

Greener Pastures for Chiral Phosphine Separations

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Abstract

A novel enantioselective liquid-liquid extraction of a water-soluble P-chiral phosphine ligand with a lipophilic Co(III) host was investigated. Two Co(III)Salen host complexes were successfully synthesized to look at the steric effects of groups at the 3 position on the selective binding of the chiral phosphine P(Ph)(Me)($PhSO_3K$). A selectivity study of the host complex with a t-butyl group at the 3 position showed nonpreferential binding of both enantiomers.

Introduction

Now more than ever, chemistry is at the heart of medical advancement. Headway made in organic chemistry and biochemistry fosters progress in pharmacology and the global treatment of disease. While the concept of chirality within organic molecules is not new, our understanding of its role in the context of biological interactions has increased dramatically in last few decades. For many years the pharmaceutical industry ignored seemingly "inert" enantiomers of chiral pharmaceutical drugs because virtually all of the physical properties of the molecule remain unchanged and it is cheaper to synthesize chiral drugs in their racemic mixture. However after several large scandals involving detrimental reactions to the unwanted enantiomer, as in the case of thalidomide and albuterol, the importance of chiral centers could no longer be ignored. The intrinsic chirality in proteins and their active sites causes different enantiomers of the same molecule to have distinct effects. In many cases the unwanted enantiomer can act as an inhibitor to biological pathways causing major health problems. Currently two-thirds of prescription drugs are chiral and new FDA regulations require drug companies to complete medical testing for both enantiomers of any new chiral drug leading to an increase in single enantiomer drugs.[1] However, the search for viable synthetic routes to chiral drug intermediates is hindered by limitations in methodology to selectively synthesize or separate

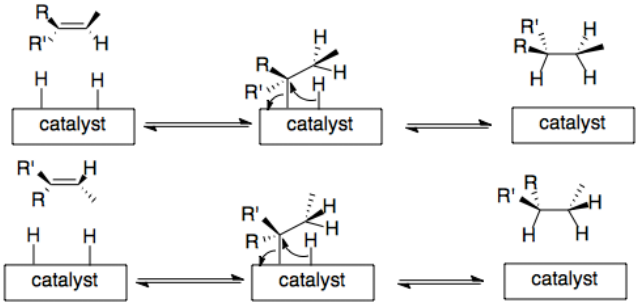


Figure 1 The hydrogenation of an alkene using a heterogeneous metal catalyst showing chemisorbed hydrogen adding across the double bond. The planar geometry and equal probability of addition to either face results in a racemic mixture.

enantiomers on a larger industrial scale.

Many of the synthetic techniques used to form chiral tetrahedral carbon centers cause the formation of two enantiomers in near equal amounts due to the symmetrical nature of trigonal planar carbon reactants (Fig. 1). The chiral resolution of enantiomers via formation of diastereomers is difficult even on a small scale; consequently onerous industrial scale product separation and the loss of experimental yield to the useless racemate can debilitate the practicality of a viable drug. For this reason, the pharmaceutical industry has a vested interest in the development of asymmetric transformations to form enantiopure chiral drug intermediates.

1. Asymmetric Catalysis

The need to synthesize specific enantiomers of target chiral molecules has produced a huge interest in asymmetric catalysis. Asymmetric catalysis is innately cost-effective because of its atom economy. In addition it is logical to mirror nature's own approach to asymmetric transformations, in which enzymes with chiral active sites transfer chirality to prochiral substrates. Synthetic chemists commonly use transition metals as the bases for catalytic complexes because of their ability to donate and accept electrons by moving between oxidation states. In the last half-century phosphine ligands have been recognized as ideal ancillary ligands because of their compatibility with metals in multiple oxidation states and their natural ability to pull electron density out of metal *d* orbitals into the phosphines own unfilled *d* orbitals through π-backbonding.[2] In addition, organophosphorus ligands can be strong π-donors depending on the functional groups attached to the phosphorus, which allows synthetic chemists to tailor ligand electronics to

specific catalytic reactions. Strong-field phosphine ligands with are advantageous for many transition metal catalysts because their increased π-backbonding causes larger *d*-orbital splitting between the T_{2g} and E_g molecular orbitals of octahedral complexes.[3] This can induce diamagnetism in previously highspin metal complexes. Nevertheless, in order for a catalyst to transfer chirality to a substrate it first needs a chiral component.

1.1 P-Chiral Phosphine Ligands

Chirality is commonly associated exclusively with carbon centers. However, because of its trigonal pyramidal geometry and high inversion barrier (30-35 kcal/mol) phosphines can also be chiral and maintain their stereochemistry without risk of steromutation (Fig 2).[4] Early efforts to exploit the sterics of bulky moieties on chiral phosphine ligands to induce asymmetric catalytic transformations concentrated on the development of phosphorus ligands with chirality located on the carbon backbone of the phosphine. The successful production of *L*-DOPA, the chiral drug used to treat Parkinson's disease, using the P-chiral ligand DIPAMP (Fig. 3), developed by Knowles et al. in 1975, ignited general interest in P-chiral phosphorus ligands.[5] It was suggested that by bringing chirality closer to

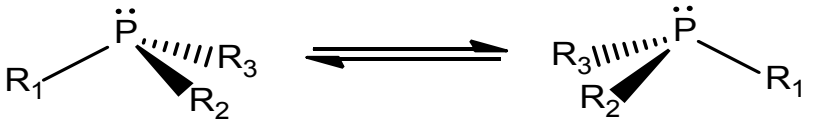
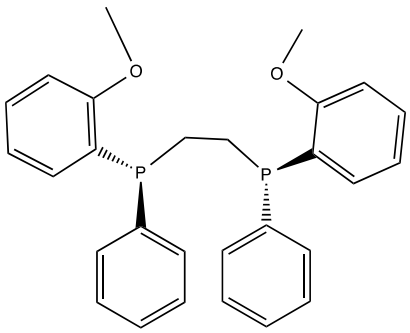


Figure 2 Stereomutation of the phosphine would switch the stereochemistry of the phosphine, effectively negating its chirality.



DIPAMP

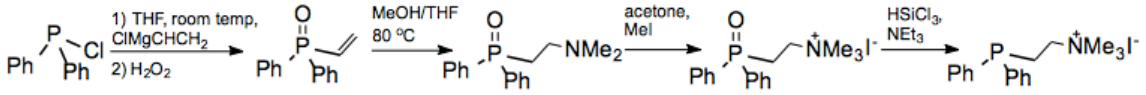
Figure 3 Noyori et al.'s DIPAMP ligand

the metal center, P-chiral phosphines give better enantioselectivity than many of their axially chiral counterparts.[6] Interest in P-stereogenic phosphine ligands waned for many years in favor of axially chiral phosphines because they are easier synthetic targets. Recently developed synthetic strategies for P-chiral phosphines has revived their relevance.[7] Nevertheless, synthetic routes for producing enantiopure P-chiral phosphines are primarily limited to using chiral auxiliaries with fewer examples utilizing resolution or chiral catalysis.

1.2 Water Soluble P-chiral Phosphines

Water is a poor solvent for many organic molecules and can be very reactive with reagents. However, this does not mean its utility in organic chemistry should be overlooked. One of the major deficiencies of homogenous catalysis is the onerous recovery of catalysts.[8] For this reason heterogeneous catalysis, by way of phase transfer in a biphasic system of two immiscible solvents, has received significant attention because of the ease with which the catalyst can be recovered. In this system, a water-soluble catalyst is confined to the aqueous phase of the biphasic system while the substrate remains in the organic phase. By stirring the two phases, the catalyst and substrate can interact in the ensuing emulsification. After some time, the phases will reform with the lipophilic product in the organic phase and the hydrophilic catalyst in aqueous phase. This technique achieves the goal of readily separating the catalyst from the product mixture, although these systems show decreased reaction rates of compared to homogenous catalytic reactions.[9]

Water is an ideal candidate for the organic immiscible solvent because of its high immiscibility with a majority of organic solvents due to hydrogen bonding dipole-dipole interactions and London forces. Additionally, it is environmentally friendly and relatively inexpensive. The major obstacle for this biphasic catalysis technique is the development of water-soluble catalysts. Transition metal catalysts with P-chiral phosphine ligands have been used extensively for homogenous asymmetric transformations in organic media.[10] The hydrophobicity of these complexes is attributed to the bulky and nonpolar phosphine substituents that are necessary for asymmetric induction. In order to alter the solubility of these catalysts in water, a number of groups have successfully introduced ionic ammonium and sulfonate moieties to phosphine ligands.[11] In this manner the attractive ion-dipole interaction will override the entropic cost of having the phosphine's bulky nonpolar moieties in the aqueous phase.



Scheme 1 Synthesis for AMPHOS ligand

Among the growing libraries of water-soluble phosphine ligands, the monodentate AMPHOS ligand has been known for three decades now and has shown similar activities to comparable ligands such as $P(Ph)_3$.[12] This ligand's utility and relatively simple synthesis make it a good candidate for applications in asymmetric transformations in biphasic systems by simply substituting the achiral starting material $P(Ph)_2Cl$ seen in Scheme 1 for chiral PPhMeCl. Relatedly, it's fairly common structure makes it a good standard for evaluating enantioselective extraction mechanisms for chiral phosphines.

2. Introduction to Enantioselective liquid-liquid Extraction (ELLE)

ELLE is a novel approach to chiral resolution that uses the stereoselective recognition of a chiral host-complex to preferentially extract a single enantiomer of a racemic mixture. Originally conceived in the 1960's it has been primarily used to resolve synthetically designed amino acids. An example of this is Verkuijl's group's recent use of a lipophilic host-complex to bind a target water-soluble amino acid racemate at the interface between the feeding phase and transport phase of a biphasic system (Fig. 4). Verkuijl et al. accomplished this chiral separation by use of the axially chiral bidentate phosphorus ligand BINAP coordinated to a Pd metal center. The host complex uses the sterics of BINAP's asymmetrically tilted phenyl moieties to favorably bind D-tryptophan. Once bound, the [Pd(II)Cl((S)-BINAP)(D-Trp)] moves through the stirring organic transport phase and releases the D-Trp by counterion exchange with a chloride ion into the .1M HCl receiving phase (Fig. 5).[13] Verkuijl's group's use of a U-tube apparatus allowed

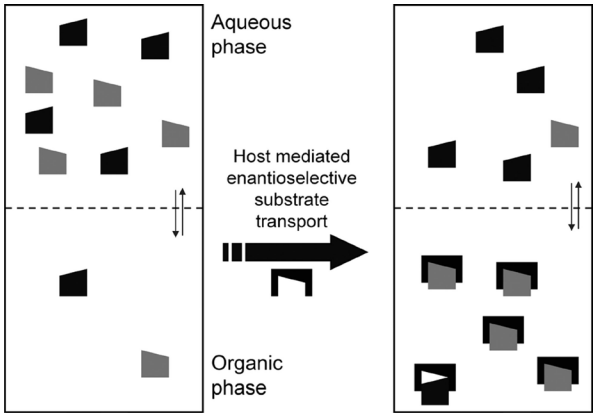


Figure 4 Enantioselective extraction by a chiral host can then be released back into an acidic aqueous phase, regenerating the host complex. (grey symbols) (L)-amino acid; (black symbol) (D)-amino acid; (black rectangle) host. From Verkuijl et al.[13]

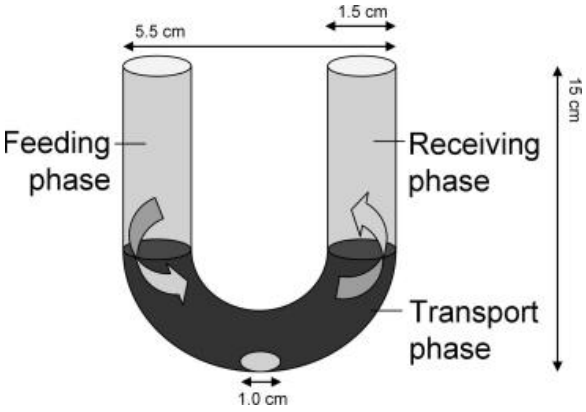


Figure 5 Verkuijl et al. U-tube biphasic system for ELLE allows for catalytic extraction of amino acids by including an acidic receiving phase to collect extracted D-Trp. From Verkuijl et al.[13]

them to run the separation with catalytic amounts of the host complex. The host complex was able to extract 4 equiv of Trp before enantioselectivity fell below 30%.

Verkuijl's group's work is a good example of ELLE because it highlights the important factors that control chiral separation: chiral recognition by the host when coordinating the guest and the extraction mechanism. Chiral recognition in the host-guest interaction is obviously critical to chiral separation. However, there must be a cooperative relationship between the intermolecular attraction of the host complex and the manner in which it recognizes chirality. The major intermolecular attractions include covalent bonding, ion pairing, hydrogen bonding, π-π interactions and dipole-dipole interactions.[14] These attractive relationships must be paired with either steric or electronic interactions, or a combination of the two, to cause favorable binding to the host complex of one enantiomer over the other.[15]

2.1 Chiral Recognition

A good example of this cooperative relationship and rational ligand design is the N-type ligand developed by Chin et al (Fig. 6A).[16] When coordinated to cobalt it forms a rigid octahedral complex due to its rigid pyridine backbone and four

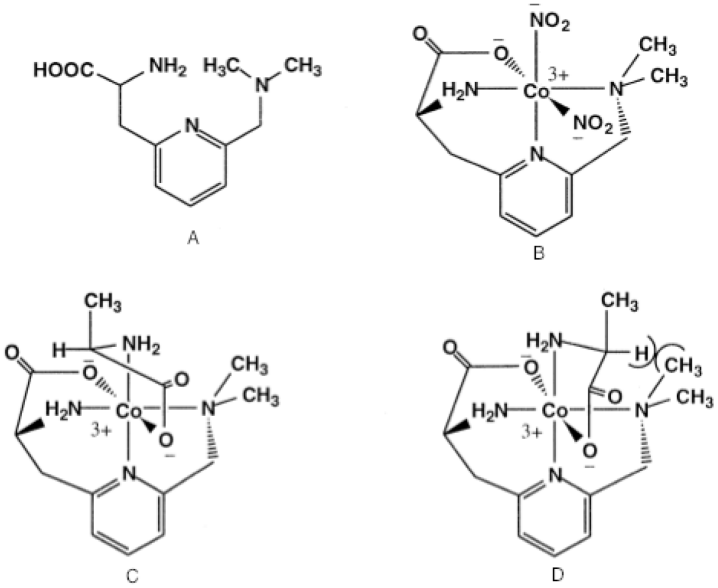


Figure 6 Chin et al's N-type ligand (A), Co(III) complex (B) and the complex binding with both alanine enantiomers (C,D) with sterics shown to indicate the disfavored coordination of the L enantiomer. From Chin et al.[16]

chelating groups. When considering the chiral recognition of one alanine enantiomer, there are two factors to consider, regioselectivity and stereoselectivity. Regioselectivity is important because of the bidentate nature of amino acids coordinating to metals. This means there are two conformations in which amino acids can bind with the metal. Chin et al's group used the electrostatic tendency of carboxylate groups to bind *trans* to each other to allow for regioselective binding of alanine to the metal (Fig. 6A and 6B).[16]

This regioselective binding of amino acids allows for meaningful tailoring of stereoselective features of the ligand since both enantiomers will coordinate in the same fashion. Consequently, the formation of a five membered metallocycle, formed by the amino acid and metal, will force the residues to arrange themselves in the equatorial position and prevent steric congestion with the N-ligand's coordinating appendages. This makes steric recognition between the ligand and the positioning of the axial α-H conceivable. This manner of recognition is particularly desirable because the α-H is a fundamental component of every amino acid and stereoselective binding based on its positioning makes this recognition potentially applicable to a vast array of amino acids. For this reason Chin's group used a chelating amine with bulky methyl groups to make the coordination of L-alanine sterically unfavorable (Fig. 6D). Chin et al's Co(III) N-type complex successfully uses a cooperative combination of covalent bonding and steric interactions to achieve stereoselective coordination.

2.2 Separation

Chiral recognition is critical to any enantioselective separation. However, there must be an effective extraction mechanism in place to make it functional. There are two common extraction mechanisms for biphasic systems by which a lipophilic host can bind substrates in ELLE. The first is an interfacial reaction model in which the guest is insoluble in the organic phase and must coordinate to the host complex at the interface of the two phases (Fig. 7).[17] This is common in ion-exchange mechanisms, wherein an ionic ligand transfer occurs between the host and aqueous phase to balance the charge of the

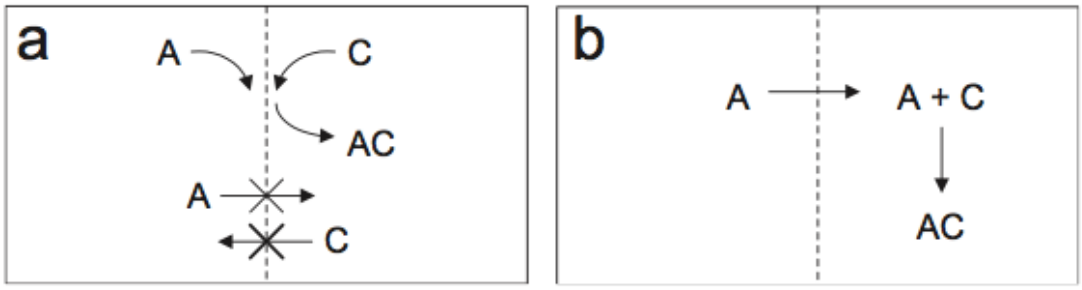


Figure 7 Two common models of biphasic host-guest extraction. (a) interfacial (heterogeneous) model and (b) homogenous model.

complex.[15] Depending on the partition coefficient of the guest complex involved in the separation, a second model can arise. In this model either the host or the guest is soluble in both the aqueous and organic phase. This case is more commonly associated with gas-liquid reactions with gas adsorption to aqueous hosts. The kinetics of this extraction are partially dependent on the partition coefficient of the guest because that will determine the concentration of guest in the organic layer. However, the lability of the transition metal core of the host complex will also play a large role. Low spin Co^{3+} is usually an inert metal center that will form strong, stable ligand bonds because of its unpopulated T_{2g} antibonding molecular orbital. However, by utilizing a strong trans-affecting ligand in the axial position of a square-planar Co^{3+} you can change the lability of the metal and tune the kinetics of guest coordination in the vacant trans coordination site.

The AMPHOS guest complex (Scheme 1 pg. 5) has a long tail with a charged ammonium group on it. The favorable ion-dipole interactions of this group with polar solvents are what make this ligand water-soluble. These IMF's are strong enough to override the entropic cost of keeping the large nonpolar aryl groups located on the phosphine in an aqueous solution. Consequently, this ligand is a very attractive candidate for interfacial separations. The guest may be able to bridge the interface of the two phases keeping its charge tale in the aqueous phase while exposing the hydrophobic end of the phosine to the organic phase. Steensma et al looked at varying interfacial area and stirring rate to both elucidate extraction mechanisms and optimize extraction kinetics.[18] These represent two more factors to be considered in developing a viable chiral extraction technique. Advancement in the comprehension of the mechanisms at work in chiral extraction, ultimately allows for the translation of this technique to extract non amino acid targets.

3. Rational ELLE for P-Chiral Phosphines

Enantioselective binding of amino acids by a wide variety of host complexes has been well documented over the years. Among these amino acid ELLE host complex motifs, there are multiple candidates that are conceivably comparable to chiral phosphine guest binding. The first step in narrowing down the field of host complexes is recognizing that organometallic complexes represent a compelling starting point because of phosphines' strong binding affinity for transition metals and the extant capacity to adjust a variety of factors including metal size, charge, lability and d orbital splitting by coordinating strong or weak field ligands.

Amino acids typically coordinate to metal centers in a bidentate nature. Consequently the majority of ELLE organometallic host complexes developed to date incorporate tridentate or tetradentate ligands to form enantiopure octahedral complexes with bidentate amino acids. Of these, several Co(III)-Salen complexes have shown excellent enantioselectivity in ELLE models.[19] Recently, Kim et al. developed at Co(III) Salen complex that utilizes a quinoline group attached to the chiral diamine backbone to construct a five coordinate species which elicits monodentate coordination from it's target amino acid enantiomer (Fig. 8).[20] They were able to demonstrate increased stereospecific recognition generated by a bulky nitrophenyl substituent axial to the chiral diamine backbone.

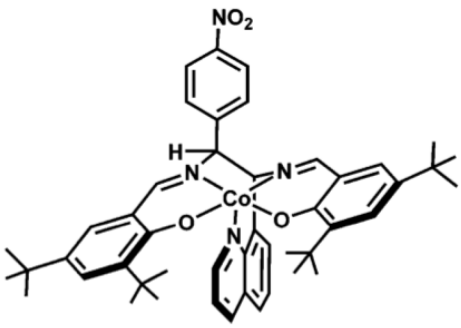


Figure 8 Kim et al's five coordinate Co(III)-Salen ligand with a chelating quinoline group and bulky nitrophenyl group in the axial positions of the chiral diamine backbone. From Kim et al.[20]

This development is of particular interest when considering Salen complexes for phosphine ELLE because the correct positioning of bulky groups provides the sterics necessary for chiral recognition. Tetradentate Salen ligands prefer a pseudo-planar, *mer*, configuration when forming four-coordinate complexes with cobalt.[21] However, Carrol et al showed that Salen ligands can adopt a helical conformation when a bidentate ligand forces one of the salen's chelating oxygens

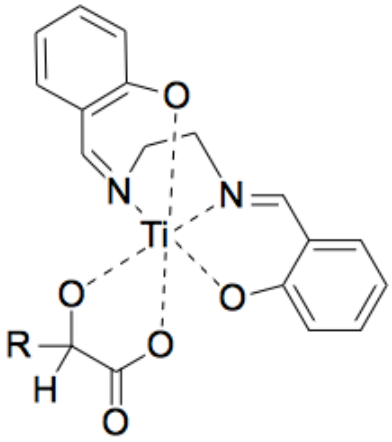


Figure 9 Carrol et al's octrahedral Ti complex with the salen ligand in its helical conformation due to the coordination of a bidentate amino alcohol. From Carrol et al.[22]

out of its equatorial position into a *fac* geometry (Fig. 9).[22] This means that utilizing the sterics of a particular bulky group to govern chiral recognition in the helical conformation

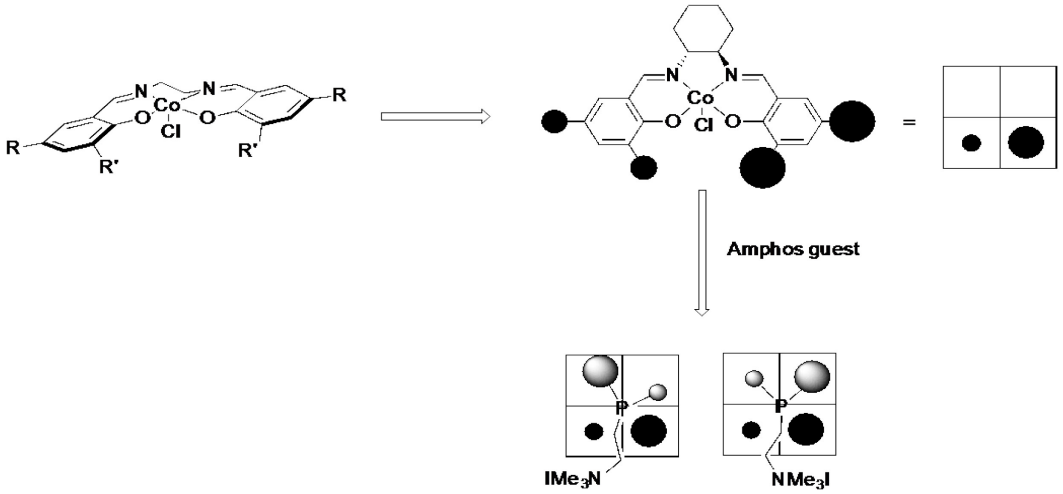


Figure 10 The host complex is not completely planar because of the trans nature of the cyclohexyldiamine backbone. This causes a tilt of the R and R' groups on either side and in conjunction with fixed carbon stereocenters should allow this chiral host to selectively bind the left guest AMPHOS enantiomer as shown in the quadrant diagram.

may not be applicable to achieving enantioselectivity in the pseudo-planar conformation. The high enantioselectivities achieved by Kim et al's ligand when extracting bulky amino alcohols demonstrates the close proximity of the nitrophenyl group to the vacant coordination site of the amino alcohol when the salen ligand is in the pseudo-planar conformation. Consequently, the axial positions on the diamine backbone represent attractive sites for the addition of bulky substituents to govern the chiral recognition of monodentate phosphine ligands. Conversely, Co(III)-salen ligands have shown excellent enantioselectivities and activities with bulky substituents in the 3 and 5 positions for a number of asymmetric transformations as well as in ELLE.[19,23] The *trans* nature of the chiral diamine backbone causes an asymmetric tilt of the ligand's aryl groups so that the right aryl group tilts into the plane of the vacant axial site on the metal. Figure 10 shows a postulated schematic of how bulky substituents in the *ortho* and *para*

positions would interact with the Co(III)'s axial vacant coordination site. The quadrant diagrams demonstrate how one or both of the aryl substituents might interact with a chiral AMPHOS ligand guest to preferentially bind the enantiomer on the left.

To implement the use of a Co(III)-Salen host in an ELLE scenario for chiral phosphines, a catalytic release of the guest complex must be realized. To accomplish this, previous groups have used an acidic receiving phase, which is ideal for an ionic exchange of amino acids between phases. While phosphine is a neutral ligand and will probably not participate in an ion exchange, an acidic receiving phase could help promote the disassociation of the phosphine from the host complex once it reaches the interface.

The purpose of my senior composition is to investigate the impact of the sterics produced by substituents in the 3' ortho positions of the salen ligand on the selectivity of Co(III)-salen host complexes in ELLE systems. By developing a library of salen ligands with varying degrees of steric bulk at the R' position in Figure 11, it will be possible to determine the role of this group in the chiral recognition of chiral AMPHOS guests by the resulting Co(III)salen host complexes. Binding selectivity of these complexes will be measured by ^{31}P NMR spectroscopy. The project has a great capacity to grow as the role of the X-type ligand and its ability to govern the strength of the P-Co bond is investigated. This X-type ligand could possible be substituted for a neutral PMe_3 ligand to increase the *trans* effect and facilitate guest release.

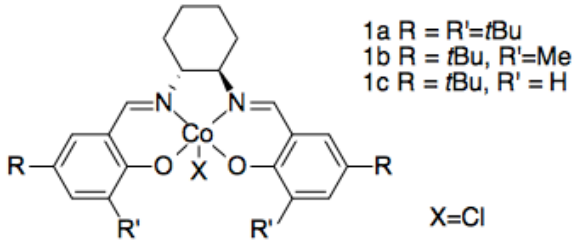
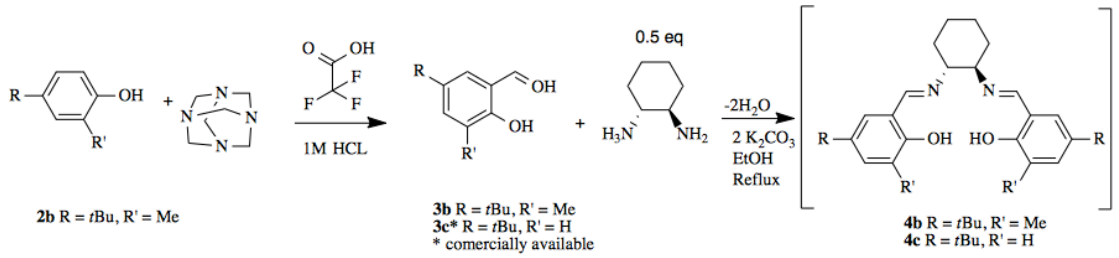


Figure 11 Target Co(III)SalenCl host complexes with varying steric bulk at the R' group.

Results and Discussion

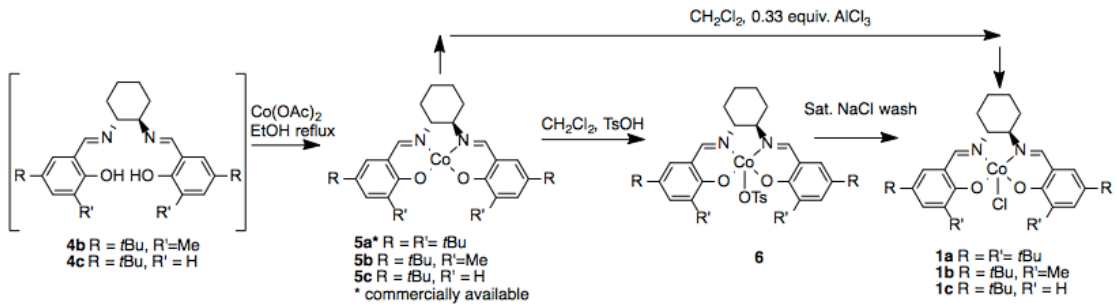
Synthesis of Salen Ligands and Host Complexes

Two Salen ligands with different R' groups were synthesized (Scheme 2). ^{1}H NMR spectra for ligands **4a, 4b** and the salicylic aldehyde **3b** were matched to the



Scheme 2 Synthesis of Salen ligands with varying steric bulk at R' position.

published values. These ligands were then metallated with Co(II)acetate to give **5a-c**. The paramagnetic nature of d7 Co(II) makes characterization by ^{1}H NMR difficult, so coordination of the Salen ligand was confirmed by published IR values. However, presence of unbound ligand was later confirmed by HPLC-MS. Possible exposure to ambient air oxidized **5c**, causing it to form a nonhomogenous black mixture that was insoluble in $CHCl_2$ and could not be



Scheme 3 Metallation of Salen ligands and subsequent oxidation to Co^{3+} and coordination of chloride ligand.

recrystallized. Oxidation of Co(II) complex **5a** and coordination of the chloride was

achieved by two methods, the oxidative addition of a tosylate ligand and replacement with a chloride and also a direct oxidation with aluminum chloride.

Initial attempts to characterize the host complexes by HPLC-MS failed because of the large cobalt complexes ability to stick to the silica in the column. A novel mobile phase was developed and used with a C18 reverse-phase column. By utilizing a high concentration of acetic acid in an acetonitrile mobile phase we were able to elute the Co(III)SalenCl complexes and confirm them by there molecular weights with the mass spectrometer.

Inducing Diamagnetism in Co(III) Host Complex

Once oxidized the Co(III) host complexes all showed paramagnetism in their ^{1}H NMR spectra. This paramagnetism remained after further attempts to oxidize the host complexes. In this square pyramidal geometry, it was assumed that the π-donation from

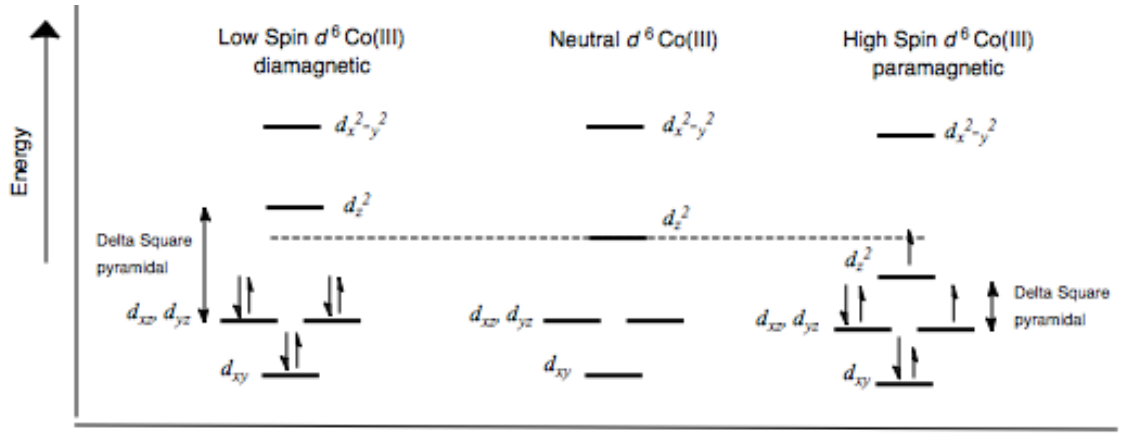
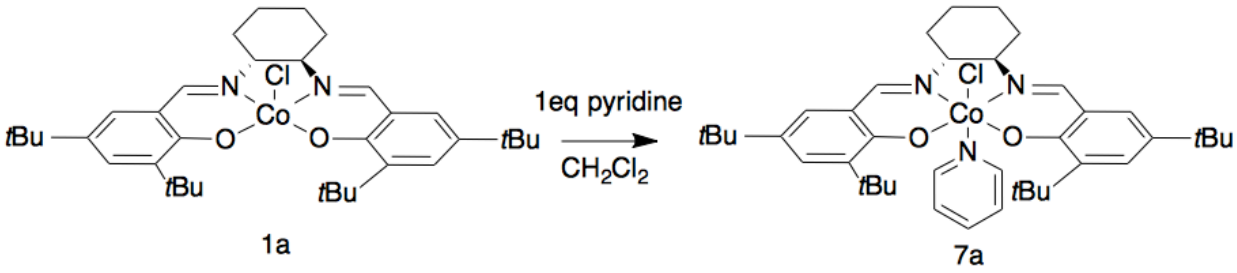


Figure 32 High spin and low spin D orbital splitting of d⁶ Co(III) in the square pyramidal conformation.

the chloride ligand should move the d_z^2 orbital high enough in energy that the d^6 Co(III) would transition to low spin and populate the lower atomic orbitals first, leading at a low-spin diamagnetic Co(III) (Fig 12). Kemper et al. reported paramagneticism in complex

utilizes **1a** and used the strongly coordinating solvent pyridine to elicit diamagnetism in the Co(III)SalenCl complex [24]. Coordinating a good π-acceptor such as pyridine will shift the complex to an octahedral conformation, altering the energies of the complexes *d*-orbitals (Fig. 13). Metal-to-ligand π-backbonding with strong-field ligands lowers the energy of the HOMO t_{2g} molecular orbital. Consequently one equivalence of pyridine was introduced to a solution of **1a** in a noncoordinating solvent (Scheme 4). Paramagnetic signals were resolved slightly but not enough to obtain meaningful ^{1}H NMR spectra. This possible signifies to the presence of unoxidized d^7 Co(II) in the reaction mixture.



Scheme 4 Coordination of pyridine to square pyramidal 1a to form octahedral complex 7a.

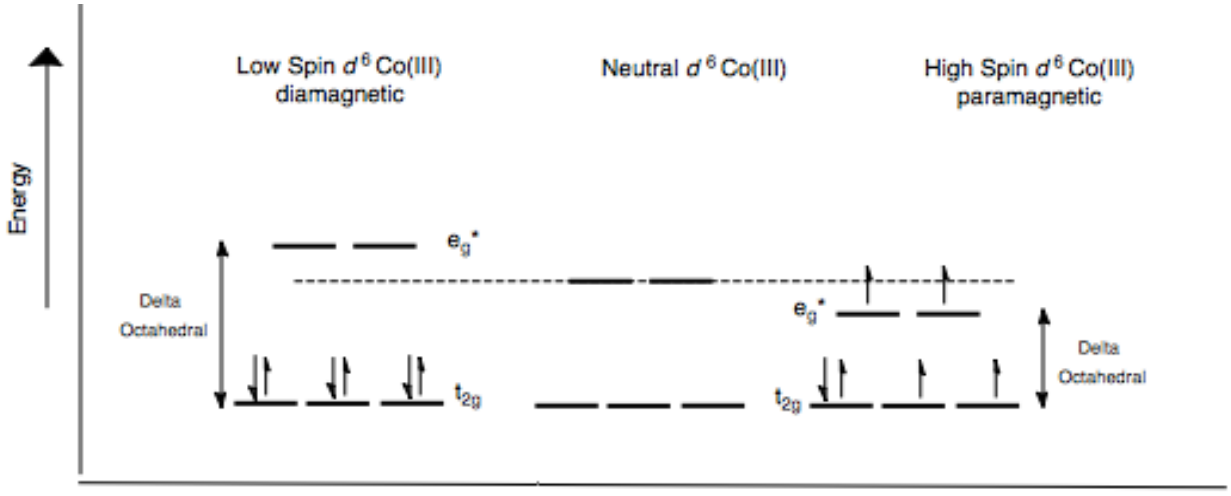
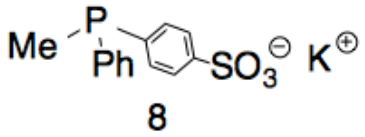


Figure 13 D orbital splitting for transition metal octahedral complexes. High spin d6 transition metals result in paramegnetism, while low spin results in diamagnetism. Strong field π-acceptor ligands will increase the Δ octahedral by lowering the t_{2g} molecular orbital in energy.

Host Enantioselectivity Study

An enantioselectivity study was begun with host complex **7a**. The host complex **7a** (0.006 mmol) was combined with a racemic mixture of the water-soluble chiral phosphine **8 (**2.5 eq) in CH_2Cl_2. ^{31}P NMR showed a large peak at 2.98ppm with a possible second finely split peak at 2.55ppm. The peak for noncomplexed **8** at -27ppm was not present, however may have been diminished by the presence of paramagnetic Co(II). The absence of a free phosphine peak suggests the nonselective binding of both chiral phosphine enantiomers. . The possible second peak of equal magnitude potentially indicates the disassociation of the chloride ligand and the binding of two phosphines to each host complex *trans* to each other.



8

Figure 4 5 Chiral water-soluble phosphine ligand used in enantioselectivity study. Prepared by M Reik.

Conclusion

The enantioselective binding of only one of the three host complexes was assessed. However, because host complex **1a** had the most steric bulk at the R' position this could possibly indicate that the positioning of the R' group does not have a sterioselective effect on the binding of chiral phosphine ligands at the open coordination site. Although complete oxidation of the Co(III) complexes was not achieved, a successful protocol for characterization by reverse-phase HPLC-MS was developed to facilitate future work with paramagnetic cobalt Salen complexes.

Future Work

Moving forward it would be advantageous to develop a host synthesis that started with pure Co(III). There is the possibility that putting even bulkier groups, such as mesityl functionalities, at the R' position might elicit preferential binding of one guest enantiomer. However, it may be more advantageous to look at putting *t*-butyl groups in the axial positions of the diamine backbone.

Experimental

General Experimental Information

^{1}H NMR, ^{13}C NMR and ^{31}P NMR spectra were recorded using an Ellipse 400MHz spectrometer. Flash column chromatography was performed using silica gel (60 μM). All hexanes were distilled prior to use in columns. All chemical reagents were obtained from Acros, or Sigma Aldrich.

Combined HPRPLC mass spectrometric analysis was performed using an Agilent Technologies 6110 Quadropole LC/MS with a Phenomenex Hyperclone 5 micron ODS C18 column. Flow rate was 1mL/min with a mobile phase of acetonitrile with 1% by vol. glacial acetic acid (17M) and 0.05% by vol. triethylamine. Eluted components were monitored spectrophotometrically at 250 nm.

5-*tert*-Butyl-2-hydroxy-3-methylbenzaldehyde.[25], 3b

Hexamethylenetetramine (10.67g, 75mmol) and 4-*tert*-butyl-2-methylphenol (2.5g, 15mmol) were added to a 100mL round-bottom flask and dissolved in trifluoroacetic acid (30 ml). The mixture was heated to 90℃ and stirred for 18 h under reflux. The mixture was poured still hot into 1 M HCl (200 ml), stirred for 6 h and extracted with CH_2Cl_2 (3 x 50 ml). The combined organic phases were washed with water, dried over $MgSO_4$ and the solvent removed under reduced pressure. 1g of the sticky yellow solid was purified by flash column chromatography (25% ethyl acetate in hexane eluent) to yield a pale yellow solid (805mg, 80%). 1H NMR (250 MHz, $CDCl_3$): δ=11.02 (s, 1H, O*H*), 9.79 (s, 1H, C*H*O), 7.37 (s, 1H, Ar*H*), 7.28 (s, 1H, Ar*H*), 2.20 (s, 3H, CH_3), 1.24 (s, 9H, C(CH_3)$_3$.

(R,R)-N,N 7-Bis(5-tert -butyl-salicylidene)-1,2-cyclohexanediamine[26], 4c

(R,R)-1,2-diaminocyclohexane (320mg, 2.81mmol) and potassium carbonate (783mg, 5.62mmol) were added to a oven-dried 100mL round-bottom flask and dissolved in DI water (4mL). The solution was stirred until dissolution and then 13 mL of ethanol was added. The resulting mixture was heated to 65°C and refluxed for 30min. 5-tert-Butyl-2-hydroxybenzaldehyde (1g, 5.62mmol) was added dropwise over a period of 10 minutes, a vibrant yellow precipitate was seen immediately. The resulting mixture was vigorously stirred over 3h and then cooled to room temperature. The product was collected by filtration and washed with cold ethanol. The solid product was redissolved in 10mL of CH_2Cl_2 and washed with water (3x, 5mL) and brine (7mL). After drying over Mg_2SO_4, the solvent was removed under vacuum, and the product was isolated as a yellow powder (84% yield). ^{1}H NMR ($CDCl_3$): δ 8.25 (s, 2H), 7.27 (dd, J=2.5 Hz, 8.7 Hz, 2H), 7.12 (s, 2H), 6.82 (d, J=8.7 Hz, 2H), 3.30–3.28 (m, 2H), 1.9–1.4 (m, 8H), 1.23 (s, 18H)

(1R,2R)-N,N'-Bis(5-tert-butyl-3-methysalicylidene)-1,2-cyclohexanediamine[27], 4b

A 250-mL round-bottom flask was charged with (R,R)-1,2-diaminocyclohexane (237mg, 2.08mmol), K_2CO_3 (575mg, 4.16 mmol) and H_2O (8 mL). The mixture was stirred to dissolve the solids, then EtOH (15 mL) was added and the yellow suspension was heated to 65 °C for 30 min. A solution of 2- hydroxy-3-methyl-benzaldehyde (805mg, 4.16mmol) in EtOH (5 mL) was added dropwise over 15 min. The mixture was refluxed at 65 °C for 3 h, then cooled to room temperature. The resulting yellow precipitate was collected by filtration and washed with cold EtOH. The solid was dissolved in CH_2Cl_2 (20 mL) and washed with H_2O (2 x 15mL) and brine (7mL) then the organic phase was dried with Mg_2SO_4 and solvent was removed under reduced pressure to give the product

as a yellow oil, which solidified and was then recrystallized (CH_2Cl_2/ethanol) (yield 52%).

(*R,R*)-(salen)Co(II) 5b

(1R,2R)-N,N'-Bis(5-tert-butyl-3-methysalicylidene)-1,2-cyclohexanediamine (100mg, .216mmol) and Co(II) acetate (38mg, .216mmol) were added to a 100mL ampule under inert atmosphere. This mixture was dissolved in distilled anhydrous ethanol (8mL). The reaction was heated to 70°C and refluxed under N_2 for 24 hours. A dark red precipitate was formed. The product was then filtered off and washed with cold ethanol. It was then recrystallized in CH_2Cl_2/hexanes.

(*R,R*)-(salen)Co(II) 5c

(R,R)-N,N 7-Bis(5-tert -butyl-salicylidene)-1,2-cyclohexanediamine (964mg, 2.22mmol) and Co(II) acetate (392mg, 2.22mmol) were added to a 100mL ampule. This mixture was dissolved in distilled anhydrous ethanol (25mL). The reaction was heated to 70°C and refluxed under N_2 for 24 hours. A red precipitate was formed. The product was then filtered off and washed with cold ethanol. The product failed to recrystallize in CH_2Cl_2/hexanes and when the solvent was removed the complex was exposed to oxygen and formed a nonhomogenous black mixture.

Co(III) (*R,R*)-(salen)Cl 1a, 1b[28]

To a 20-mL reaction vial was added (*R,R*)-(salen)Co(II)**5a** (200mg, .332mmol) and $AlCl_3$ (15mg, 0.111mmol) and dissolved in CH_2Cl_2 (4mL). The reaction was stirred vigorously at rt for 24h open to ambient atmosphere. 4mL of CH_2Cl_2 was added twice due to solvent evaporation (crude yield 98%).

Co(III) (*R,R*)-(salen)Cl 1a

To a 20-mL reaction vial was added (*R,R*)-(salen)Co(II)**5a** (200mg, .332mmol) and p-toluenesulfonic acid monohydrate (63mg, .332mmol). The mixture was dissolved in 10mL CH_2Cl_2 and the reaction was stirred vigorously for 24 hours open to ambient atmosphere and then washed with concentrated brine (3x, 10mL). The organic phase was collected and solvent was removed under vacuum (crude yield 99%).

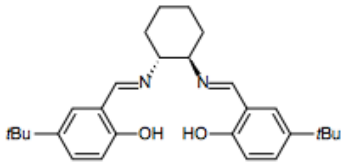
Co(III) (*R,R*)-(salen)pyridineCl[24] **7a**

To 20-mL reaction vial was added **1a** (68mg, 0.106mmol) and dissolved in 12mL of $CDCl_3$. The mixture was stirred open to the air for 10 min until the solute had dissolved. 8.6μL of pyridine (0.106mmol) was added to the mixture drop wise by gas tight syringe. The solution was stirred for 20 min and ^1H NMR was taken directly from reaction mixture.

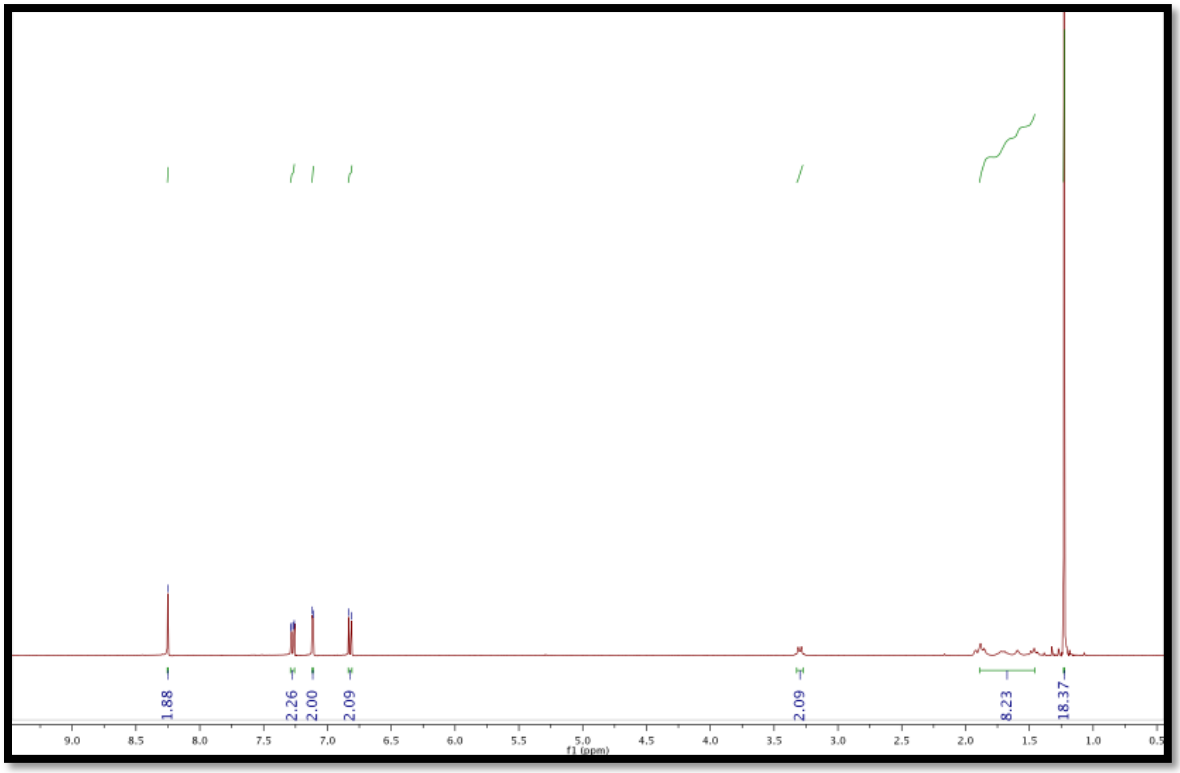
Selectivity Study for 7a

The selectivity study was adapted from Dzygiel et al. In the glove box 5mg (0.006mmol) of the host **7a** was added to an NMR tube and dissolved in 1mL of CH_2Cl_2. 4.5mg (2.5

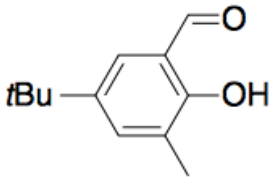
eq) of phosphorus guest was added to the NMR tube. The mixture was left under N_2 for 48 h and ^{31}P NMR was taken.

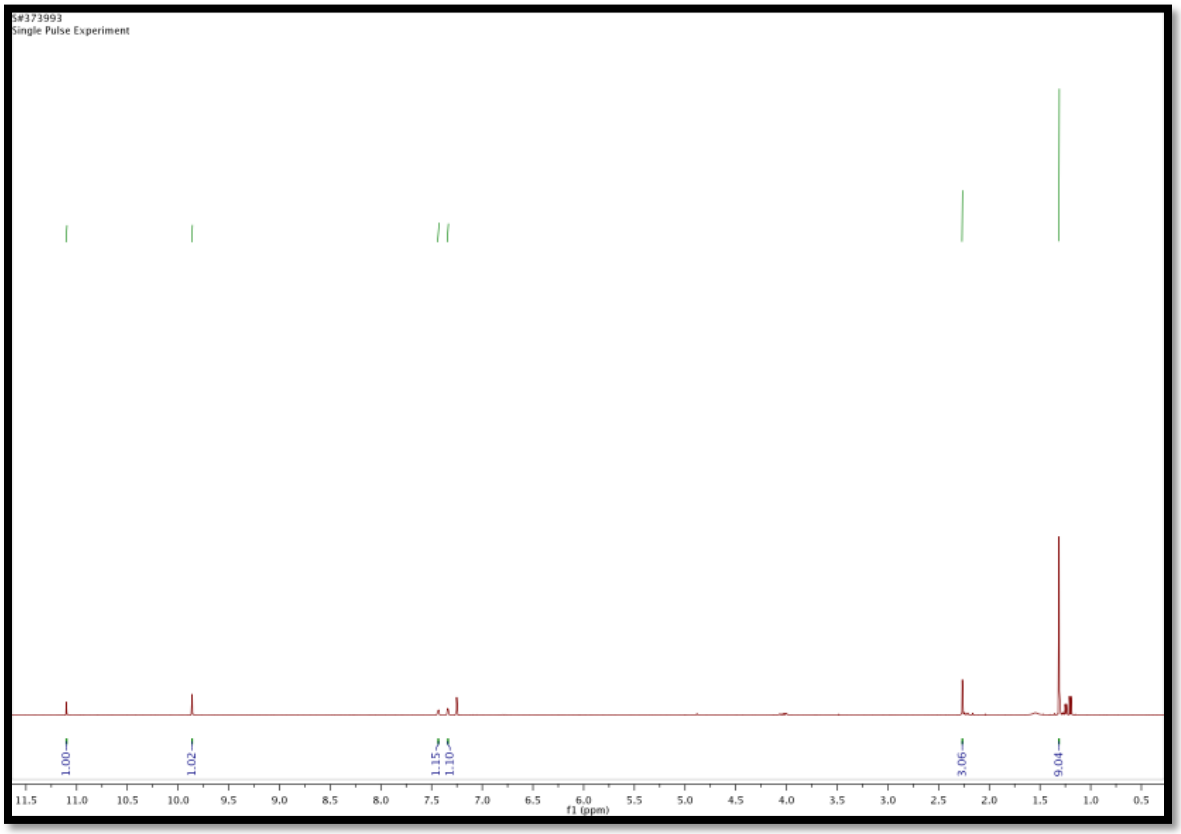


^{1}H NMR ($CDCl_3$)

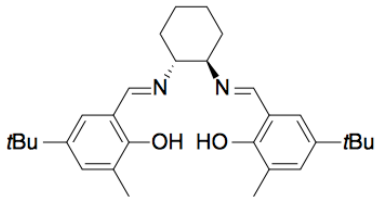


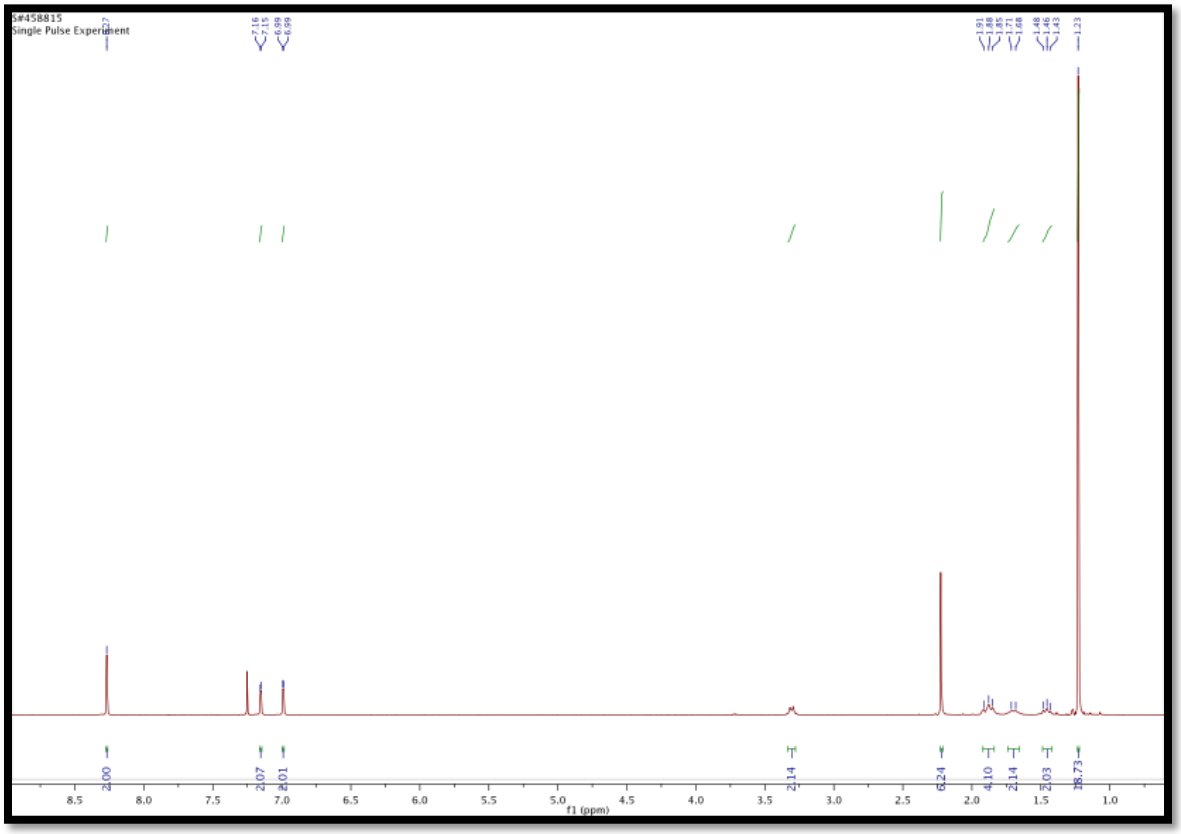
^{1}H NMR ($CDCl_3$)


O
tBu
OH

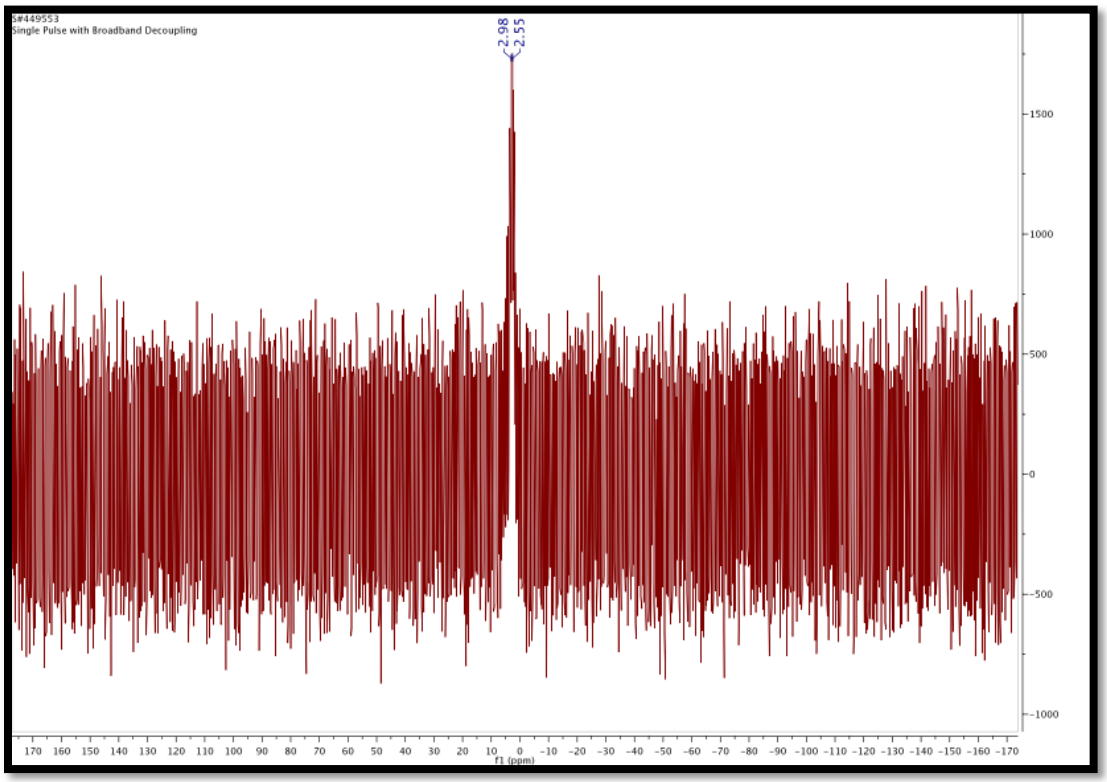

S#373993
Single Pulse Experiment
1.00
1.02
1.15
1.10
3.06
9.04
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

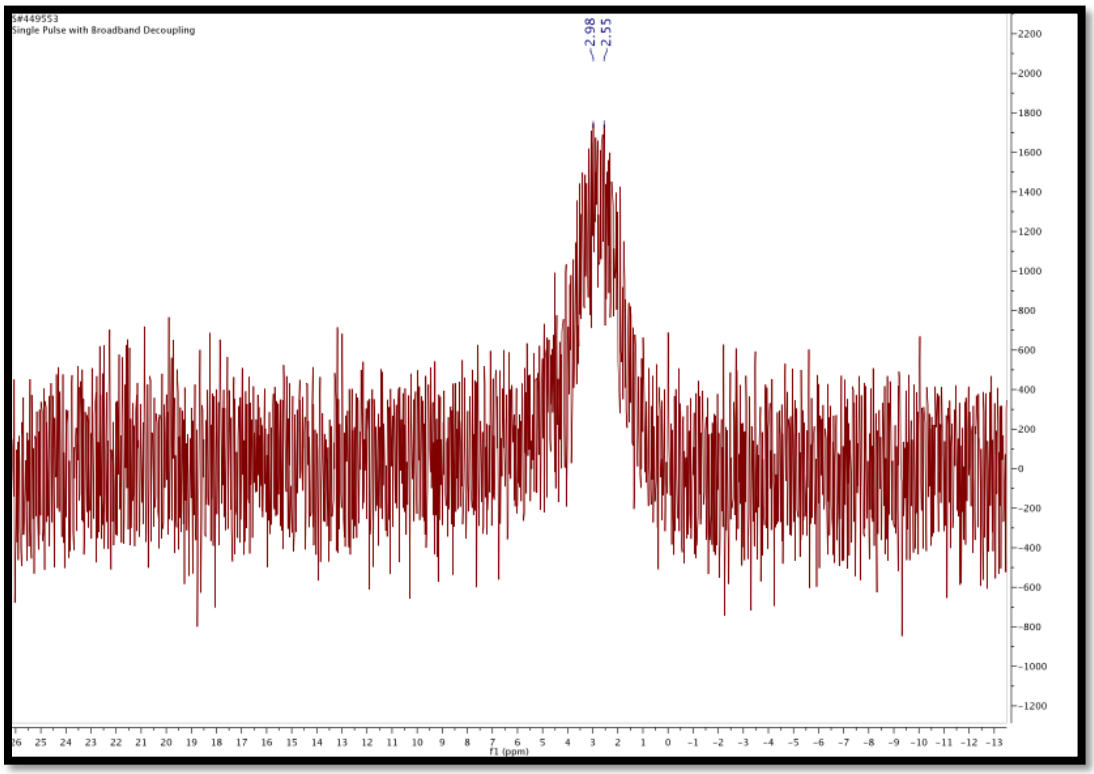
^{1}H NMR ($CDCl_3$)



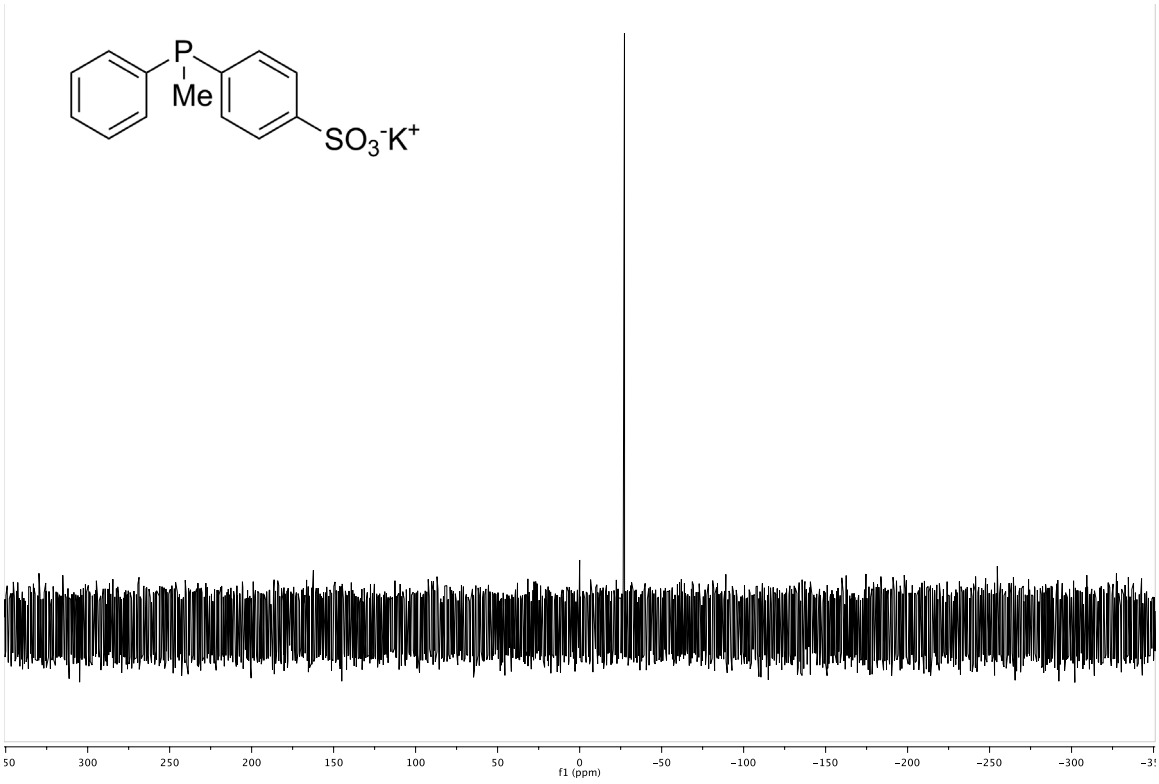


^{31}P NMR CH_2Cl_2 Selectivity Study





^{31}P NMR (DMSO-D6)



Works Cited

(1) Bommarius, A. S.; Schwarm, M.; Drauz, K. Biocatalysis to Amino Acid-Based Chiral Pharmaceuticals—Examples and Perspectives. *Journal of Molecular Catalysis B: Enzymatic* **1998**, *5*, 1–11.

(2) Dutta, S. Phosphine Supported Metal-Dihydrogen Complexes: Elongation of H−H Bond to Reversible Release of H2. *Comptes Rendus Chimie* **2011**, *14*, 1029–1053.

(3) Crabtree, R. H. NHC Ligands Versus Cyclopentadienyls and Phosphines as Spectator Ligands in Organometallic Catalysis. *Journal of Organometallic Chemistry* **2005**.

(4) Baechler, R. D.; Mislow, K. Effect of Structure on the Rate of Pyramidal Inversion of Acyclic Phosphines. *Journal of the American Chemical ...* **1970**.

(5) Imamoto, T.; Tamura, K.; Zhang, Z.; Horiuchi, Y.; Sugiya, M.; Yoshida, K.; Yanagisawa, A.; Gridnev, I. D. Rigid P-Chiral Phosphine Ligands with Tert-Butylmethylphosphino Groups for Rhodium-Catalyzed Asymmetric Hydrogenation of Functionalized Alkenes. *J. Am. Chem. Soc.* **2012**, *134*, 1754–1769.

(6) Kolodiazhnyi, O. I. Recent Developments in the Asymmetric Synthesis of P-Chiral Phosphorus Compounds. **2012**, *23*, 1–46.

(7) GRABULOSA, A.; GRANELL, J.; MULLER, G. Preparation of Optically Pure P-Stereogenic Trivalent Phosphorus Compounds. *Coordination Chemistry Reviews* **2007**, *251*, 25–90.

(8) Shaughnessy, K. H. Hydrophilic Ligands and Their Application in Aqueous-Phase Metal-Catalyzed Reactions. *Chem. Rev.* **2009**, *109*, 643–710.

(9) Machnitzki, P.; Tepper, M.; Wenz, K.; Stelzer, O.; Herdtweck, E. Water-Soluble Phosphines. *Journal of Organometallic Chemistry* **2000**, *602*, 158–169.

(10) Imamoto, T. Asymmetric Hydrogenation; 2012.

(11) Pinault, N. Homogeneous Catalysts Based on Water-Soluble Phosphines. *Coordination Chemistry Reviews* **2003**, *241*, 1–25.

(12) Smith, R. T.; Baird, M. C. Metal Carbonyl Derivatives of a Water Soluble Phosphine. *Inorganica Chimica Acta* **1982**, *62*, 135–139.

(13) Verkuijl, B. J. V.; Minnaard, A. J.; de Vries, J. G.; Feringa, B. L. Chiral Separation of Underivatized Amino Acids by Reactive Extraction with Palladium−BINAP Complexes. *J. Org. Chem.* **2009**, *74*, 6526–6533.

(14) Pirkle, W. H.; Pochapsky, T. C. Considerations of Chiral Recognition Relevant to the Liquid Chromatography Separation of Enantiomers. *Chem. Rev.* **1989**, *89*, 347–362.

(15) Schuur, B.; Verkuijl, B. J. V.; Minnaard, A. J.; de Vries, J. G.; Heeres, H. J.; Feringa, B. L. Chiral separation by enantioselective liquid-liquid extraction (accessed Nov 14, 2013).

(16) Chin, J.; Lee, S. S.; Lee, K. J.; Park, S.; Kim, D. H. A metal complex that binds α-amino acids with high and predictable stereospecificity (accessed Nov 13, 2013).

(17) Steensma, M.; Kuipers, N. J. M.; de Haan, A. B.; Kwant, G. Modelling and Experimental Evaluation of Reaction Kinetics in Reactive Extraction for Chiral Separation of Amines, Amino Acids and Amino-Alcohols. *Chemical Engineering Science* **2007**, *62*, 1395–1407.

(18) Steensma, M.; Kuipers, N. J.; de Haan, A. B.; Kwant, G. Influence of Process Parameters on Extraction Equilibria for the Chiral Separation of Amines and Amino-Alcohols with a Chiral Crown Ether. *J. Chem. Technol. Biotechnol.* **2006**, *81*, 588–597.

(19) Reeve, T. B.; Cros, J.-P.; Gennari, C.; Piarulli, U.; de Vries, J. G. A Practical Approach to the Resolution of RacemicN-Benzyl A-Amino Acids by Liquid–Liquid Extraction with a Lipophilic Chiral Salen–Cobalt(III) Complex. *Angew. Chem. Int. Ed. Engl.* **2006**, *45*, 2449–2453.

(20) Kim, H.-J.; Kim, W.; Lough, A. J.; Kim, B. M.; Chin, J. A Cobalt(III)−Salen Complex with an Axial Substituent in the Diamine Backbone: Stereoselective Recognition of Amino Alcohols. *J. Am. Chem. Soc.* **2005**, *127*, 16776–16777.

(21) Calligaris, M.; Nardin, G.; Randaccio, L. Crystal and Molecular Structure of [NN'-Ethylenebis(Salicylideneiminato)]Pyridine(Vinyl)Cobalt(III). Evidence of Trans- and Cis-Influence in Octahedral Complexes. *J. Chem. Soc., Dalton Trans.* **1972**, 1433.

(22) Carroll, K. M.; Schwartz, J.; Ho, D. M. Reaction Between (Salen)TiCl2 and Chiral .Alpha.-Hydroxy Carboxylic Acids. *Inorg. Chem.* **1994**, *33*, 2707–2708.

(23) Furrow, M. E.; Schaus, S. E.; Jacobsen, E. N. Practical Access to Highly Enantioenriched C-3 Building Blocks via Hydrolytic Kinetic Resolution. *J. Org. Chem.* **1998**, *63*, 6776–6777.

(24) Kemper, S.; Hrobárik, P.; Kaupp, M.; Schlörer, N. E. Jacobsen'S Catalyst for Hydrolytic Kinetic Resolution: Structure Elucidation of Paramagnetic Co(III) Salen Complexes in Solution via Combined NMR and Quantum Chemical Studies. *J. Am. Chem. Soc.* **2009**, *131*, 4172–4173.

(25) Forgan, R. S.; Roach, B. D.; Wood, P. A.; White, F. J.; Campbell, J.; Henderson, D. K.; Kamenetzky, E.; McAllister, F. E.; Parsons, S.; Pidcock, E.; et al. Using the Outer Coordination Sphere to Tune the Strength of Metal Extractants. *Inorg. Chem.* **2011**, *50*, 4515–4522.

(26) Yao, X.; Qiu, M.; Lü, W.; Chen, H.; Zheng, Z. Substituted Salen–Ru(II) Complexes as Catalysts in the Asymmetric Cyclopropanation of Styrene by Ethyl Diazoacetate: the Influence of Substituents and Achiral Additives on Activity and Enantioselectivity. *Tetrahedron: Asymmetry* **2001**, *12*, 197–204.

(27) Kowalczyk, R.; Kwiatkowski, P.; Skarżewski, J.; Jurczak, J. Enantioselective Nitroaldol Reaction Catalyzed by Sterically Modified Salen−Chromium Complexes. *J. Org. Chem.* **2009**, *74*, 753–756.

(28) Kim, D. H.; Shin, U. S.; Song, C. E. Oxidatively Pure Chiral (Salen)Co(III)-X Complexes in Situ Prepared by Lewis Acid-Promoted Electron Transfer From Chiral (Salen)Co(II) to Oxygen: Their Application in the Hydrolytic

Kinetic Resolution of Terminal Epoxides. *Journal of Molecular Catalysis A: Chemical* **2007**, *271*, 70–74.