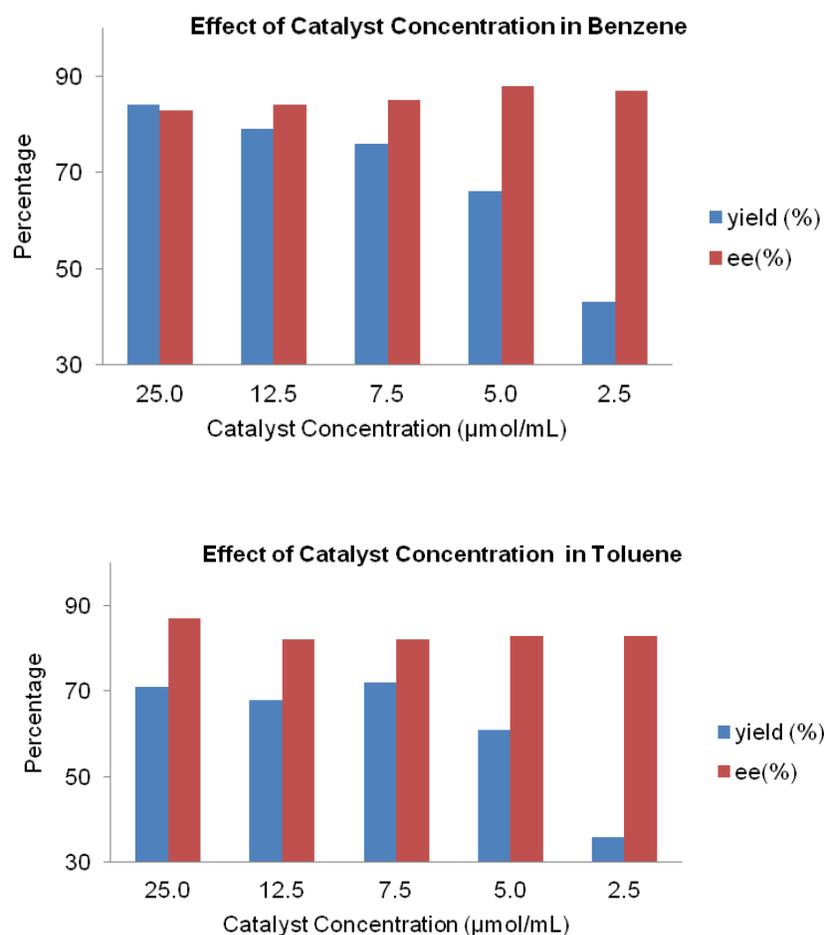


Figure 3-3. The effect of catalyst concentration on yield and selectivity.

This observation suggests that even at lower catalyst concentrations, our system maintains its self-assembled structure to enforce the more selective bimetallic pathway. Despite the marginally higher ee when toluene is used as solvent, we felt the higher yield in benzene was worth the small sacrifice in enantioselectivity and was selected as our optimized solvent.

As it has been previously noted, the careful choice of counter ion to the Co(III) center can have a considerable effect on substrate turnover. In general, non-coordinating, weakly nucleophilic ions, such as sulfonates, are known to give superior results. In some cases, the choice of counter ion can also impact the enantioselectivity,

although it is currently unclear why. A small series of substituted sulfonic acids were screened in order to fine tune our catalyst and bring it to a more competitive level with state-of-the-art technology.

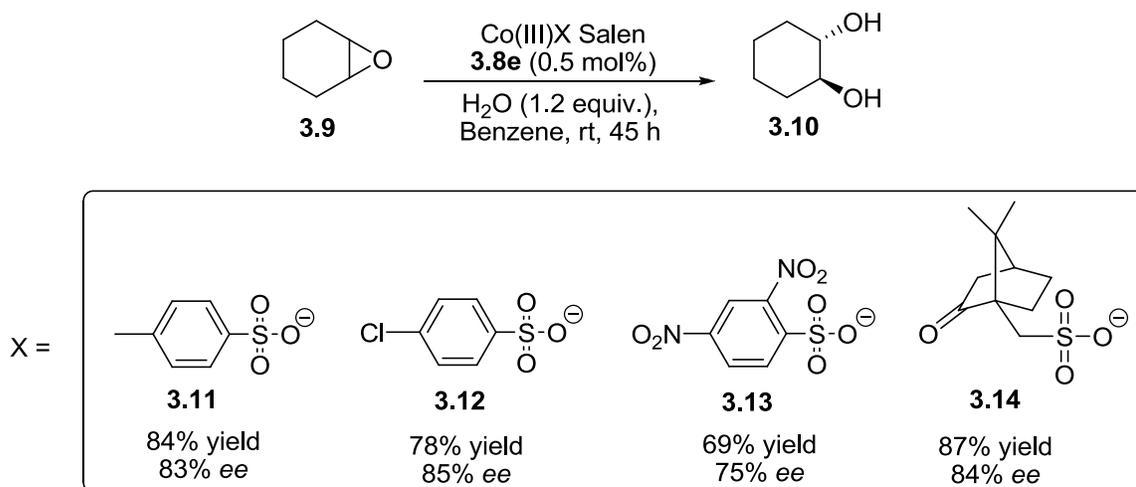
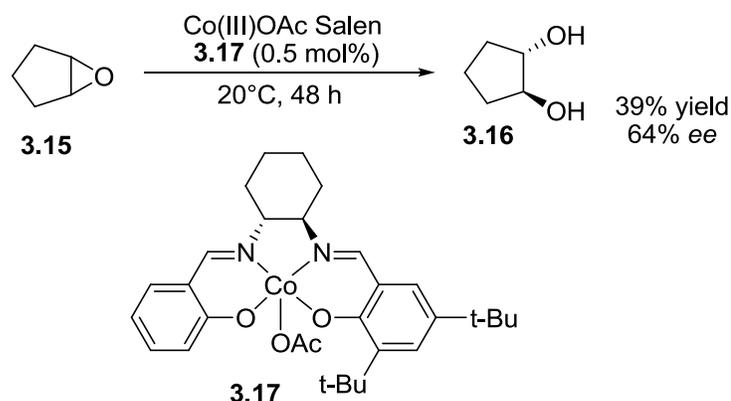


Figure 3-4. Screening of sulfonate counter ions for Co(III) bis-salen.

Compared to the originally selected tosyl sulfonate, other sulfonates gave either comparable or worse results terms of yield and selectivity. As a result, the original tosyl sulfonate was retained as the counter ion of choice.

Given the general lack of literature precedent, we were intrigued to finally explore the substrate scope of this hydrolytic ring opening. In contrast to the HKR of terminal epoxides or even the desymmetrization of meso epoxides by other nucleophiles with metal salen catalysts, there is only one report of asymmetric hydrolytic ring opening of meso epoxides other than cyclohexene oxide. While investigating polymer bound Co(III) salen catalysts, Kim and co-workers²²² found that simple Co(III)OAc salen was capable of hydrolyzing cyclopentene oxide in modest yield and moderate selectivity under neat conditions (Scheme 3-2).



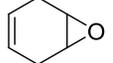
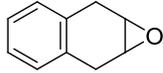
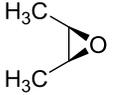
Scheme 3-3. Asymmetric hydrolysis of cyclopentene oxide by Kim and co-workers.

A series of meso epoxides were selected of varying ring size, substitution and saturation to determine the scope of our catalyst. We were surprised to observe that in nearly all cases the yield was consistently poor over the series of substrates and simply resulted in un-reacted starting material. The enantioselectivity varied considerably though, being as high as 89% (entry 1) or as low 43% (entry 6). The origin of this low turnover is presently unclear as even epoxides whose ring opened diol products are similar to 1,2-cyclohexane diol (**3.22** and **3.24**) also give low yield. Some measures were explored in an effort to trap the diol products with various reagents such as boronic acids, acid chlorides or anhydrides, all of which gave unsatisfactory results. As a result, this problem is still under current investigation.

While investigating the scope of the hydrolytic ring opening reactions we were also interested in applying our new ligand system to other ring opening reactions known to be catalyzed by metallosalen catalysts such as the asymmetric addition of TMSN_3 to meso epoxides. As previously discussed, the asymmetric addition of TMSN_3 to meso epoxides catalyze by Cr(III)Cl salen has been previously explored in Jacobsen's

seminal work on epoxide opening and was the reaction involved in much of the early multimeric salen chemistry.

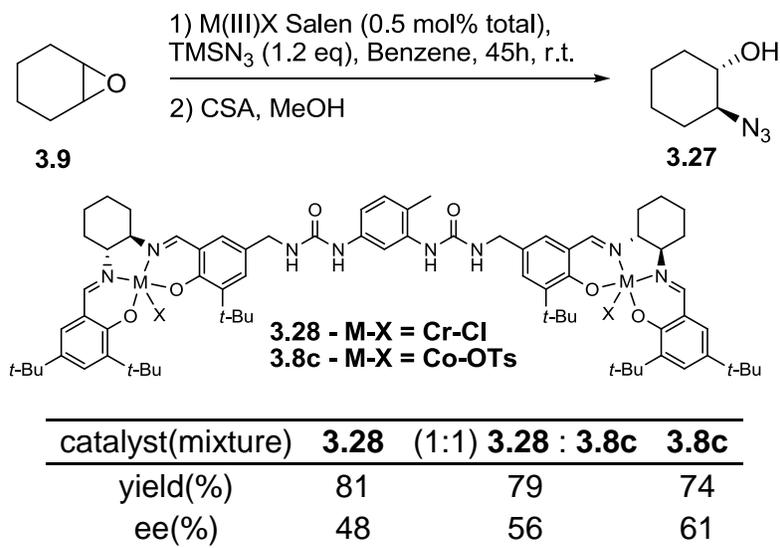
Table 3-3. Substrate scope with bis-urea(bis-salen).

Entry	Compound Number	Epoxide ^a	Product	yield(%) ^b	ee(%) ^c
1	3.15		3.16	16	89
2	3.17		3.18	nr ^d	n/a
3	3.19		3.20	13	66
4	3.21		3.22	28	85
5	3.23		3.24	13	43
6	3.25		3.26	12	64

^a All reactions were performed on a 0.5 mmol scale at a 5.0 M concentration. Reactions were run at room temperature in a screw-capped vial. ^b Values are isolated yields after chromatographic purification. ^c Enantiomeric excess of the bis-TFA ester was determined by GCMS using a Supelco G-TA column. ^d nr = no reaction.

It was our hope that we could contribute to the current methodologies by capitalizing on the unique strength of our self-assembling design to create heterobimetallic catalysts simply by mixing different prepared metal salen catalysts. In this way, we sought to employ the demonstrated ability of Cr(III) to deliver the azide nucleophile while at the same time relying on Co(III) to activate the epoxide for nucleophilic attack. Cr(III)Cl bis-urea(bis-salen) **3.28** was prepared in a similar manner

as the corresponding Co(III) bis-urea(bis-salen) complexes from ligands **3.7a-g** and evaluated under similar conditions that were selected for epoxide hydrolysis.

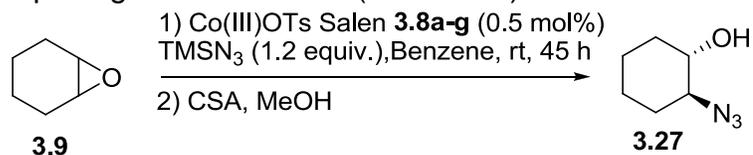


Scheme 3-4. Cr(III)Cl and Co(III)OTs complex mixtures for the ARO with TMSN₃.

We were intrigued to discover that when Cr(III)Cl complex **3.28** was used alone as the catalyst, the asymmetric addition of TMSN₃ proceeded in high yield but with only moderate % ee. A 1:1 mixture of the Cr(III)Cl complex and original Co(III)OTs complex **3.8e** gave slightly lower yield but improved % ee. Unexpectedly, in the final scenario, when **3.8e** was used exclusively, yield was depressed further but enantioselectivity was improved further still. In general, chromium salen complexes are used in the delivery of nitrogen nucleophiles while cobalt salen complexes are used for the delivery of oxygen nucleophiles. Examples of using cobalt for the delivery of nitrogen nucleophiles are quite rare.²²³ Although, from these result alone there is no way to determine the type of aggregation that forms in solution by the mixture and may simply be an average of the two independently acting catalysts.

We were curious if further similarities existed between epoxide hydrolysis and the addition of azide in terms of catalyst structure and chosen conditions. We returned to a screening of the central spacer as our first point of comparison.

Table 3-4. Survey of spacing unit on bis-urea(bis-salens)for azide addition to epoxide.



Entry ^a	R	Complex	yield(%) ^b	ee(%) ^c
1	-(CH ₂) ₆ -	3.8a	40	45
2	-(CH ₂) ₁₂ -	3.8b	50	51
3		3.8c	60	49
4		3.8d	70	66
5		3.8e	74	61
6		3.8f	51	42
7		3.8g	55	56

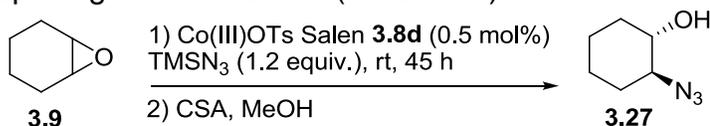
^a All reactions were performed on a 0.5 mmol scale at a 5.0 M concentration. Reactions were run at room temperature in a screw-capped vial. ^b Values are isolated yields of the azidoalcohol after chromatographic purification. ^c Enantiomeric excess was determined by GCMS using a Supelco G-TA column.

It was observed that variation of the spacing unit for the addition of azide gave consistent results in terms of yield and selectivity for spacers of different types. The alkyl spacers (entries 1+2) performed poorly under the given conditions while more ridged aryl spacers (entries 3-5) gave the best results. Spacers that contained both alkyl and aryl units gave yields and selectivities between the two extremes. The symmetric

1,3-phenylene linked catalyst **3.8d** gave the best results in terms of enantioselectivity and was chosen for further optimization.

A brief survey of reaction solvents was carried out and revealed that solvents more common to asymmetric epoxide opening by metal salen catalysts (entries 2-4) proved to be superior in terms of yield and enantioselectivity.

Table 3-5. Survey of spacing unit on bis-urea(bis-salens) for azide addition to epoxide.



Entry ^a	Solvent	yield(%) ^b	ee(%) ^c
1	CHCl ₃	48	47
2	Et ₂ O	71	76
3	THF	43	82
4	MTBE	70	81
5	Benzene	70	66

^a All reactions were performed on a 0.5 mmol scale at a 5.0 M concentration. Reactions were run at room temperature in a screw-capped vial. ^b Values are isolated yields of the azidoalcohol after chromatographic purification. ^c Enantiomeric excess was determined by GCMS using a Supelco G-TA column.

Due to the rarity of Co(III)salen catalyst used for the addition of nitrogen nucleophiles, we were interested in our catalysts efficiency versus the monomeric Co(III)salen (**1.5c**•OTs). Our catalyst was indeed more efficient, providing the azidoalcohol from cyclohexene oxide (**3.17**) in 70% yield and 81% ee while monomeric salen **1.5c**•OTs yielded less than 5% of the desired product in only 9% ee. Similar results were observed for a small range of substrates (Table 3-6).

Increasing the catalyst loading to 1.0 mol% helped to increase our chemical yield and while we are encouraged by the current level of conversion and efficiency compared to the un-functionalized monomeric parent metal salen catalyst, the

enantioselectivity is not yet to a competitive level with the current technology. Efforts to further improve this selectivity and expand the substrate scope are currently underway.

Table 3-6. Substrate scope for epoxide desymmetrization by TMSN_3 .

Entry ^a	Catalyst	Epoxide	Product	yield(%) ^c	ee(%) ^d
1	3.8d		3.27	88	83
2	1.5c		3.27	5	9
3	3.8d		3.28	73	68
4	1.5c		3.28	3	0
5	3.8d		3.29	82	67
6	1.5c		3.29	3	0

^a All reactions were performed on a 0.5 mmol scale at a 5.0 M concentration. Reactions were run at room temperature in a screw-capped vial. ^b Determined by GCMS using an internal standard. ^c Values are isolated yields of the azidoalcohol after chromatographic purification. ^d Enantiomeric excess was determined by GCMS using a Supelco G-TA column.

Meso-Aziridine Opening

Background

Analogous to the value and synthetic utility of enantioenriched epoxides and their ring opened products, aziridines and their ring opened products are equally valuable intermediates in organic synthesis.^{224,225} In particular, vicinal diamines are extensively used as chiral auxiliaries and ligands, and can also be found in anti-cancer agents, anti-influenza drugs, as well as many other biologically active compounds. Similar to the chemistry associated with epoxides, access to optically active amines by nucleophilic

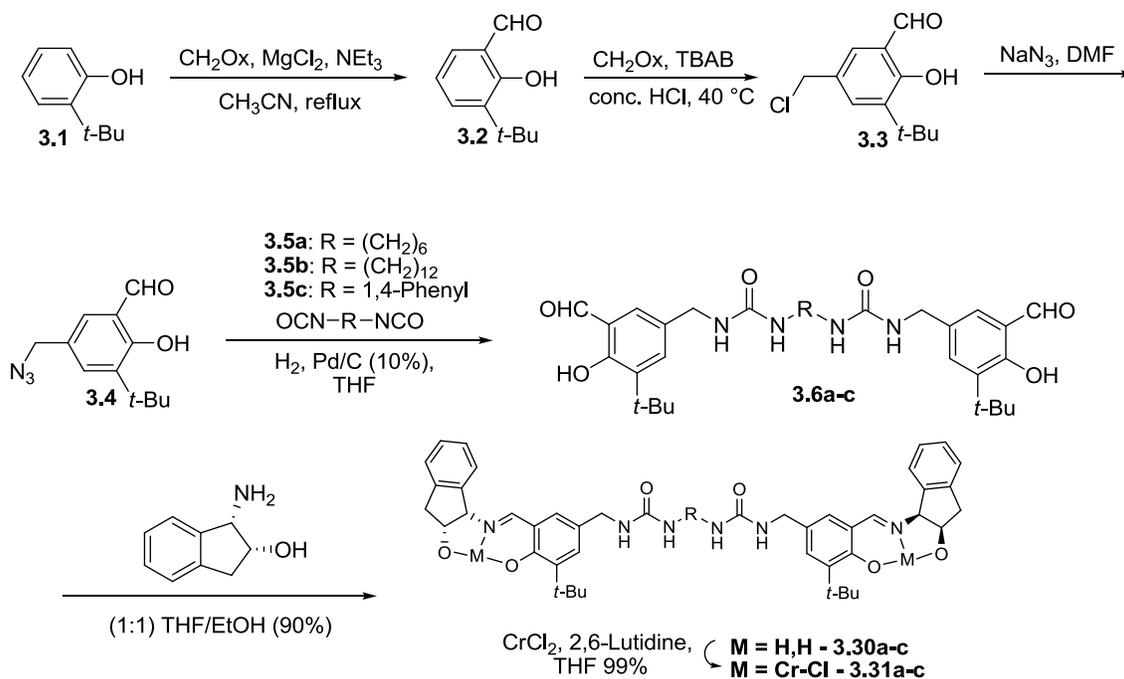
ring opening often requires either the use of enantiomerically enriched aziridines or enantioselective methods of ring opening the meso compounds. While researchers have developed many methods for the synthesis of these diamines,²²⁶ one of the more direct methods for their synthesis is the ring opening of aziridines with nitrogen nucleophiles.^{227,228} Methods for asymmetric aziridination have been well developed²²⁹ but not until more recently have methods been developed for the desymmetrization of the meso compounds using nitrogen nucleophiles. In 1999, Jacobsen and co-workers reported enantioselective ring opening of meso benzyl substituted aziridines with TMSN_3 using a chiral chromium complex of tridentate Schiff bases.²³⁰ Shibasaki and co-workers have reported the use of chiral yttrium complexes for the desymmetrization of meso aziridines in route to the synthesis of Tamiflu.^{231,232} In 2007, Antilla and co-workers reported the enantioselective ring opening of benzoyl substituted aziridines with chiral phosphoric acids.²³³ It was Jacobsen's early report of chiral tridentate Schiff base chromium complexes that led us to consider if our internal bis-urea approach could be applied to develop self-assembling metal complexes as aziridine ring opening catalysts.

Results and Discussion

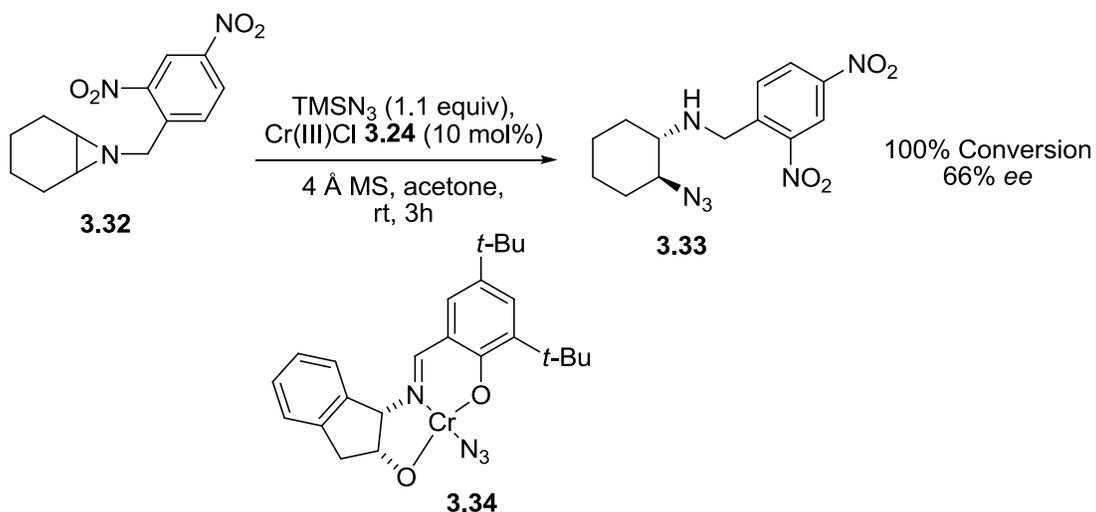
The construction of bis-urea, bis-tridentate Schiff base ligands is considerably more straightforward than the corresponding tetradentate bis-salen ligands. The synthesis relies only on a single imine condensation from readily available chiral amino alcohols with our existing bis-urea dialdehydes **3.6a-c**, which were chosen for our preliminary screening (Scheme 3-6).

In Jacobsen and co-worker's report,²³⁰ chiral amino-indanol in combination with sterically demanding ortho substituted salicaldehydes provided Schiff base ligands that gave the fastest rates and highest levels of enantioselectivity. Electron deficient *N*-

benzyl substituted aziridines were opened in high conversion with good enantioselectivity (Scheme 3-7).



Scheme 3-6. Synthesis of bis-urea bis-tridentate Schiff base ligands.

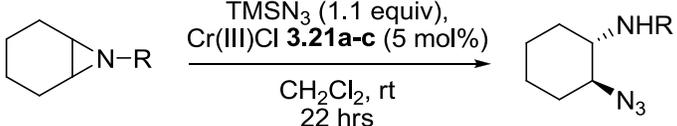


Scheme 3-7. Example of asymmetric addition of TMSN_3 to N-alkyl meso aziridine.

It was also determined that the *N*-substituent on the aziridine played an important role in terms of both rate and selectivity. Amide and carbamate substituted aziridines gave high conversions but suffered from low selectivity while sulfonyl substituted aziridines were completely unreactive under the selected conditions. For our preliminary screening, simple *N*-benzyl and benzoyl substituted aziridines were chosen as model substrates. Under our conditions, bis-urea catalysts with both alkyl (**3.31a+b**) and aryl (**3.31c**) spacers were sluggish compared to the monomeric catalyst **3.34** requiring considerably longer reaction times to reach appreciable conversion. To our surprise, *N*-benzyl substituted aziridines gave better yields than *N*-benzoyl substituted aziridines. The ring opened azidoamide product (**3.38**) was found to be a racemic mixture of isomers. Unfortunately, enantiomers from the ring opened azidobenzylamine product (**3.37**) could not be resolved via chiral HPLC, despite a variety of conditions and derivatization.

While initial results may have warranted further exploration, the inability to confidently analyze reaction products forced us to delay further study.

Table 3-7. Preliminary screening of asymmetric aziridine ring opening.



Entry ^a	Aziridine	R	Complex	yield(%) ^b	ee(%) ^c	Product
1	3.35	Bn	3.31a	97	n.d. ^d	3.37
2	3.35	Bn	3.31b	90	n.d.	3.37
3	3.35	Bn	3.31c	96	n.d.	3.37
4	3.36	Bz	3.31a	73	rac.	3.38
5	3.36	Bz	3.31b	73	rac.	3.38
6	3.36	Bz	3.31c	75	rac.	3.38

^a All reactions were performed on a 0.5 mmol scale at a 1.0 M concentration. ^b Values are isolated yields after chromatographic purification. ^c Enantiomeric excess was determined by HPLC using Chiralpak® IA column. ^d n.d. = not determined.

Summary

Described here is the development of chiral tri- and tetradentate dimeric Schiff base ligands, designed to self-assemble in solution through hydrogen bonding provided by a bis-urea scaffold. The concept of self-assembly was introduced to create multinuclear transition metal complexes without the need for covalently linked supramolecular structures. These ligands were designed with the intent to provide an alternative to covalently linked supramolecular catalysts known to provide accelerated rates and high levels of stereoselectivity in asymmetric ring opening reactions.

Bis-urea, dimeric Co(III)salen catalyst **3.8e** was found to be an efficient catalyst for the asymmetric hydrolysis of cyclohexene oxide versus the monomeric Co(III)salen catalyst, providing the *trans*-diol in 84% yield and 83% ee with only 0.5 mol% catalyst under the optimized conditions. Interestingly, the closely related bis-urea Co(III)salen **3.8d** was also found to be an efficient catalyst for the asymmetric addition of TMSN₃ to cyclohexene oxide versus the monomeric Co(III)salen catalyst, providing the *trans*-azidoalcohol with up to 88% yield and 83% ee with only 1.0 mol% catalyst. The use of Co(III) catalysts for the delivery of nitrogen nucleophiles is quite rare.

Currently, these self-assembling catalysts fall just short in terms of efficiency compared to the more traditional, covalently bonded, supramolecular catalysts for the desymmetrization of meso epoxides by hydrolysis or by the addition of TMSN₃. In respect to the advantages over the covalently linked catalysts in terms of ease of synthesis and characterization, the use of self-assembly through hydrogen bonding in place of covalent bonds still provides a reasonable alternative to access multinuclear catalysts.

At the present time, it is difficult to make any clear conclusions about the use of this bis-urea architecture to construct self-assembling tridentate Schiff base catalysts for the asymmetric ring opening of meso aziridines. Further optimization of reaction conditions as well as better methods for the resolution of reaction products are needed if this chemistry is to be developed further.

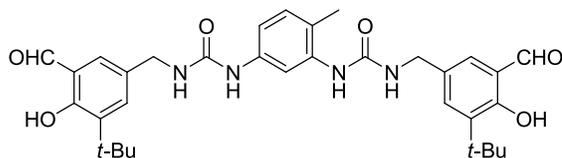
Experimental

All reactions were conducted in flame-dried glassware under an inert atmosphere of dry argon unless otherwise specified. THF, CH₂Cl₂, CH₃CN and Et₂O were passed through two packed columns of neutral alumina under positive pressure of argon prior to use. All other chemicals used were commercially available and were used as received without further purification. NMR spectra were recorded using an FT-NMR machine, 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 Me₄Si (δ 0.0 ppm) for ¹H and ¹³C or residual signals from (CDCl₃) (δ 7.24 ppm) for ¹H and (δ 77.23) for ¹³C. High resolution mass spectra were recorded on a DIP-CI-MS spectrometer, an APCI-TOF spectrometer, an ESI-TOF spectrometer, or a TOF-LC/MS spectrometer. Enantiomeric ratios were determined by chiral HPLC analysis (Shimadzu) using Chiralpak[®] IA, IB or by Chiral GCMS analysis (Shimadzu) using an Astec CHIRALDEX[™] column (G-TA) with helium as the carrier gas. Meso epoxides were purchased from Sigma-Aldrich and used without further purification. Known compounds have been identified by comparison of spectral data (¹H NMR, and ¹³C NMR) with those previously reported.

Synthesis and Characterization of Bis-Urea Bis-Salen Ligands

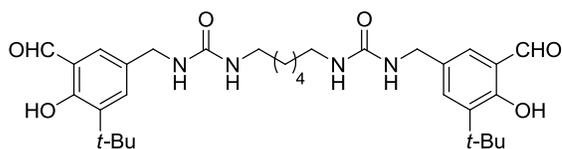
Compounds **5**²³⁴, **6** and **7**²³⁵ were prepared according to known literature method.

A representative procedure for the synthesis of bis-ureas, bis-salens and respective cobalt complexes are described below.



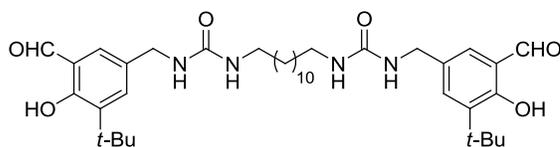
1,-(4-Methyl-1,3-phenylene)bis(3-(3-*tert*-butyl-5-formyl-4-hydroxybenzyl)urea)

(3.6e) To a solution of 5-(azidomethyl)-3-*tert*-butyl-2-hydroxybenzaldehyde (0.663 g, 2.84 mmol) in THF (50 mL) was added toluene-2,4-diisocyanate as a solution in THF (4 mL). A slurry of Pd/C (10%) in THF was added (3 mL) and the reaction mixture was then exposed to a atmosphere of H₂ via balloon and stirred vigorously for 18h. The reaction mixture was then diluted with THF (20 mL) and vacuum filtered over a pad of Celite. The solvent was then removed under reduced pressure and the crude solid dissolved in acetone and triturated with hexanes/Et₂O to give a white solid (0.223 g, 48%) ¹H NMR (300 MHz, DMSO-*d*₆) δ ppm 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); ¹³C NMR (75 MHz DMSO-*d*₆) δ ppm 198.5, 158.8, 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 C₃₃H₄₀N₄O₆ [M+H]⁺: 589.3021, found 589.30307



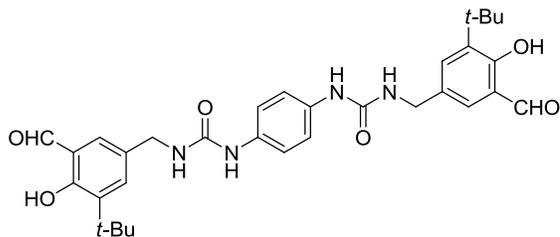
1,1'-(Hexane-1,6-diyl)bis(3-(3-*tert*-butyl-5-formyl-4-hydroxybenzyl)urea) (3.6a)

(48%) ^1H NMR (300 MHz, $\text{DMSO-}d_6$) δ ppm 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, $J=6.10$ Hz, 4 H) 2.98 - 3.03 (m, 4 H) 2.48 - 2.52 (m, 4 H) 1.36 (s, 18 H) 1.25 (br. s., 1 H) 1.25 (m, 4 H); ^{13}C NMR (75 MHz, $\text{DMSO-}d_6$) ppm 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 $\text{C}_{32}\text{H}_{46}\text{N}_4\text{O}_6$ $[\text{M}+\text{H}]^+$: 583.3490, found 583.3484



1,1'-(Dodecane-1,12-diyl)bis(3-(3-*tert*-butyl-5-formyl-4-hydroxybenzyl)urea) (3.6b)

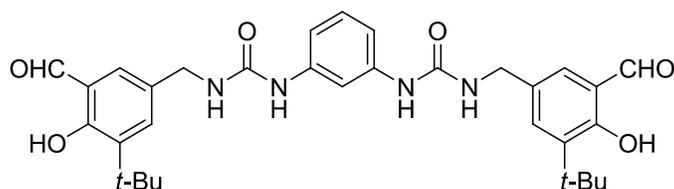
(62%) ^1H NMR (300 MHz, $\text{DMSO-}d_6$) δ ppm 11.73 (s, 2 H) 9.93 - 9.98 (m, 2 H) 7.47 (s, 4 H) 6.30 (s, 2 H) 5.89 - 5.95 (m, 2 H) 4.16 (dd, $J=6.12, 0.09$ Hz, 4 H) 2.92 - 3.02 (m, 4 H) 1.36 (s, 18 H) 1.22 - 1.29 (m, 20 H); ^{13}C NMR (75 MHz, $\text{DMSO-}d_6$) δ ppm 198.5, 158.8, 158.1, 137.0, 133.3, 132.1, 130.3, 120.3, 42.3, 34.4, 30.1, 29.1, 28.9, 26.4; HRMS (APCI) calcd for $\text{C}_{38}\text{H}_{58}\text{N}_4\text{O}_6$ $[\text{M}+\text{H}]^+$: 667.4429, found 667.4447



1,1'-(1,4-phenylene)bis(3-(3-*tert*-butyl-5-formyl-4-hydroxybenzyl)urea) (3.6c)

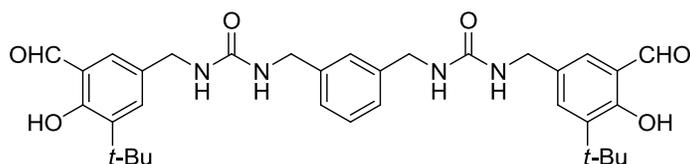
(44%) ^1H NMR (300 MHz, $\text{DMSO-}d_6$) δ ppm 11.75 (s, 5 H), 9.95 (s, 5 H), 8.35 (s, 4 H), 7.52 (d, $J=2.9$ Hz, 11 H), 7.24 (s, 11 H), 6.52 (t, $J=5.9$ Hz, 4 H), 4.24 (d, $J=5.8$ Hz, 10 H), 1.36 ppm (s, 48 H); ^{13}C NMR (75 MHz, $\text{DMSO-}d_6$) δ ppm 199.3, 159.5, 156.1, 137.8,

135.0, 134.2, 132.2, 131.2, 121.0, 119.2, 42.8, 35.1, 29.7 HRMS (APCI) calcd for $C_{32}H_{38}N_4O_6$ $[M+H]^+$: 575.2864, found 575.2861; calcd for $C_{32}H_{38}N_4O_6$ $[M+Na]^+$: 597.2684, found 597.2679

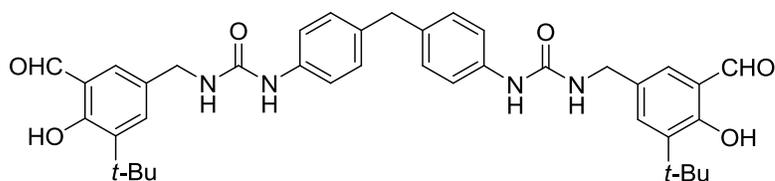


1,1'-(1,3-Phenylene)bis(3-(3-tert-butyl-5-formyl-4-hydroxybenzyl)urea) (3.6d)

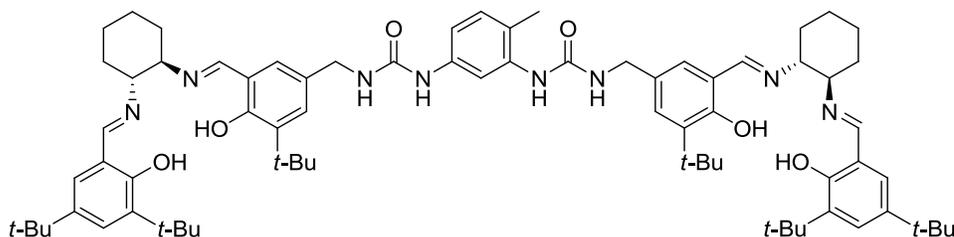
(79%) 1H NMR (300 MHz, DMSO- d_6) δ ppm 11.77 (s, 2 H) 9.97 (s, 2 H) 8.50 - 8.56 (m, 2 H) 7.52 - 7.57 (m, 4 H) 7.52 (br. s., 1 H) 6.95 - 7.08 (m, 3 H) 6.55 (s, 2 H) 4.26 (dd, $J=6.04, 0.20$ Hz, 4 H) 1.38 (s, 18 H); ^{13}C NMR (75 MHz, DMSO- d_6) δ ppm 198.5, 158.8, 155.1, 140.7, 137.1, 133.4, 131.4, 130.4, 128.7, 120.3, 110.8, 107.2, 42.1, 40.3, 34.4, 29.1, 22.7; HRMS (ESI) calcd for $C_{32}H_{38}N_4O_6$ $[M+Na]^+$: 597.2684, found 597.2702



1,1'-(1,3-Phenylenebis(methylene))bis(3-(3-tert-butyl-5-formyl-4-hydroxybenzyl)urea) (3.6f) (53%) 1H NMR (300 MHz, DMSO- d_6) δ ppm 11.74 (s, 2 H) 9.94 (s, 2 H) 7.49 (s, 4 H) 7.20 - 7.25 (m, 1 H) 7.08 - 7.14 (m, 3 H) 6.42 - 6.50 (m, 4 H) 4.21 (d, $J=5.99$ Hz, 8 H) 1.37 (s, 18 H); ^{13}C NMR (75 MHz, DMSO- d_6) δ ppm 198.4, 158.7, 158.0, 140.8, 137.0, 133.3, 131.9, 130.2, 128.1, 125.8, 125.2, 120.3, 43.0, 42.3, 34.4, 29.1; HRMS (APCI) calcd for $C_{34}H_{42}N_4O_6$ $[M+H]^+$: 603.3177, found 603.3170

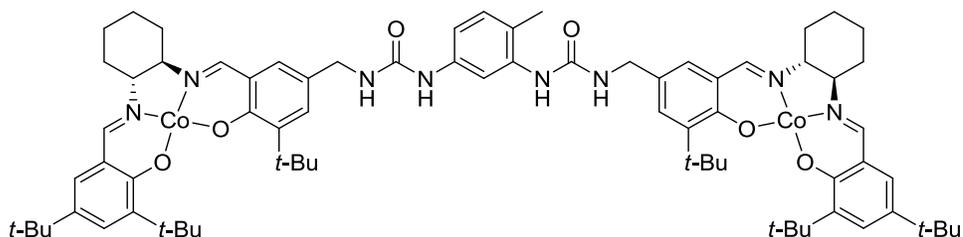


1,1'-(4,4'-Methylenebis(4,1-phenylene))bis(3-(3-*tert*-butyl-5-formyl-4-hydroxybenzyl)urea) (3.6g) (30%) ^1H NMR (300 MHz, $\text{DMSO-}d_6$) δ ppm 11.76 (s, 2 H) 9.96 (s, 2 H) 8.47 (s, 2 H) 7.53 (d, $J=2.48$ Hz, 4 H) 7.29 (d, $J=8.62$ Hz, 4 H) 7.04 (d, $J=8.62$ Hz, 4 H) 6.55 – 6.59 (m, 2 H) 4.26 (d, $J=5.84$ Hz, 4 H) 3.75 (s, 2 H) 1.37 (s, 18 H); ^{13}C NMR (75 MHz, $\text{DMSO-}d_6$) δ ppm 198.7, 158.9, 155.3, 138.3, 137.1, 134.4, 133.5, 131.4, 130.5, 128.8, 120.4, 117.9, 42.1, 34.4, 29.1; HRMS (APCI) calcd for $\text{C}_{39}\text{H}_{44}\text{N}_4\text{O}_6$ $[\text{M}+\text{H}]^+$: 665.3334, found 665.3355



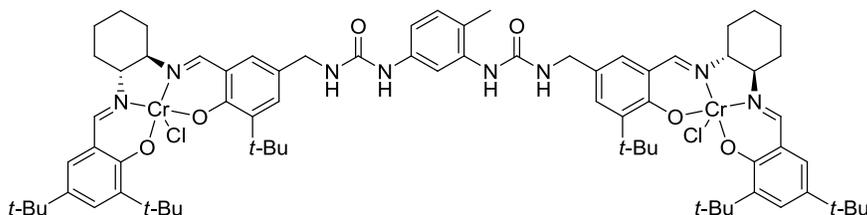
1,1'-(4-Methyl-1,3-phenylene)bis(3-(3-*tert*-butyl-5-((*E*)-((1*R*,2*R*)-2-((*E*)-3,5-di-*tert*-butyl-2-hydroxybenzylideneamino)cyclohexylimino)methyl)-4-hydroxybenzyl)urea) (3.7e) A solution of (1*R*,2*R*)-1,2-cyclohexanediamine (0.133 g, 1.17 mmol) in absolute ethanol (6.0 mL) was cooled to 0 °C via ice bath for 10 minutes. An HCl solution (2.0 M in Et_2O) was then added drop wise (0.58 mL, 1.17 mmol) and allowed to stir for 1 h. 3 Å MS were then added (98.4 mg) followed by 3,5-di-*tert*-butyl-2-hydroxybenzaldehyde (0.274 g, 1.17 mmol) as a solution in absolute ethanol (6.0 mL) and allowed to stir for 3 h. A solution of 9e was then added (0.344 g, 0.585 mmol) in a (1:1) mixture of absolute ethanol and THF (6.0 mL) followed by triethylamine (0.33 mL, 2.34 mmol). The reaction was allowed to stir for another 18 h, slowly warming to room

temperature. The reaction mixture was then vacuum filtered over a pad of celite and the solvent then removed under reduced pressure. The crude residue was then purified by column chromatography on silica-gel eluted with hexanes/ethyl acetate [10:1→5:1→2:1] to give a yellow solid (0.298 g, 42%) ^1H NMR (300 MHz, $\text{DMSO-}d_6$) δ ppm 14.10 - 14.13 (m, 2 H) 13.86 - 13.88 (m, 2 H) 8.45 - 8.49 (m, 4 H) 8.32 (s, 1 H) 7.72 (s, 1 H) 7.49 (s, 1 H) 7.20-7.23 (m, 2 H) 7.15 - 7.18 (m, 2 H) 7.07 - 7.13 (m, 5 H) 6.89 (s, 1 H) 6.75 - 6.79 (m, 1 H) 6.25- 6.29 (m, 1 H) 4.11 (d, $J=5.84$ Hz, 4 H) 3.40 (br.s., 4 H) 2.03 (s, 3 H) 1.88 - 1.92 (m, 4 H) 1.75 - 1.81 (m, 4 H) 1.63 (br.s., 4 H) 1.38-1.46 (m, 4 H) 1.31 (d, $J=3.94$ Hz, 36 H) 1.18 (s, 18 H); ^{13}C NMR (75 MHz, $\text{DMSO-}d_6$) δ ppm 166.4, 158.8, 158.8, 157.4, 155.1, 139.5, 138.5, 138.1, 136.3, 135.5, 129.9, 129.3, 129.0, 128.8, 128.6, 126.1, 119.2, 117.9, 117.9, 117.5, 71.3, 40.3, 34.5, 34.4, 33.7, 32.5, 31.2, 29.2, 29.1, 23.8, 17.2 HRMS (ESI) calcd for $\text{C}_{75}\text{H}_{104}\text{N}_8\text{O}_6$ $[\text{M}+\text{H}]^+$:1213.8152, found 1213.8153

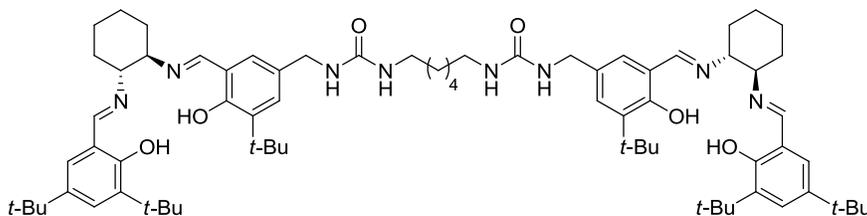


1,-((4-Methyl-1,3-phenylene)bis-(urido-salen))cobalt (3.8e) A schlenk flask was charged with a magnetic stir bar, bis-salen ligand **3.7e** (0.203 g, 0.168 mmol) and $\text{Co}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$ (83.6 mg, 0.336 mmol). The flask was evacuated then back filled with argon. MeOH (17 mL) was added and the flask was heated to 60 °C with stirring for 18h. The reaction mixture was allowed to cool to room temperature and the solid collected by vacuum filtration, washing with MeOH. The resultant solid was then re-suspended in boiling MeOH, allowed to cool to room temperature and collected by

vacuum filtration to give a deep red microcrystalline solid (0.142 g, 64%) HRMS (ESI) calcd for $C_{75}H_{100}N_8O_6Co_2$ $[M]^+$:1326.6424, found 1326.6344; calcd for $C_{75}H_{100}N_8O_6Co_2$ $[M]^{+2}$: 663.3209, found 663.3200

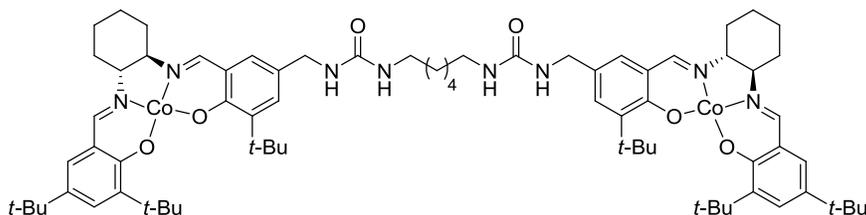


1,1'-((4-Methyl-1,3-phenylene)bis-(urido-salen))cobalt (3.8e) A schlenk flask was charged with a magnetic stir bar, bis-salen ligand **3.7e** (0.250 g, 0.21 mmol) and $CrCl_2$ (0.123 g, 50.6 mmol). The flask was evacuated then back filled with argon. THF (21 mL) was added and the flask was heated to 60 °C with stirring for 3h. The flask was then exposed to the atmosphere and allowed to stir over night. Hexane was then added (25 mL) and the solid collected by vacuum filtration. The resultant solid was triturated with THF and hexanes and collected by vacuum filtration to give a green solid (0.210 g, 74%) HRMS (ESI) calcd for $C_{75}H_{100}N_8O_6ClCr_2$ $[M-Cl]^+$:1347.6266, found 1347.6290; calcd for $C_{75}H_{100}N_8O_6ClCr_2$ $[M+4H-Cl]^+$: 1351.6580, found 1351.5935

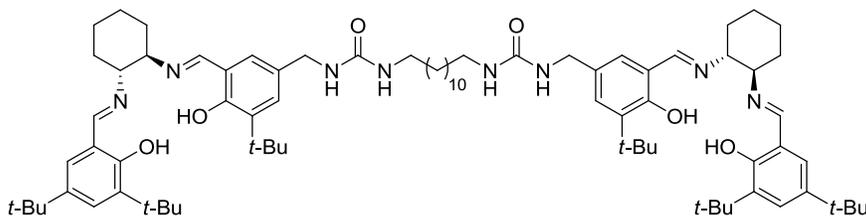


1,1'-((Hexane-1,6-diyl)bis(3-(3-tert-butyl-5-((E)-((1R,2R)-2-((E)-3,5-di-tert-butyl-2-hydroxybenzylideneamino)cyclohexylimino)methyl)-4-hydroxybenzyl)urea) (3.7a) 1H NMR (300MHz, $DMSO-d_6$) δ ppm 14.06 (br. s., 2 H), 13.87 (br. s., 2 H), 8.47 (d, $J=6.0$ Hz, 4 H), 6.91 - 7.34 (m, 8 H), 6.08 (br. s., 2 H), 5.78 (br. s., 2 H), 4.03 (br. s.,

4 H), 3.40 (br. s., 4 H), 2.96 (br. s., 4 H), 1.89 (d, $J=10.4$ Hz, 4 H), 1.80 (br. s., 4 H), 1.64 (br. s., 4 H), 1.44 (br. s., 4 H), 1.32 (d, $J=4.5$ Hz, 40 H), 1.18 ppm (br. s., 22 H); ^{13}C NMR (75 MHz, $\text{DMSO-}d_6$) δ ppm 166.3, 165.8, 158.5, 157.9, 157.3, 139.4, 136.0, 135.4, 129.8, 128.5, 126.1, 117.7, 117.5, 71.3, 70.7, 42.6, 34.5, 34.3, 33.7, 32.5, 31.2, 30.0, 29.2, 29.1, 26.1, 23.8; HRMS (ESI) calcd for $\text{C}_{74}\text{H}_{110}\text{N}_8\text{O}_6$ $[\text{M}+\text{H}]^+$:1207.8621, found 1207.8601

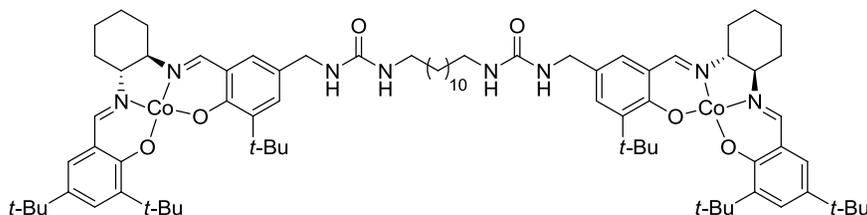


1,1'-(Hexane-1,6-diyl)bis-(urido-salen)cobalt (3.8a) HRMS (ESI) calcd for $\text{C}_{74}\text{H}_{106}\text{N}_8\text{O}_6\text{Co}_2$ $[\text{M}]^+$:1320.6894, found 1320.6885; calcd for $\text{C}_{74}\text{H}_{106}\text{N}_8\text{O}_6\text{Co}_2$ $[\text{M}]^{+2}$:660.3444, found 660.3471



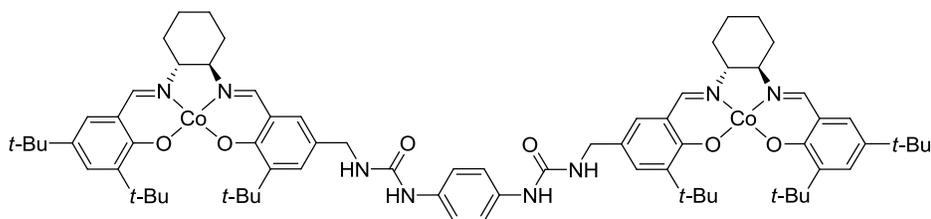
1,1'-(Dodecane-1,12-diyl)bis(3-(3-tert-butyl-5-((E)-((1R,2R)-2-((E)-3,5-di-tert-butyl-2-hydroxybenzylideneamino)cyclohexylimino)methyl)-4-hydroxybenzylideneamino)cyclohexylimino)methyl)-4-hydroxybenzylideneamino)cobalt (3.7b) ^1H NMR ($\text{DMSO-}d_6$, 300MHz) δ ppm 13.99 (s, 2 H), 13.81 (s, 2 H), 8.40 (d, $J=8.1$ Hz, 4 H), 7.18 (d, $J=1.9$ Hz, 2 H), 7.06 (d, $J=5.4$ Hz, 4 H), 6.95 (s, 2 H), 6.02 (s, 2 H), 5.71 (s, 2 H), 3.97 (d, $J=5.4$ Hz, 4 H), 3.31 - 3.38 (m, 4 H), 2.90 (d, $J=6.0$ Hz, 2 H), 1.81 - 1.86 (m, 2 H), 1.36 - 1.43 (m, 4 H), 1.22 - 1.32 (m, 44 H), 1.07 - 1.21 (m, 42 H); ^{13}C NMR (75 MHz, $\text{DMSO-}d_6$) δ ppm 166.4, 165.8, 158.5, 157.9, 157.3, 139.4, 136.0, 135.4, 129.8, 128.4, 126.1, 117.7, 117.5, 71.3, 70.8, 42.6, 40.3,

34.5, 34.3, 33.7, 32.6, 31.2, 30.1, 29.2, 29.1, 28.9, 26.4, 23.8, 22.7; HRMS (ESI) calcd for $C_{80}H_{122}N_8O_6$ $[M+H]^+$:1291.9560, found 1292.9546

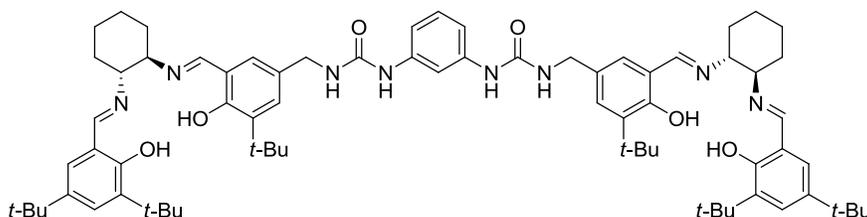


1,1'-(Dodecane-1,12-diyl)bis-(urido-salen)cobalt (3.8b) 1 HRMS (ESI) calcd for $C_{80}H_{118}N_8O_6Co_2$ $[M+H]^+$:1405.7911, found 1405.7878; calcd for $C_{80}H_{118}N_8O_6Co_2$ $[M]^+$:1404.7833, found 1404.7825; calcd for $C_{80}H_{118}N_8O_6Co_2$ $[M]^+2$:702.3914 found 702.3948

1,1'-(1,4-phenylene)bis(3-(3-tert-butyl-5-((E)-((1R,2R)-2-((E)-3,5-di-tert-butyl-2-hydroxybenzylideneamino)cyclohexylimino)methyl)-4-hydroxybenzyl)urea) (3.7c)

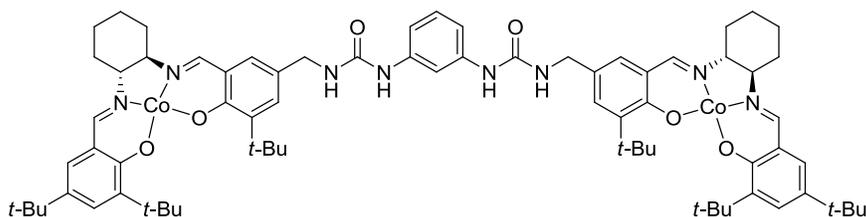


1,1'-(1,4-phenylene)bis-(urido-salen)cobalt (3.8c) HRMS (APCI) calcd for $C_{74}H_{98}N_8O_6Co_2$ $[M]^+$: 1312.6268, found 1312.6226

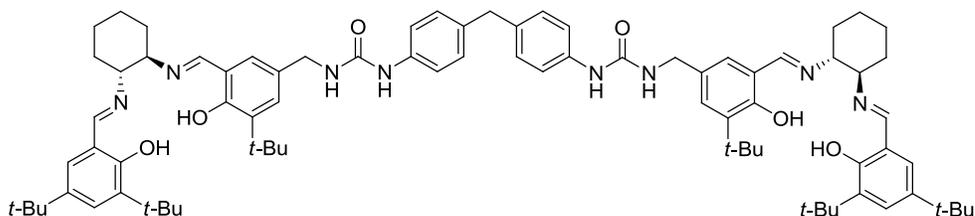


1,1'-(1,3-Phenylene)bis(3-(3-tert-butyl-5-((E)-((1R,2R)-2-((E)-3,5-di-tert-butyl-2-hydroxybenzylideneamino)cyclohexylimino)methyl)-4-hydroxybenzyl)urea) (3.7d)
(0.182 g, 57%) 1 H NMR (300 MHz, DMSO- d_6) δ ppm 14.09 - 14.15 (m, 2 H) 13.85 -

13.90 (m, 2 H) 8.48 (d, $J=3.07$ Hz, 4 H) 8.36 (s, 2 H) 7.44 (s, 2 H) 7.22 (d, $J=2.12$ Hz, 2 H) 7.17 (s, 2 H) 7.11 (d, $J=2.23$ Hz, 2 H) 7.08 (s, 2 H) 6.98 - 7.05 (m, 1 H) 6.96 (s, 2 H) 6.93 (s, 1 H) 4.12 (d, $J=5.15$ Hz, 4 H) 3.37 - 3.47 (m, 4 H) 1.89 (s, 4 H) 1.80 (d, $J=7.01$ Hz, 4 H) 1.66 (d, $J=7.05$ Hz, 4 H) 1.37 - 1.52 (m, 4 H) 1.32 (d, $J=4.24$ Hz, 36 H) 1.18 (s, 18 H); ^{13}C NMR (75 MHz, $\text{DMSO-}d_6$) δ ppm 166.4, 165.9, 158.7, 157.3, 154.9, 140.7, 139.4, 136.2, 135.4, 129.1, 128.6, 126.1, 117.8, 117.5, 110.6, 106.9, 71.2, 70.7, 42.4, 34.5, 34.3, 33.7, 32.5, 31.2, 29.2, 29.1, 23.8; HRMS (ESI) calcd for $\text{C}_{74}\text{H}_{102}\text{N}_8\text{O}_6$ $[\text{M}+\text{Na}]^+$:1221.7815, found 1221.7816

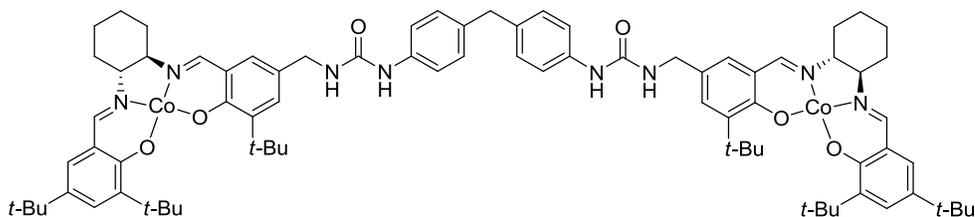


1,1'-(1,3-Phenylene)bis-(urido-salen))cobalt (3.8d) HRMS (ESI) calcd for $\text{C}_{74}\text{H}_{98}\text{N}_8\text{O}_6\text{Co}_2$ $[\text{M}]^+$:1312.6268, found 1320.6265; calcd for $\text{C}_{74}\text{H}_{98}\text{N}_8\text{O}_6\text{Co}_2$ $[\text{M}]^{+2}$:656.3131, found 656.3148



1,1'-(4,4'-Methylenebis(4,1-phenylene))bis(3-(3-tert-butyl-5-((E)-((1R,2R)-2-((E)-3,5-di-tert-butyl-2-hydroxybenzylideneamino)cyclohexylimino)methyl)-4-hydroxybenzyl)urea) (3.7f) ^1H NMR ($\text{DMSO-}d_6$, 300MHz) δ ppm 14.11 (s, 2 H), 13.87 (s, 2 H), 8.47 (s, 4 H), 8.33 (s, 2 H), 7.15 - 7.32 (m, 8 H), 6.96 - 7.14 (m, 8 H), 6.38 (s, 2 H), 4.12 (d, $J=5.2$ Hz, 4 H), 3.74 (s, 2 H), 3.39 (br. s., 4 H), 1.91 - 1.87 (s, 4 H), 1.78 (br. s., 4 H), 1.63 (br. s., 4 H), 1.37 - 1.50 (m, 4 H), 1.24 - 1.36 (m, 36 H), 1.13 - 1.21 (m, 18

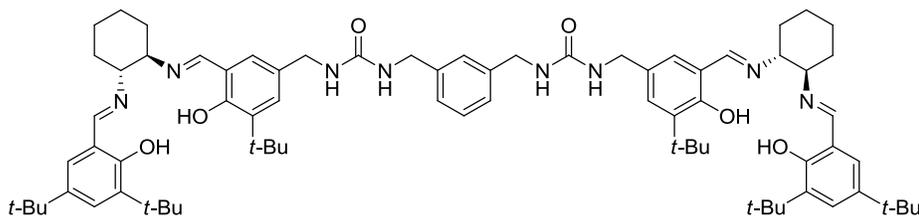
H); ^{13}C NMR (DMSO- d_6 , 75MHz) δ ppm 166.3, 165.9, 158.7, 157.3, 155.0, 139.4, 138.3, 136.2, 135.4, 134.2, 129.2, 128.7, 126.1, 126.1, 117.8, 117.7, 117.5, 71.3, 70.7, 42.4, 34.5, 34.3, 33.7, 32.5, 31.2, 29.2, 29.1, 23.8; HRMS (ESI) calcd for $\text{C}_{81}\text{H}_{108}\text{N}_8\text{O}_6$ $[\text{M}+\text{H}]^+$:1289.8465, found 1289.8491



1,1'-(4,4'-Methylenebis(4,1-phenylene))bis-(urido-salen)cobalt (3.8f) HRMS

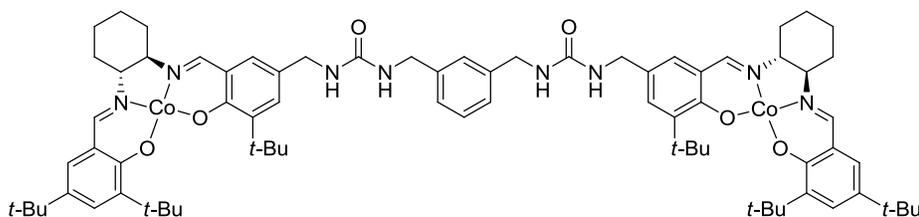
(ESI) calcd for $\text{C}_{81}\text{H}_{104}\text{N}_8\text{O}_6\text{Co}_2$ $[\text{M}]^+$:1402.6731, found 1402.6763; calcd for

$\text{C}_{81}\text{H}_{104}\text{N}_8\text{O}_6\text{Co}_2$ $[\text{M}]^{+2}$:701.3366, found 701.3396



1,1'-(1,3-Phenylenebis(methylene))bis(3-(3-tert-butyl-5-((E)-((1R,2R)-2-((E)-3,5-di-tert-butyl-2-hydroxybenzylideneamino)cyclohexylimino)methyl)-4-hydroxybenzyl)urea) (3.7g) ^1H NMR (DMSO- d_6 , 300MHz) δ ppm 14.05 (s, 2 H), 13.85 (s, 2 H), 8.45 (d, $J=6.6$ Hz, 4 H), 7.21 (d, $J=2.2$ Hz, 2 H), 7.00 - 7.17 (m, 10 H), 6.22 - 6.32 (m, 4 H), 4.16 (d, $J=5.8$ Hz, 4 H), 4.06 (d, $J=5.6$ Hz, 4 H), 3.33 - 3.45 (m, 4 H), 1.87 (d, $J=13.5$ Hz, 4 H), 1.75 (br. s., 4 H), 1.60 (br. s., 4 H), 1.36 - 1.50 (m, 4 H), 1.31 (d, $J=3.5$ Hz, 36 H), 1.17 (s, 18 H) ^{13}C NMR (75 MHz, DMSO- d_6) δ ppm 166.4, 165.9, 158.6, 157.9, 157.4, 140.9, 139.5, 136.1, 135.5, 129.8, 128.47, 128.1, 126.1, 125.8, 125.2, 117.8, 117.5, 71.4, 70.7, 56.1, 42.7, 43.0, 34.5, 34.3, 33.7, 32.6, 32.5, 31.2, 29

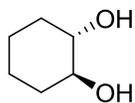
HRMS (ESI) calcd for $C_{76}H_{106}N_8O_6 [M+H]^+$:1227.8308, found 1227.8271; calcd for $C_{76}H_{106}N_8O_6 [M+Na]^+$:1249.8128, found 1249.8135



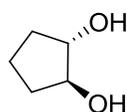
1,1'-(1,3-Phenylenebis(methylene))bis-(urido-salen)cobalt (3.8g) HRMS (ESI) calcd for $C_{76}H_{102}N_8O_6Co_2 [M]^+$:1340.6581, found 1340.6569; calcd for $C_{76}H_{102}N_8O_6Co_2 [M]^+$:670.3288, found 670.3309

General Procedure for the Asymmetric Hydrolysis of Meso Epoxides

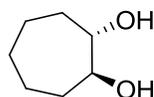
Under air, a 3.0 dram vial was charged with a magnetic stir bar and Co(II)bis-salen catalyst (2.5 μ mol). A solution of TsOH (0.01 M) in THF was added (0.50 mL) and allowed to stir for 1 h. The solvent was then removed under vacuum and to the residue was added epoxide (0.50 mmol), followed by solvent (0.10 ml) and water (0.60 mmol, 11 μ L). The reaction was then allowed to stir for 45h. After the indicated time the reaction mixture was loaded onto a plug of silica gel and sequentially eluted with hexanes/ethyl acetate [10:1 \rightarrow 5:1 \rightarrow 2:1 \rightarrow 1:1 \rightarrow ethyl acetate \rightarrow 1:1 (ethyl acetate/acetone)] to give the desired 1,2-diol. The bis-TFA ester derivative was prepared by adding 0.2 mL TFAA to 5 mg product and allow to stand for 5 min. The volatiles were then removed under vacuum and the residue dissolved in CH_2Cl_2 (2.0 mL). The enantiomeric excess of the bis-TFA ester was then determined by chiral GC (Astec ChiraldexTM G-TA) or chiral HPLC (Chiralcel OJ-H).



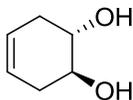
(1S,2S)-Cyclohexane-1,2-diol (3.10) ^1H NMR (300 MHz, CDCl_3 -*d*): δ ppm 3.77 (s, 2 H), 3.35 (br. s., 2 H), 1.91 - 2.02 (m, 2 H), 1.70 (d, $J=2.2$ Hz, 2 H), 1.26 ppm (br. s., 4 H); ^{13}C NMR (75MHz, CDCl_3 -*d*): δ ppm 75.9, 33.1, 24.5 (83% yield, 85% ee)
Enantiomeric excess was determined by chiral GCMS, G-TA, 80 °C, isothermal, t_{R} (minor) = 10.8 min, t_{R} (major) = 14.1 min.



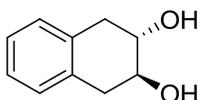
(1S,2S)-cyclopentane-1,2-diol (3.16) ^1H NMR (300 MHz, CDCl_3 -*d*): δ ppm 3.92 - 4.22 (m, 2 H), 3.64 (br. s., 2 H), 1.91 - 2.07 (m, 2 H), 1.71 (m, $J=7.4$ Hz, 2 H), 1.25 - 1.60 (m, 2 H); ^{13}C NMR (75MHz, CDCl_3 -*d*): δ ppm 79.3, 31.3, 19.7 (16% yield, 89% ee)
Enantiomeric excess was determined by chiral GCMS, G-TA, 80 °C, isothermal, t_{R} (minor) = 4.5 min, t_{R} (major) = 5.8 min.



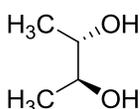
(1S,2S)-cycloheptane-1,2-diol (3.20) ^1H NMR (300 MHz, CDCl_3 -*d*): δ ppm 3.39 - 3.47 (m, 2 H), 3.25 (s, 2 H), 1.82 - 1.92 (m, 2 H), 1.61 - 1.71 (m, 2 H), 1.42 - 1.57 (m, 6 H); ^{13}C NMR (75MHz, CDCl_3 -*d*): δ ppm 78.1, 32.6, 26.6, 22.3 (13% yield, 66% ee)
Enantiomeric excess was determined by chiral GCMS, G-TA, 50 °C - 100 °C, ramp = 1°C/min, t_{R} (minor) = 39.3 min, t_{R} (major) = 41.1 min.



(1S,2S)-cyclohex-4-ene-1,2-diol (3.22) ^1H NMR (300 MHz, Acetone- d_6): δ ppm 5.38 - 5.61 (m, 2 H), 3.98 (br. s., 2 H), 3.45 - 3.66 (m, 2 H), 1.85 - 2.16 (m, 4 H); ^{13}C NMR (75MHz, Acetone- d_6): δ ppm 125.4, 72.2, 34.1, 30.7, 30.4, 30.2, 29.9, 29.7, 29.4, 29.1 (28% yield, 85% ee) Enantiomeric excess was determined by chiral GCMS, G-TA, 80 °C, isothermal, t_{R} (minor) = 8.3 min, t_{R} (major) = 11.0 min.



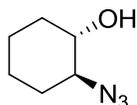
(2S,3S)-1,2,3,4-tetrahydronaphthalene-2,3-diol (3.24) ^1H NMR (300 MHz, Acetone- d_6): δ ppm 7.03 - 7.10 (m, 4 H), 4.13 (s, 2 H), 3.74 - 3.84 (m, 2 H), 3.07 - 3.15 (m, 2 H), 2.66 - 2.77 (m, 2 H); ^{13}C NMR (75MHz, Acetone- d_6): δ ppm 134.7, 128.8, 125.9, 71.4, 36.4 (13% yield, 43% ee) Enantiomeric excess was determined by chiral HPLC, Chiralcel OJ-H (97.0 : 3.0 *n*-hexane:isopropanol, 1.0 mL/min, 254 nm); t_{R} (major) = 19.3 min, t_{R} (minor) = 26.1 min.



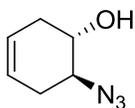
(2S,3S)-butane-2,3-diol (3.26) (12% yield, 64% ee) Enantiomeric excess was determined by chiral GCMS, G-TA, 60 °C - 70 °C, ramp = 0.5°C/min, t_{R} (minor) = 5.1 min, t_{R} (major) = 7.1 min. The diol product mixture was compared to an authentic sample of (2*R*,3*R*)-butane-2,3-diol. The corresponding signals were found to have the same Total Ion Chromatogram (TIC) as the authentic sample.

General Procedure for the Asymmetric Addition of TMSN₃ to Meso Epoxides

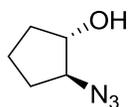
Under air, a 3.0 dram vial was charged with a magnetic stir bar and Co(II)bis-salen catalyst (5.0 μmol). A solution of TsOH (0.02 M) in THF was added (0.50 mL) and allowed to stir for 1 h. The solvent was then removed under vacuum and to the residue was added epoxide (0.50 mmol), followed by solvent (0.10 mL) and mesitylene as an internal standard (10 μL). A 1 μL aliquot was then removed and diluted with Et₂O (0.5 mL) for GCMS analysis. TMSN₃ was then added (0.6 mmol) and the reaction was then allowed to stir for 45h. After the indicated time the reaction mixture diluted with Et₂O (1.0 mL), loaded onto a plug of dry silica gel (1 x 3 cm) and eluted with Et₂O (2 x 5.0 mL). The crude mixture was then analyzed by GCMS to determine substrate conversion versus the internal standard and the enantiomeric excess of the azido-silylether (Astec ChiralDEX™ G-TA). The Et₂O was then removed under vacuum and the residue dissolved in MeOH (1.0 mL). A solution of CSA (0.05 M) was added (0.25 mL) and the mixture was allowed to stir for 30 min. The MeOH was then removed under vacuum and the residue purified on silica gel eluting with hexanes/ethyl acetate (10:1→5:1) to give the desired azidoalcohol.



(1S,2S)-2-azidocyclohexanol (3.27) ¹H NMR (300 MHz, CDCl₃-d): δ ppm 3.28-3.16 (m, 1H), 3.06-2.97 (m, 1H), 1.94-1.79 (m, 3H), 1.66-1.46 (m, 2H), 1.3-0.97 (m, 4H). ¹³C NMR (75MHz, CDCl₃-d): δ 74.0, 67.0, 30.0, 29.5, 24.1, 23.5 (99% conversion, 83% ee) Enantiomeric excess of the azidosilylether determine by chiral GCMS, G-TA, 80 °C, isothermal, t_R (minor) = 24.8 min, t_R (major) = 27.8 min.



(1S,6S)-6-azidocyclohex-3-enol (3.28) ^1H NMR (300 MHz, CDCl_3-d): δ ppm 5.52 (m, 2H), 3.70 (m, 1H), 3.51 (m, 1H), 2.67 (br s, 1H) 2.45 (m, 2H), 2.09 (m, 2H) ^{13}C NMR (75MHz, CDCl_3-d): δ 124.7, 123.6, 63.1, 32.9, 30.0. Enantiomeric excess of the azidosilylether determine by chiral GCMS, G-TA, 75 °C, isothermal, t_R (minor) = 32.7 min, t_R (major) = 35.9 min.



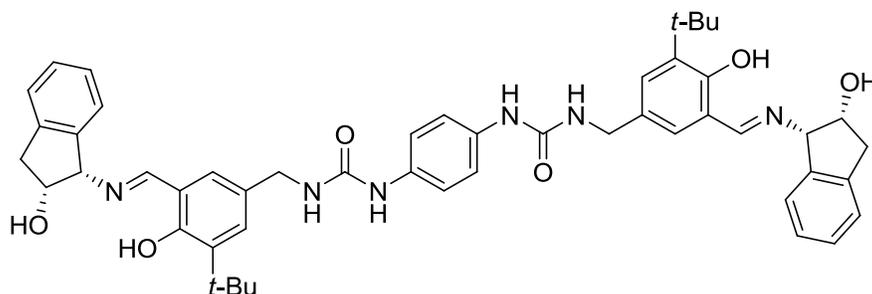
(1S,2S)-2-azidocyclopentanol (3.29) ^1H NMR (300 MHz, CDCl_3-d): δ ppm 4.04 (m, 1H), 3.66 (m, 1H), 2.14 (br s, 1H), 2.10-1.96 (m, 2H), 1.84-1.55 (m, 4H). ^{13}C NMR (75MHz, CDCl_3-d): δ 77.4, 68.5, 33.0, 28.4, 20.3' (99% conversion, 67% ee) Enantiomeric excess of the azidosilylether determine by chiral GCMS, G-TA, 55 °C, isothermal, t_R (minor) = 40.2 min, t_R (major) = 45.9 min.

Synthesis and Characterization of Bis-Urea Tridentate Ligands and Meso Aziridines

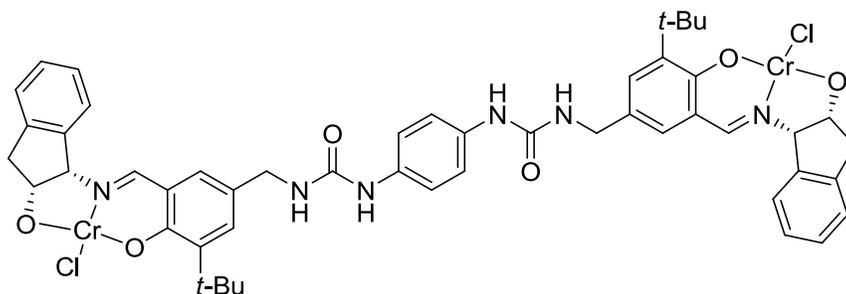
Compounds **3.35** and **3.36** were prepared according to known literature methods. A representative procedure for the synthesis of tridentate ligands, and respective chromium complex is described below.

Dialdehyde **3.6c** (0.104 mg, 0.18 mmol) was suspended in a 1:1 mixture of absolute EtOH and THF (8 mL) and gently warmed at 50°C to dissolve. (1S,2R)-(-)-*cis*-1-Amino-2-indanol (55.5 mg, 0.37 mmol) was then added and allowed to stir for 18h. TLC in 1:1 ethyl acetate/MeOH showed total consumption of starting material. Solvent was then removed under vacuum and the residue was treated with ethyl acetate. The

bright yellow liquid was decanted away from the dark residue then triturated with hexane to give a bright yellow solid (0.135 mg, 90%)

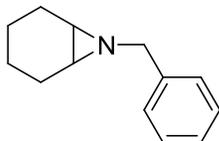


1,1'-(1,4-phenylene)bis(3-(3-tert-butyl-4-hydroxy-5-((*E*)-((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1H-inden-1-ylimino)methyl)benzyl)urea) (3.30) ^1H NMR (300 MHz, DMSO- d_6): δ ppm 14.37 (s, 2 H), 8.67 (s, 2 H), 8.32 (s, 2 H), 7.19 - 7.33 (m, 16 H), 5.24 (d, $J=4.5$ Hz, 2 H), 4.79 (d, $J=5.1$ Hz, 2 H), 4.56 (t, $J=5.0$ Hz, 2 H), 4.22 (d, $J=4.4$ Hz, 4 H), 3.07 - 3.15 (m, 2 H), 2.97 (d, $J=5.7$ Hz, 2 H), 1.76 (br. s., 2 H), 1.35 (s, 18 H); ^{13}C NMR (DMSO- d_6 , 75MHz): δ ppm 166.5, 159.9, 155.4, 142.0, 141.1, 136.6, 134.3, 128.9, 128.8, 128.1, 126.7, 125.1, 124.7, 118.5, 118.0, 73.9, 73.5, 67.0, 42.5, 34.4, 29.2, 25.1

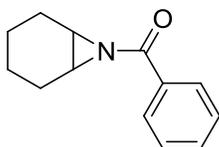


1,1'-(1,4-phenylene)bis-urea tridentate Schiff base(chromium) (3.31c) Under argon, a schlenk flask was charged with CrCl_2 (26.3 mg, 0.21 mmol) then suspended in THF (1.0 mL). Schiff base ligand **3.30c** (85.3 mg, 0.10 mmol) was then added as a solution in THF (1.0 mL) via syringe and allowed to stir for 3h. The reaction was then

exposed to air for 2h then flushed with argon and resealed. 2,6-lutidine was then added (47.5 μ L, 0.40 mmol) and then allowed to stir overnight. MTBE was then added (40 mL) and the green precipitate was collected by vacuum filtration, washing liberally with MTBE. The solid was then dried on high vacuum to give the title compound. (0.117 mg, 99%)



7-benzyl-7-azabicyclo[4.1.0]heptane (3.35) ^1H NMR (CDCl_3 , 300 MHz) δ ppm 7.36-7.19 (m, 5H), 3.46 (s, 2H), 1.87 (m, 2H), 1.75 (m, 2H), 1.61 (m, 2H), 1.45-1.35 (m, 2H), 1.24-1.12 (m, 2H); ^{13}C NMR (CDCl_3 , 75 MHz) δ ppm 140.2, 128.3, 127.5, 126.7, 64.5, 38.6, 24.6, 20.7.



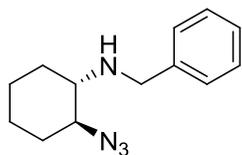
7-azabicyclo[4.1.0]heptan-7-yl(phenyl)methanone (3.36) ^1H NMR (400 MHz, CDCl_3) δ ppm 7.98 (2H, d, $J = 8.0$ Hz), 7.53 (1H, t, $J = 7.3$ Hz), 7.44 (2H, t, $J = 7.6$ Hz), 2.75 (2H, m), 2.11-2.04 (2H, m), 1.94-1.88 (2H, m), 1.58-1.53 (2H, m), 1.37-1.34 (2H, m); ^{13}C NMR (100 MHz, CDCl_3) $\delta = 180.5, 133.9, 132.7, 129.3, 128.6, 37.3, 24.2, 20.2$.

General Procedure for Enantioselective Aziridine Opening

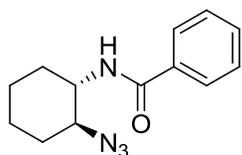
To a screw cap vial was added protected aziridine (0.5 mmol) and bis-tridentate Schiff base Cr(III)Cl complex (25.0 μ mol, 5 mol%). CH_2Cl_2 was then added (0.5 mL) and the mixture allowed to stir for 5 min. TMSN_3 was then added and the mixture was allowed to stir for 20h. The reaction was then diluted with CH_2Cl_2 (0.5 mL) and purified

on silica gel with a mixture of hexanes and ethyl acetate. Enantiomeric ratios were determined by chiral HPLC analysis (Shimadzu) using Chiralpak[®] IA.

Characterization of Ring Opened Products



(1S,2S)-2-azido-N-benzylcyclohexanamine (3.37) ¹H NMR (CDCl₃, 300 MHz) δ ppm 7.42-7.30 (m, 4H), 7.26-7.21 (m, 1H), 3.48 (s, 2H), 1.93-1.85 (m, 2H), 1.83-1.74 (m, 2H), 1.66-1.62 (m, 2H), 1.47-1.37 (m, 2H), 1.26-1.16 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ ppm 139.97, 128.12, 127.33, 126.49, 64.25, 38.43, 24.41, 20.52.



N-((1S,2S)-2-azidocyclohexyl)benzamide (3.38) ¹H NMR (CDCl₃, 300 MHz): δ ppm 7.79 (d, 2H), 7.48 (t, 1H), 7.39 (t, 2H), 6.50 (d, 1H), 3.96 (m, 1H), 3.30 (m, 1H), 2.10 (m, 2H), 1.80 (m, 1H), 1.71 (m, 1H), 1.44 (m, 1H), 1.32 (m, 3H) ppm, ¹³C NMR (100 MHz, CDCl₃) δ ppm 167.4, 134.8, 131.4, 126.9, 63.8, 52.9, 32.0, 30.7, 24.2, 24.1

CHAPTER 4 CONCLUSION

Nitrogen containing chiral ligands have become a cornerstone in asymmetric catalysis. These ligands are prized for their ease of synthesis from a readily available chiral pool, their modularity and their ability to coordinate to a variety of transition metals.

Described in Chapter 2 is the application of a series of chiral isoquinoline-based diimine ligands conveniently prepared through Bischler-Napieralski cyclization. These ligands were originally synthesized as an intermediate to novel tricyclic NHC ligands. The *i*-Bu-substituted, C₂-symmetric diimine ligand **2.1a** was found to be effective in Cu(II)-catalyzed enantioselective Henry reactions between nitromethane and various aldehydes displaying good yields and excellent enantioselectivities. Single crystal X-ray analysis of the Pd(II)Cl₂ complex of the same ligand show a unique helical chirality in addition to the expected planar chirality. The development of these ligands mark a significant addition to the diverse range of chelating *N,N*-donor ligands for asymmetric catalysis.

A synergistic relationship between two (or more) activating metal centers is common in many biological catalysts. The rate and selectivity of transformations mediated by these catalysts are often highly dependent on the cooperative nature of those metal centers within the active site. This observation has prompted significant interest in the development of asymmetric catalysts based on a cooperative relationship between two or more metals. The use of covalent bonds to link two or more metal complexes together has been a well studied and successful approach to cooperative asymmetric catalysis.

Described in Chapter 3 is the development of chiral tri- and tetradentate dimeric Schiff base ligands, designed to self-assemble in solution through hydrogen bonding provided by a bis-urea scaffold. The concept of self-assembly was introduced to create multinuclear transition metal complexes without the need for covalently bound supramolecular structures. Bis-urea, dimeric Co(III)salen catalyst **3.8e** was found to be significantly more efficient in catalyzing the asymmetric hydrolysis of cyclohexene oxide versus the unfunctionalized Co(III)salen catalyst and slightly better than our second generation, monomeric, bis-urea Co(III)salen. From the observation that progressively decreasing catalyst concentrations eroded only the reaction yield and not the enantioselectivity, suggests that a bimetallic mechanism is still in operation, even at low catalyst concentrations, and supports a self-assembled structure that behaves as if the monomers were covalently tethered.

Interestingly, the closely related bis-urea Co(III)salen **3.8d** was found to be an efficient catalyst for the asymmetric addition of TMSN_3 to cyclohexene oxide versus the un-functionalized Co(III)salen catalyst. Thus, the use of an internal bis-urea, dimeric salen scaffold has been demonstrated to be an effective and interesting method to invoke self-assembly in cooperative asymmetric catalysis.

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BIOGRAPHICAL SKETCH

Michael J. Rodig was born at Sinai Hospital in Baltimore, MD. Soon after his birth his family moved farther outside the city to the rural suburb of Westminster, where he spent his formative years with mother Paula, father Charles, and brother Anthony and attended public primary school. After high school he earned his Associates in Arts and Science at a local junior college then enrolled at Salisbury University on Maryland's eastern shore. At Salisbury University he worked in the laboratories of Dr. Miguel Mitchell and Dr. Elizabeth Papish on the synthesis of biologically active compounds and the development of transition metal catalysts for the hydrolysis of phosphotriesters, respectively. He earned his bachelor's degree in chemistry in 2005. At Salisbury, he also met his wife, Jennifer, and they were married a year after his graduation in 2006. Michael started graduate school at the University of Florida the same year, working in the laboratory of Dr. Sukwon Hong developing chiral transition metal catalysts for asymmetric reactions. Michael and Jennifer were blessed with a son, Ryan, in 2010. Michael and his family plan to move back north to begin his post-doctoral study.