DESIGN, SYNTHESIS, AND APPLICATIONS OF STEREODYNAMIC CHIRALITY PROBES

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Abstract

Novel stereodynamic chirality probes were developed for enantioselective sensing of chiral compounds, utilizing the concepts of dynamic covalent chemistry and metal-ligand coordination. Upon interaction with a chiral substrate, the probes generate strong circular dichroism (CD) responses due to asymmetric transformation of the first kind. Analysis of the magnitude and sign of the CD output was used for determination of the absolute configuration and enantiomeric excess (ee) of the analytes tested. Changes in the fluorescent readouts of several sensors were used for substrate concentration analysis.

Three new chirality probes were synthesized for the analysis of chiral amino compounds. These sensors consisted of an axially chiral salicylaldehyde moiety and a cofacial aromatic fluorescence reporter unit bound to a rigid naphthalene scaffold. Imine formation between the chiral analyte and the salicylaldehyde unit generates a CD response that can be correlated to the absolute configuration and enantiomeric excess of the substrates. Optimization of the sensor structure led to a fluorophore unit that is capable of intramolecular hydrogen bonding. Substrate binding was most efficient with the N-oxide of 1-(3’-Formyl-4’-hydroxyphenyl)-8-(4’-pyridyl)naphthalene, and this sensor proved to be a highly versatile probe that transforms a binding event into an enantioselective CD signal and a nonenantioselective fluorescence response.
1,1'-Dihydroxy-2,2'-binaphthalene was developed for absolute configuration and ee analysis of many diverse substrates. This ligand forms stereolabile zinc and boron complexes that undergo asymmetric transformation of the first kind upon substrate coordination. Strong CD signals were observed at high wavelength and with minute amounts of sample. The concept of chirality sensing with stereodynamic metal complexes was further developed and a new binaphthol ketone probe was introduced for the assignment of absolute configuration, enantiomeric excess, and concentration of a wide variety of chiral analytes. The ligand was used for the generation of stereodynamic zinc and aluminum complexes for enantioselective sensing of a large variety of chiral substrates. The use of this probe with Ti(OiPr)$_4$ expanded the substrate scope to chiral 1,2-, 1,3- and 1,4-diols. The practicality of this approach and the potential for high-throughput screening was demonstrated with the analysis of crude reaction mixtures obtained by the Sharpless asymmetric dihydroxylation of stilbene.
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<td>Acetonitrile</td>
</tr>
<tr>
<td>AD</td>
<td>Asymmetric Dihydroxylation</td>
</tr>
<tr>
<td>BINOL</td>
<td>1,1''-Bi-2-naphthol</td>
</tr>
<tr>
<td>CD</td>
<td>Circular Dichroism</td>
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<tr>
<td>COD</td>
<td>Cyclooctadiene</td>
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<tr>
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<td>Dichloromethane</td>
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<td>Density Functional Theory</td>
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<td>Electronic Circular Dichroism</td>
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<td>Enantiomeric Excess</td>
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<td>Electrospray Ionization – Mass Spectrometry</td>
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<td>Ethyl Acetate</td>
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<tr>
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<td>High Performance Liquid Chromatography</td>
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<tr>
<td>HTS</td>
<td>High-Throughput Screening</td>
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<tr>
<td>ICD</td>
<td>Induced Circular Dichroism</td>
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<td>Infrared (Spectroscopy)</td>
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<tr>
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<td>3-Chloroperbenzoic Acid</td>
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xxix
<table>
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<tr>
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<tr>
<td>NEt₃</td>
<td>Triethylamine</td>
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<tr>
<td>NMR</td>
<td>Nuclear Magnetic Resonance</td>
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<tr>
<td>TBAF</td>
<td>Tetrabutylammonium Fluoride</td>
</tr>
<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
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<tr>
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<td>N,N,N′N′-Tetramethylethylene Diamine</td>
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<td>Trimethylsilyl Cyanide</td>
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<tr>
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Chapter I. Introduction*

1.1 Chirality in Natural and Synthetic Products

Chirality plays an essential role in everyday life. The basic building blocks of life, i.e. carbohydrates, amino acids, proteins, and DNA are all chiral. It is unsurprising, then, that chemists have spent more than a hundred years to understand properties of stereoselective interactions between chiral compounds and to develop means for efficient asymmetric synthesis. Chiral compounds play a prime role in the pharmaceutical sciences.¹ Recent blockbuster drugs, such as Gilead’s Sofosbuvir (Sovaldi®) GSK’s Fluticasone (Advair®), and Astra Zeneca’s Rosuvastatin (Crestor®), which totaled sales of $22.6 billion in 2014, are all sold as single enantiomers (Figure 1.1). Many drugs listed on the World Health Organization’s list of essential medicines are chiral, including Ibuprofen, Morphine, and Ketamine. It is therefore essential that chemists develop robust and efficient methods for the synthesis and characterization of chiral products. More than half of the drugs marketed in the United States today are sold as single enantiomers. For a century or more, chemists have sought to understand the intricate and specific interactions between naturally occurring chiral molecules and their biological targets, whether it be proteins or nucleic acids. In the late 1980’s, the rapidly increasing need for small molecules with therapeutic potential led to an exponential increase in the study of asymmetric synthesis.² In contrast to trial-and-error testing of naturally occurring substances or mixtures thereof, so-called “rational design” allowed introduction of small drugs through an understanding of the three-dimensional interactions between the compound and the target.³

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1.2. General Aspects of Circular Dichroism Sensing

In order to address the need for chiral compounds, particularly in the pharmaceutical industry, synthetic chemists have begun using automated high throughput instrumentation to run a large number of reactions simultaneously. A recent report from Santanilla et al. describes a robotic set up that is capable of performing 1536 nano-scale reactions at one time. It is essential that the analysis of such a large number of reactions is efficient, cost-effective, and environmentally sustainable. Traditional methods for the chiral analysis of asymmetric reactions, such as chiral HPLC and NMR, have several drawbacks. These methods can often require several minutes to analyze a single reaction, and purification or even derivatization of the target compound is often required. New directions including mass spectrometry and ultra-fast HPLC that address the bottleneck in today’s synthesis development have received increasing attention.

Figure 1.1. Structures of chiral pharmaceuticals.
Optical methods, such as indicator displacement assays and fluorescence sensing are also emerging as attractive alternatives for high-throughput reaction screening.

Circular dichroism spectroscopy has found widespread use in the stereochemical analysis of configurational and conformational isomers, and it has become the most powerful method for the elucidation of the absolute configuration of chiral compounds when crystallographic techniques cannot be used. In addition to structural analysis, CD spectroscopy provides invaluable insights into the kinetics of racemization and diastereomerization reactions and molecular recognition events. Many important chiral compounds cannot be directly investigated by electronic CD spectroscopy because they lack a strong chromophoric group and therefore produce none or only negligible Cotton effects in the UV region. In these cases, formation of inclusion complexes or solute-solute association with UV light absorbing compounds can induce characteristic new CD effects that extend the application scope of this technique. The circular dichroism phenomena discussed in the following section typically originate from well-defined molecular interactions between a scalemic chiral substrate that is preferably CD-silent and a UV-active reporter molecule that can undergo an asymmetric induction process resulting in the preferred population of a chiral structure with distinctive chiroptical output.

In recent years, stereodynamic molecular sensors that translate a chiral recognition event into a strong characteristic CD output have been increasingly utilized for the determination of the absolute configuration and enantiomeric composition of chiral compounds. The power of ECD spectroscopy stems in part from the inherent sensitivity, operational simplicity, and the compatibility with automation and fast parallel analysis of many samples, which makes this technique attractive for HTS applications. In addition, ECD measurements utilize minute amounts of chromophoric probes that are either achiral or exist as a racemic mixture of rapidly
interconverting enantiomers. This eliminates the need for asymmetric synthesis of expensive chiral stationary phases, solvating agents and derivatizing reagents that are required for chromatographic, electrophoretic and NMR studies. The success of CD analysis and the general usefulness of a chiroptical sensor can be evaluated based on the following criteria:

1. The sensor should be readily available, effective in stoichiometric amounts, recyclable and applicable to a wide range of substrates.

2. The molecular recognition and asymmetric induction process should be fast and allow time-efficient in-situ CD measurements without the need for elaborate purification steps.

3. The sensor should produce intense Cotton effects at high wavelengths to reduce interference with CD active impurities or catalysts that might be present when asymmetric reactions are screened.

4. A strong CD output is a general requisite for accurate ee determination and reduces the consumption of sample and sensor.

5. The sensor should provide reliable information about the absolute configuration of a large number of substrates that is based on well-defined molecular interactions and a consistent chiral induction outcome.

1.3. Analysis of Chiral Compounds by Circular Dichroism

Nakanishi, Berova and others have introduced metalloporphyrins for exciton-coupled CD sensing of the absolute configuration of a wide variety of compounds.\textsuperscript{16,17} 5,10,15,20-Tetraarylporphyrins exhibit a strong Soret band located above 400 nm with extinction coefficients typically ranging from 400,000 to more than 800,000. The strong absorption at relatively high wavelengths and effective asymmetric induction observed for tweezer-like metalloporphyrins allow ECCD measurements with micromolar amounts of both sensor and
analyte while interference from the CD signals of chromophoric substrates and impurities are excluded. The relatively simple modification or modular synthesis of porphyrins simplifies the formation of a range of metal complexes with varying solubility, absorbance and Lewis acidity, and this has significantly propelled the progress in this area. Several monomeric metalloporphyrins have been applied as chiroptical probes to determine secondary DNA structures,\textsuperscript{18} and in the stereochemical CD assignment of various chiral substrates,\textsuperscript{19} including amino esters,\textsuperscript{20} carbohydrates,\textsuperscript{21} and carboxylic acids.\textsuperscript{22} Because fairly weak Cotton effects are often observed and in some cases covalent attachment of the analyte to the porphyrin ring is required, more effective tweezers have been developed. Tweezer I shown in Figure 1.2 consists of two porphyrin units that are connected via a 1,5-pentandiol tether.\textsuperscript{23} This sensor design can accommodate substrates of varying size due to the length and flexibility of the linker. Binding of diamine substrates is accomplished through bridging coordination to the two Zn(II) centers. Upon substrate binding, the two porphyrin rings adopt a twisted chiral orientation that minimizes steric repulsion with the largest substituent L. The resulting strong Cotton effects can be correlated to a preferentially populated porphyrin twist that places L outside the two ring moieties. Because the substrate does not need to be covalently attached to the porphyrin ring, the tweezer can be recycled if desirable.
Figure 1.2. Schematic representation of the mechanism for the generation of a CD signal utilizing a porphyrin tweezer complex and a chiral diamine.

The general need for derivatization of substrates that do not afford two amino groups has been overcome with the development of increasingly Lewis acidic metalloporphyrins and tweezer designs exhibiting a short or rigid linker.\(^{24-26}\) Borhan and coworkers introduced fluorinated porphyrin tweezer 2 for the direct determination of the absolute configuration of amino alcohols, epoxy alcohols and diols (Figure 1.3).\(^{27-29}\) Computational modeling showed that the perfluorination of the peripheral phenyl groups lowers the LUMO energy of the porphyrin ring and increases the Lewis acidity of the Zn(II) center. This allows strong binding of the substrate and it affords effective asymmetric induction and strong ECCD signals. Alternatively, introduction of a melamine bridge between the two metalloporphyrin moieties has been found to facilitate binding of substrates lacking two amino groups. The rigid linker decreases the interporphyrin distance and limits the lateral freedom of the two porphyrin rings. Accordingly, sensor 3 and analogues thereof produces large Cotton effects in the presence of several chiral substrates, including \(\alpha\)-amino esters and amides, secondary alcohols and 1,2-amino alcohols.\(^{30,31}\)
The intrinsic connection between axial chirality, sterodynamics and chiroptical properties of biphenyls provides an excellent advantage for the development of CD probes. The interconversion of the enantiomers of chiral biphenyls can be conveniently analyzed by dynamic NMR spectroscopy or chromatography and has been studied in some detail. The energy barrier to rotation is mostly controlled by steric effects and electronic effects play a minor role in most cases. With the exception of 2,2′-disubstituted biphenyls bearing bulky isopropyl, phenyl or tert-butyl groups, axially chiral biphenyls that have less than three ortho-substituents are typically not stable to racemization and cannot be isolated at 25 °C. The conformational stability of bridged biaryls varies significantly with the ring size. As a rule of thumb, biaryls that possess one bridging atom are not stable to rotation at room temperature even if the remaining two ortho-positions are occupied by bulky groups. An increase in the bridge length enhances the torsion angle between the two aryl rings and increases both the CD signal and the energy barrier to
racemization. Nevertheless, biaryls that incorporate the pivotal aryl-aryl bond into a five- or six-membered ring are typically more prone to racemization than their acyclic analogues. This effect diminishes with increasing bridge length and biaryls exhibiting seven-membered or larger rings are generally at least as stable as their acyclic analogues.

Rosini and coworkers have attached bridged biphenyls to several aliphatic 1,2- and 1,3-diols and demonstrated that the spiro dioxolanes formed exhibit distinct CD signals that can be directly correlated to the central chirality of 4a-h (Figure 1.4).\textsuperscript{33,34} UV, CD and NMR spectroscopic analysis of the isolated dioxolanes showed that dioxolanes 6a-h exist as a mixture of rapidly interconverting diastereomers. For example, derivatization of (R,R)-4a gave (R,R,M)-6a in 84% de at 5 °C and the energy barrier for the rotation towards the minor (R,R,P)-conformer was determined as 62.0 kJ/mol by variable-temperature NMR spectroscopy. The UV spectrum of this mixture revealed the characteristic biphenyl absorptions at 215 nm and 250 nm and CD analysis showed a positive Cotton effect at 250 nm which is generally associated with $M$ torsion at the C$_{aryl}$-C$_{aryl}$ bond in the probe. Molecular mechanics calculations suggesting that (R,R,M)-6a-h experience less steric repulsion between the diol residues and the biaryl framework than the corresponding (P)-isomers were found to be in perfect agreement with the observed Cotton effects and the deduced $M$ conformation. The predictability of the sense of asymmetric induction and the unambiguous correlation of the sign of the Cotton effect to the axial chirality of the biphenyl unit thus allows one to use 5 to determine the absolute configuration of UV transparent diols by a simple CD measurement.
The same principles have been exploited for the assignment of the absolute configuration of chiral carboxylic acids using a biphenyl-derived azepine probe. Rosini et al. found that stirring of 2-substituted carboxylic acids 7 and amine 8 in the presence of EDC (1-ethyl-3-(3-dimethylaminopropyl)carbodiimide) overnight affords diastereomeric mixtures of amides 9 in 50-80% yield (Scheme 1.1). Chiroptical analysis of the purified coupling products showed that the sign of the CD signals can be correlated with the structure of the acid used. The close proximity of the bridged biphenyl unit, which undergoes rapid rotation about the chiral axis, to the chiral carbon center and the limited degree of rotational freedom of 9 exhibiting a seven-membered ring directly connected to a planar peptide bond are important features that allow for predictable axial chirality induction. The relative thermodynamic stability of the diastereomeric rotational isomers of 9 is effectively controlled by intramolecular interactions between the probe and the substituents at the chiral center in 7. The induced bias towards either $M$ or $P$ torsion in the biphenyl unit gives rise to a characteristic Cotton effect at approximately 250 nm which can be used to deduce the absolute configuration of the carboxylic acid.
Scheme 1.1. Introduction of the azepine probe to carboxylic acid 7.

Hong, Kim, Chin and coworkers reported that imine formation between amino acids and the tolyl azo-substituted 2,2’-dihydroxybenzophenone, 10, results in effective imprinting of helical chirality on this fluxional receptor in aprotic solvents. DFT calculations, NMR spectroscopy and crystallographic analysis demonstrated that the condensation product 11 obtained with (S)-alanine and other amino acids heavily populate the (P)-form which is stabilized by two internal hydrogen bonds while steric repulsion between the methyl group of the amino acid and the phenol moiety is kept at a minimum (Scheme 1.2). This chiral amplification process coincides with a strong CD output due to the extended π-system which is spread out to the aromatic azo branches. Interestingly, the CD amplitude measured is almost independent of the amino acid used and can be correlated to the absolute configuration and the enantiomeric composition of the substrate.
Scheme 1.2. Imprinting of $(P)$-helicity on the benzophenone receptor 10 with $(S)$-alanine.

The trityl group is frequently used for protection of alcohols, amines and thiols. It is also well known to exhibit propeller chirality. The propeller blades, i.e. the phenyl rings in the trityl group, are twisted and adopt clockwise or counterclockwise arrangements that give rise to helical conformations. Because of steric interference between the adjacent aryl rings, molecular propellers show gearing or cog-wheeling effects and the blades do not rotate independently about the blade-hub axes but undergo energetically favored correlated movements. The interconversion of the conformational isomers of the trityl moiety is fast at room temperature and it is generally believed to involve a so-called two-ring flipping mechanism by which 2 blades undergo conrotatory rotation and the third non-flipping ring rotates in the opposite direction through the propeller plane (Scheme 6).\(^{15}\)

Scheme 1.3. Interconversion of the enantiomeric conformations of the $C_3$-symmetric triphenylmethane propeller via 2-ring flipping.
Gawronski’s and Rosini’s groups realized that the local $C_3$-symmetry of triphenylmethane can be disturbed by the presence of other chiral elements, for example when the trityl moiety is attached to chiral alcohols and amines (Figure 1.5). Molecular modeling and CD analysis of 12 trityl ethers 12 derived from chiral secondary alcohols showed that almost exclusively the $MPM$-conformer is the predominant species when the alcohol has $S$-configuration, whereas the trityl group adopts a $PMP$-conformation when it is attached to an ($R$)-alcohol. The residual stereoisomerism in these ethers corresponds to characteristic CD signals and the $C_1$-symmetric trityl group can be used as an effective stereodynamic chromophore to sense the absolute configuration in the alcohol substrate: Trityl ethers derived from ($S$)-alcohols typically show negative Cotton effects at approximately 200 and 225 nm while positive couplets are observed with the trityl derivatives of ($R$)-alcohols (Scheme 1.4). Similar principles apply to $N$-tritylamines 13 which generally show more complicate dynamic equilibria due to nitrogen inversion which is correlated with both the absolute configuration in the carbon scaffold of the amine and the propeller helicity of the trityl CD reporter unit.

**Figure 1.5.** Selected structures of trityl ethers and amines studied by Gawronski et al.
Scheme 1.4. Favored residual C\textsubscript{1}-symmetric $MPM$- and $PMP$-conformations of chiral trityl ethers. Newman projection shows the view along the O-CPh\textsubscript{3} bond with the oxygen atom in front.

Canary and coworkers investigated the stereodynamics and chiroptical properties of pentacoordinate Zn(II) and Cu(II) complexes of \textit{N,N}-bis[(2-quinolyl)methyl]-1-(2-quinolyl)ethylamine, 14, and derivatives thereof and observed strong exciton-coupled circular dichroism (ECCD) signals that can be correlated to the absolute configuration at the chiral carbon atom in the ligand backbone (Scheme 1.5). CD and NMR measurements combined with crystallographic and computational analysis revealed that the chiral center controls the spatial arrangement of the η\textsuperscript{4}-ligand and consequently the whole propeller-like coordination sphere. The three quinolyl propeller blades reside in close proximity and afford three couplets that contribute to a large CD amplitude. Similarly, the (S)-methionine-derived Cu(II) complex 15 shown in Scheme 8 favors a helical quinolyl twist that is controlled by the absolute configuration of the amino acid.\textsuperscript{41-43} Through incorporation of many proteinogenic amino acids in the same ligand scaffold, Canary’s group demonstrated that (S)-amino acids induce a $P$ (Δ) twist generating a distinct negative Cotton effect at approximately 240 nm while the (R)-enantiomers favor an $M$ (Λ) propeller-like arrangement with a positive CD couplet.\textsuperscript{44} Studies with scalemic ligand mixtures gave a linear relationship between the differential extinction coefficient, \(\Delta\varepsilon\), and the ee
of the samples. The sign and the amplitude of the bisignate CD spectrum can thus be directly used for absolute configuration assignment and determination of enantiopurity, respectively. The same principles apply to related copper and zinc complexes carrying quinolyl amd pyridyl ligands derived from chiral alcohols, amino alcohols or amines.$^{45-48}$

Scheme 1.5. Top: Views of a propeller-like Cu(II) coordination complex derived from (S)-$N,N$-bis[(2-quinolyl)methyl]-1-(2-quinolyl)ethylamine, 14. Bottom: Structure basis for exciton-coupled circular dichroism of the (S)- and (R)-methionine-derived Cu(II) complex 15.

To improve the practicality of this ECCD method, Canary and Anslyn introduced a simplified assay for the analysis of carboxylic acids and amino acids that does not require derivatization of the substrate prior to stereochemical analysis.$^{49,50}$ They observed that the equilibrium between enantiomeric forms of the copper(II) complex 16 bearing achiral $N,N$-bis[(2-quinolyl)methyl]-1-(2-pyridyl)methylamine as ligand is disturbed upon replacement of the water molecule by 2-phenylbutyric acid, 17d, and other chiral analytes (Figure 1.6).
Crystallographic analysis showed that 16 has a square pyramidal coordination sphere with one quinolyl nitrogen in the apical position that is somewhat distorted towards a trigonal bipyramidal structure and expected to afford a twisted ligand arrangement capable of providing a strong ECCD output. Indeed, the coordination of (S)-17d generates a positive couplet at 238 nm which was attributed to an M propeller geometry of the stereodynamic ligand. As expected, the (R)-enantiomer of 17d gave the corresponding negative Cotton effect with the same amplitude because the corresponding asymmetric induction produces a P propeller twist. Several other carboxylic acids, 17a, 17b, 17c, 17e, and 17f, showed the same behavior albeit with varying CD amplitude, i.e. (S)-enantiomers gave a positive ECCD signal at 238 nm while the (R)-analytes gave a negative CD couplet. This attractive sensing system was successfully applied to quantitative analysis of enantiomeric compositions of samples of 17b, 17d and 17e and gave ee results with only 1.8-4.1% error.

Figure 1.6. Structures of 16 and 17a-f.

The Anslyn group has developed a very effective 4-component sensing strategy for chiral secondary mono-alcohols (Figure 1.7). Reaction between 2-pyridinecarboxaldehyde and di-(2-picoly)amine in the presence of an acid catalyst generates the iminium, which is then attacked
by a chiral alcohol to generate a neutral tertiary amine. The amine and pyridine nitrogens coordinate to a Zn(II) center to form a chiral species that is CD active. This strategy does not require derivatization of the chiral secondary alcohol, and is generated in a one-pot reaction with all components mixed simultaneously. The absolute configuration and ee of the substrates was determined by considering the sign and intensity of the resultant CD spectra.

\[
\text{O} \quad \text{N} \quad \text{N} \quad \text{H} \quad \text{N} \quad \text{R} \quad \text{R'} \quad \text{OH} \quad \text{O} \quad \text{N} \quad \text{N} \quad \text{N} \quad \text{N} \quad \text{Zn(OTf)}_2
\]

\[
\text{N} \quad \text{O} \quad \text{N} \quad \text{R} \quad \text{R'} \quad \text{N} \quad \text{O} \quad \text{N} \quad \text{R} \quad \text{R'} \quad \text{N} \quad \text{O} \quad \text{R'} \quad \text{R}
\]

**Figure 1.7.** Sensing of chiral alcohols by reversible addition of the analyte to an iminium.

Zhang and Wolf reported the use of tropos Pd(II)-phosphine complexes for the enantiomeric and concentration determination of chiral amino alcohols and diamines (Scheme 1.6).\(^{52}\) Two bidentate phosphine ligands, DPPF (1,1’-bis(diphenylphosphino)ferrocene) and BDPDE (2,2’-bis(diphenylphosphino)diphenylether), were chosen as stereodynamic ligands for this study. First, the ligands were added to a solution PdCl\(_2\)(COD), allowing for coordination of the phosphine ligands to Pd. The chloride counterions were then replaced with hexafluoroantiminate using acetonitrile as solvent, resulting in Pd(dppf)(ACN)\(_2\) or Pd(bdpde)(ACN)\(_2\) as detected by ESI-MS. The two molecules of acetonitrile were easily displaced upon addition of a chiral diamine (1 equivalent) or amino alcohol (2 equivalents). An asymmetric induction event then occurred on the bidentate phosphine ligand, generating a strong CD output. The absolute configuration and enantiomeric excess of the analyte was determined by observation of the sign and intensity of the CD readout. Additionally, the concentration of the substrate could be determined by monitoring the change in the UV absorbance of the Pd-ligand complex. A linear relationship between the molar ratio of the substrate and Pd complex was
observed at two wavelengths, and the concentration of several samples was determined using the linear regression analysis from a calibration curve.

Scheme 1.6. Chiral induction process for Pd(bdpde) and a chiral analyte.

Irfanoglu and Wolf also utilized an achiral ligand-metal complex for enantioselective sensing of chiral amino alcohols, amino acids, and carboxylic acids (Figure 1.8). Here, a cobalt(III)-salen complex was generated by mixing meso-18 with Co(NO₃)₂, which was subsequently oxidized to Co(III). Addition of a chiral analyte was expected to generate an octahedral Co-salen complex, with the meso salen ligand adopting a chiral conformation that is directly related to the absolute configuration of the analyte. Strong CD signals were observed for a variety of different substrate classes, and the absolute configuration and ee were again determined from the CD outputs. In analogy to the sensing system presented by Zhang et al., the ligand-metal complex was generated from commercially available components and generated CD signals at very low concentration.
Figure 1.8. Structure of the meso salen ligand and schematic representation of the possible octahedral species formed with Co(III).

1.4. References


16 X. Huang, K. Nakanishi, N. Berova, Chirality, 2000, 12, 237-255.


Chapter II. Objectives

The advent of automated high-throughput instrumentation enables today’s chemists to run hundreds of asymmetric reactions simultaneously. The analysis of such a large number of reactions has become the bottleneck of the discovery process. Traditional enantioselective analysis of reaction mixtures often requires time-consuming chromatography that generates large amounts of waste. Optical spectroscopy offers an attractive alternative and has potential to match the fast pace of parallel synthesis. In particular, circular dichroism (CD) spectroscopy has been utilized for absolute configuration determination of many types of chiral compounds. However, many chiral products have limited CD activity. Stereodynamic chemosensors can amplify the chirality of these compounds and greatly increase the general utility of CD spectroscopy for stereochemical analysis. Association of a chiral substrate with a stereodynamic chromophoric chemosensor induces a chiral bias in the sensor, generating a characteristic CD signal. The absolute configuration and, in many cases, the enantiomeric composition of the target compound can be determined by analyzing the shape and intensity of the chiroptical sensor signal.

The main objectives of this thesis were:

1. to develop new stereodynamic chirality probes for enantioselective sensing of many types of chiral substrates

   At the beginning of this work, the majority of chirality sensors were limited to few substrates. To evaluate the full potential of chiroptical sensing, new stereodynamic chemosensors having a broad substrate scope were in demand. Sensors that could be used for accurate determination of the absolute configuration and enantiomeric composition of several types of chiral compounds would of course be most useful.

2. to introduce new substrate recognition strategies and sensing motifs
The development of new sensor designs and substrate binding motifs was guided by mechanistic analysis of the sensor-substrate interactions and the translation of the binding event into a strong chiroptical response. Following previous work with amines, it was expected that dynamic covalent chemistry principles could be further explored to achieve robust sensing assays. Alternatively, stereodynamic ligand-metal complexes were expected to bind many different chiral analytes. The bound substrate would induce a biased chiral conformation on the reporter ligand and generate CD signals, as well as alter the UV or fluorescence output for concentration determination. These sensors would be CD active at relatively high wavelength in order to avoid the effects of impurities that would be present in reaction mixtures.

(3) to analyze the products of an asymmetric reaction using a stereodynamic chemosensor

For HTS, analysis of crude reaction mixtures is essential to eliminate time-consuming purification steps. The direct analysis of the stereochemical outcome and yield of an asymmetric reaction with fast optical measurements is imperative to establish chemosensing as an alternative to traditional analytical techniques. Minimal workup of the asymmetric reaction would be ideal, and no interference from the reaction byproducts should be observed.
Chapter III. Stereodynamic Aryl-Acetylene Probes for Enantioselective Sensing of Chiral Amines and Amino Alcohols*

3.1 Introduction

There are several reports regarding the synthesis and use of macrocycles formed by condensation of complementary amines and aldehydes.\(^1\) Following this idea, Iwaniuk and Wolf introduced a series of aryl-acetylene probes, including 1, for the enantioselective sensing of chiral amines and diamines (Scheme 3.1).\(^2\)\(^,\)\(^3\) The acetylene axes allow for fast rotation and interconversion of conformational isomers of 1, which is CD silent.\(^4\) The sensor contains two terminal aldehyde groups that undergo condensation with chiral diamine substrates. This yields a [1+1] assembly and the chirality of the substrate is imprinted on the chromophoric scaffold of 1. As a result of this asymmetric transformation of the first kind, a CD signal is observed that can be directly correlated to the absolute configuration of the diamine substrate. Chiral monoamines also undergo condensation with the sensor to give CD active [1+2] adducts. Sensor 1 and analogues thereof generate distinct CD signals upon binding of a variety of aromatic and aliphatic chiral amines.

The absolute configuration of the substrates can be determined from the sign of the CD amplitude at a specific wavelength. Additionally, a calibration curve was generated by plotting the maxima of the CD curves for nonracemic substrates. Using the linear regression equation generated from this curve, the ee of unknown samples were accurately determined.

Because this sensor generated strong CD signals in the presence of chiral amines and diamines, it was hypothesized that other substrates containing an amino group, such as amino alcohols, would also induce a CD signal. Replacement of the terminal formyls with phenol groups was expected to extend this sensing approach to stereodynamic metal probes. Coordination of various chiral substrates to a stereodynamic metal complex would then induce strong CD signals suitable for ee analysis.

3.2 Sensing of Amino Alcohols By Imine Formation

The synthesis of 1 was accomplished in four high-yielding steps (Scheme 3.2). First, Sonogashira coupling of 1,4-diethynylbenzene and 2-bromoiodobenzene gave the dibromide 2. Subsequent Sonogashira couplings with trimethylsilylacetylene afforded 3, which was then treated with TBAF to remove the TMS groups, resulting in the terminal alkyne 4. Finally, Sonogashira coupling with 1-bromo-2-naphthaldehyde gave dialdehyde 1.
Scheme 3.2 Synthesis of 1.

Treatment of 1 with an amino alcohol resulted in the formation of the expected [1+2] imine condensation complex. ESI-MS analysis of the diimine formed between 1 and two equivalents of amino alcohol 5 showed conversion to the diimine within 2 hours (Figure 3.1). NMR analysis also confirmed that the reaction was complete. IR analysis of dialdehyde 1 and the diimine formed from 1 and 5 shows the disappearance of the carbonyl stretching absorption at 1695 cm\(^{-1}\) and the appearance of the imine stretching at 1637 cm\(^{-1}\) (Figure 3.2).

![Figure 3.1. ESI-MS spectrum of the diimine obtained from 1 and (1R,2S)-5 (m/z = 924).](image)
The use of 1 for CD sensing of amino alcohols was then tested. The condensation of 1 with a series of aliphatic and aromatic amino alcohols was performed and the CD spectra of the diimines collected (Figure 3.3). Strong Cotton effects were observed at micromolar concentrations, though the signals were less intense than previously observed with chiral amines and diamines.
Figure 3.3. Top: Structures of amino alcohols tested. Bottom: CD spectra of the imine obtained from 1 and (1R,2S)-5 (blue) and (1S,2R)-5 (red) at 9.38 x 10^{-5} M in CHCl₃.

The diimine formed between 1 and 5 is expected to exist as a complex mixture of rapidly converting stereoisomers, each with different thermodynamic and chiroptical properties. Solvent and temperature effects on the CD readout were therefore investigated. The CD readout of the diimine in ACN, chloroform, hexanes, diethyl ether, tetrahydrofuran, and ethyl acetate proved very similar (Figure 3.4). However, the intensity of the CD signal nearly doubled in methanol. By decreasing the temperature from 25 °C to 0 °C, the signal was enhanced nearly 15%. (Figure
3.5). In both cases, the increase in CD intensity is attributed to the stabilization of a CD active conformation of the diimine.

**Figure 3.4.** CD spectra of the imine obtained from 1 and (1\text{R},2\text{S})-5 at 9.38 x 10^{-5} M in methanol (blue), CHCl₃ (red), hexanes (green), ACN (orange), diethyl ether (light red), THF (purple), and ethyl acetate (light blue).

**Figure 3.5.** CD spectra of the diimine obtained from 1 and (1\text{R},2\text{S})-5 at 9.38 x 10^{-5} M in methanol at 25 °C (dashed line) and 0 °C (solid line).
In order to demonstrate the practicality of 1 for quantitative enantioselective sensing, a calibration curve was constructed (Figure 3.6). Sensor 1 was subjected to imine condensation with 5 at varying ee values ranging from +100% to -100%. CD spectra were collected, and the CD intensity at 290 nm was plotted vs. ee. A linear relationship was observed with an $R^2$ value of 0.992.

![Calibration curve of the diimines obtained from 1 and 5.](image)

**Figure 3.6.** Calibration curve of the diimines obtained from 1 and 5.

Four non-racemic samples of 5 were prepared and treated with 1, and the CD spectra were obtained in CHCl$_3$ as described above. Using the linear regression equation derived from the calibration curve, the ee values were calculated. The calculated ee’s correlated well with the actual values, and variations were within 5% (Table 3.1).

**Table 3.1.** Experimentally determined ee’s of four scalemic samples of 5.

<table>
<thead>
<tr>
<th>Actual % ee (1R,2S)-5</th>
<th>Calculated %ee (1R,2S)-5</th>
</tr>
</thead>
<tbody>
<tr>
<td>70.0</td>
<td>74.4</td>
</tr>
<tr>
<td>26.0</td>
<td>24.9</td>
</tr>
<tr>
<td>-36.0</td>
<td>-31.6</td>
</tr>
<tr>
<td>-69.0</td>
<td>-68.2</td>
</tr>
</tbody>
</table>
3.3. Sensing of Diamines and Amino Alcohols with Stereodynamic Biphenolate Zn Complexes

Dialdehyde sensor 1 generates strong CD signals upon condensation with diamines, amines, and amino alcohols. However, the substrate binding step is time-consuming in the absence of a catalyst, with amino alcohols requiring 90 minutes to completely form the CD active diimine. It was then proposed that a biphenol analogue of 1 would instantaneously form a zinc complex through a fast acid-base reaction with Et₂Zn. The zinc complex would rapidly racemize and remain CD silent. However, upon coordination of a chiral substrate, the sensor was expected to populate a preferred chiral conformation with a CD signal that can be correlated to the substrate chirality (Scheme 3.3).

Scheme 3.3. Proposed mechanism for chirality sensing with stereodynamic zinc complexes derived from biphenols 14 and 15.
The structure of 14 is very similar to 1, with the aldehyde units substituted for phenols. Sensor 1 can be described as having a “body” consisting of three phenyl rings separated by two acetylene bonds. Adjoined to the body are two flexible “arms” consisting of two benzaldehyde moieties connected via an acetylene bond. It was proposed that the length of the body could greatly affect the CD signal that is generated after coordination of a chiral substrate to the Zn-biphenolate complex. The structure of 15 therefore consists of a shortened body and does not have the central phenyl ring of 14 (Figure 3.7).

![Figure 3.7. Structures of stereodynamic biphenol ligands.](image)

The synthesis of 14 follows the previously developed synthesis of 1 until the final step.³ Sonogashira coupling of 2-iodophenol with 4 gave 14 in 65% yield (Scheme 3.4).

![Scheme 3.4. Synthesis of biphenol ligand 14.](image)
The synthesis of 15 began with a Glaser coupling of 2’-bromophenylacetylene to yield 16. Sonogashira with trimethylsilylacetylene afforded 17, which was then treated with TBAF to remove the TMS groups to give 18. Finally, Sonogashira with 2-iodophenol afforded ligand 15 (Scheme 3.5).

Scheme 3.5. Synthesis of biphenol ligand 15.

Treatment of 14 with Et₂Zn and both enantiomers of cis-1,2-diphenylethylenediamine induced a strong CD signal above 350 nm, with a maximum at 400 nm. A similar result was obtained with ligand 15, however the CD amplitudes are shifted to lower wavelengths, with the maximum shifted to 360 nm. This is due to the loss of the central phenyl ring on the body of the ligand. Both ligands produce intense CD amplitudes at very low concentration (Figure 3.8).
Figure 3.8. Left: CD spectra of the Zn complex obtained from 14 and (1R,2R)-20 (blue) and (1S,2S)-20 (red) at 1.25 x 10^{-4} M in diethyl ether. Right: CD spectra of the Zn complex obtained from 15 and (1R,2R)-20 (blue) and (1S,2S)-20 (red) at 1.25 x 10^{-4} M in diethyl ether.

The substrate scope was expanded to include both diamines and amino alcohols (Figure 3.9). As expected, aliphatic and aromatic diamines and amino alcohols generated strong CD signals in the presence of both ligands and Et₂Zn (see Experimental Section).

The effect of solvents on the CD output was also investigated. THF, diethyl ether, and ACN allowed for the generation of a strong CD output for the Zn complex obtained with 14 and (1R,2S)-20 (Figure 3.10). The reduced signal in diethyl ether can be attributed to the limited
solubility of the Zn complex. Measurements in other solvents, such as hexanes and chloroform, did not show any significant CD signal.

![Figure 3.10](image)

**Figure 3.10.** CD spectra of the Zn complex obtained with 14 and (1R,2S)-20 in THF (blue), ACN (red), and diethyl ether (green) at 1.25 x 10^{-4} M.

In order to determine the use of the stereodynamic zinc complexes for ee analysis, a calibration curve was generated for ligand 14 and diamine 20. As described above, the CD spectra of the biphenolate-Zn complex were collected with varying ee of 20, from -100% to +100%. The CD maxima at 404 nm were plotted against the %ee, giving a linear response (Figure 3.11). Using the linear regression equation from the calibration, the ee of scalemic samples of 20 were calculated. The calculated values aligned very well with the actual values (Table 3.2). It should be noted that a bimetallic Zn species is possible, which could lead to a non-linear calibration curve. This is due to the possible presence of both heterochiral and homochiral species. ESI-MS analysis with the biphenolate Zn species using ligand 15 and substrate 20 showed the presence of both the monometallic and bimetallic species.
Figure 3.11. Left: CD Spectra of the complexes obtained from 14 and 20 from -100% to +100% ee. Right: Linear relationship between the CD maxima at 404 nm and %ee.

Table 3.2. Experimentally determined ee’s of four scalemic samples of 20.

<table>
<thead>
<tr>
<th>Actual % ee (1R,2R)-20</th>
<th>Calculated %ee (1R,2R)-20</th>
</tr>
</thead>
<tbody>
<tr>
<td>12.0</td>
<td>10.2</td>
</tr>
<tr>
<td>-27.0</td>
<td>-24.3</td>
</tr>
<tr>
<td>-68.0</td>
<td>-65.5</td>
</tr>
<tr>
<td>-89.0</td>
<td>-84.1</td>
</tr>
</tbody>
</table>

3.4. Conclusions

The application scope of dialdehyde sensor 1 was extended to amino alcohols. By use of CD spectroscopy, the absolute configuration of these substrates and the ee can be determined from a fast optical response, but the substrate binding typically required 1-2 hours. Additionally, two new bidentate ligands carrying the aryl-acetylene framework of 1 and terminal phenol groups were developed. The biphenol ligands 14 and 15 showed strong Cotton effects in the presence of diamines and amino alcohols upon treatment with Et₂Zn. The absolute configuration and ee can be determined from the sign and intensity of the CD signal, respectively, and the measurements can be conducted within a few minutes. All sensors presented are appropriate for
the sensing of a variety of substrate classes, contributing to the practicality of optical sensing for HTS purposes.

3.5. Experimental Section

3.5.1. Synthesis of 1

1,4-Bis((2-Bromophenyl)ethynyl)benzene, 2

A solution of 2-iodobromobenzene (3 mL, 23.4 mmol), 1,4-diethynylbenzene (1.0 g, 7.8 mmol), Pd(PPh$_3$)$_4$ (901 mg, 0.78 mmol) and CuI (148 mg, 0.78 mmol) in 6 mL of ACN:NEt$_3$ (1:1) was stirred at 80 °C for 12 hours in a closed vessel. The resulting mixture was cooled to room temperature and concentrated in vacuo. Purification by flash chromatography on silica gel (CH$_2$Cl$_2$) followed by recrystallization from CH$_2$Cl$_2$ and hexanes afforded 3.36 g (7.73 mmol, 99%) of a yellow solid. $^1$H NMR: $\delta = 7.18$ (ddd, $J = 1.7$ Hz, 7.6 Hz, 7.9 Hz, 2H), 7.29 (ddd, $J = 1.1$ Hz, 7.6 Hz, 7.9 Hz, 2H), 7.55 (dd, $J = 1.7$ Hz, 7.6 Hz, 2H), 7.56 (s, 4H), 7.62 (dd, $J = 1.1$ Hz, 7.9 Hz, 2H). $^{13}$C NMR: $\delta = 89.9, 93.5, 123.1, 125.1, 125.6, 127.0, 131.6, 132.5, 133.2.

1,4-Bis(2-(trimethylsilyl)ethynyl)phenylethynyl)benzene, 3

A solution of 2 (3.40 g, 7.80 mmol), trimethylsilylacetylene (3.5 mL, 24.7 mmol), Pd(PPh$_3$)$_4$ (900 mg, 0.78 mmol), and CuI (148 mg, 0.78 mmol) in 6 mL of ACN:NEt$_3$ (1:1) was stirred at 80 °C for 18 hours in a closed vessel. The reaction mixture was cooled to room temperature and concentrated in vacuo. Purification by flash chromatography on silica gel (CH$_2$Cl$_2$:hexanes 2:1) afforded 4.41 g (7.26 mmol, 93%) of a red solid. $^1$H NMR: $\delta = 0.28$ (s, 18H), 7.22-7.31 (m, 4H), 7.49-7.51 (m, 4H), 7.54 (s, 4H). $^{13}$C NMR: $\delta = 0.0, 90.1, 93.1, 103.3, 123.2, 125.7, 125.8, 128.0, 131.5, 131.6, 132.2.
1,4-Bis(2-ethynylphenylethynyl)benzene, 4

A solution of 3 (3.24 g, 6.89 mmol) and tetrabutylammonium fluoride (1.0 M in THF, 10.34 mL, 35.80 mmol) in 8 mL of anhydrous THF was stirred at room temperature for 90 minutes. The reaction mixture was concentrated in vacuo. Purification by flash chromatography over silica gel (CH₂Cl₂:hexanes 2:1) afforded 1.91 g (3.28 mmol, 76%) of a red solid. ¹H NMR: δ = 3.40 (s, 2H), 7.23-7.33 (m, 4H), 7.53-7.56 (m, 8H). ¹³C NMR: δ = 81.4, 82.2, 89.9, 93.3, 123.2, 124.7, 126.0, 128.2, 128.6, 131.7, 131.8, 132.6.

1,4-Bis(2(2-formylphenylethynyl)phenylethynyl)benzene, 1

A solution of 4 (83.0 mg, 0.22 mmol), 2-bromobenzaldehyde (0.14 mL, 1.20 mmol), Pd(PPh₃)₄ (29.0 mg, 0.026 mmol) and CuI (5.0 mg, 0.026 mmol) in 2 mL of ACN:NEt₃ (1:1) was stirred at 80 °C for 20 hours in a closed vessel. The mixture was cooled to room temperature, diluted with 4 mL of diethyl ether and then stored at -20 °C for 12 hours. The precipitate was collected via vacuum filtration, dissolved in CH₂Cl₂, and washed with H₂O. The combined organic layers were dried over MgSO₄ and concentrated in vacuo to afford 107 mg (0.20 mmol, 88%) of a yellow solid. NMR analysis showed that 1 cocrystallizes with 1 equivalent of water. ¹H NMR: δ = 7.35-7.38 (m, 4H), 7.46 (d, J = 7.6 Hz, 2H), 7.53 (s, 4H), 7.56-761 (m, 6H), 7.68 (d, J = 7.7 Hz, 2H), 7.95 (d, J = 7.7 Hz, 2H), 10.78 (s, 2H). ¹³C NMR: δ = 88.9, 89.9, 93.6, 95.0, 110.0, 123.0, 124.7, 125.8, 126.8, 127.1, 128.3, 128.7, 128.8, 131.7, 132.1, 132.2, 133.3, 133.8, 135.9, 191.7. Anal. Calcd. C₄₀H₂₂O₂•H₂O: C, 86.94; H, 4.38. Found: C, 87.01; H, 3.96.

3.5.2. Synthesis of 14

1,4-Bis[2(2-hydroxyphenyl]enethynyl)phenylethynyl)], 14.

A solution of 4 (971.4 mg, 2.9 mmol), CuI (56.75 mg, 0.29 mmol), Pd(PPh₃)₄ (344.4 mg, 0.29 mmol), 2-iodophenol (1.97 mg, 8.94 mmol), and diisopropylamine (3.4 mL, 23.8 mmol) was
stirred at room temperature in 5 mL of THF. The mixture was quenched with water and extracted with dichloromethane. The combined organic layers were dried over MgSO₄ and concentrated in vacuo. Purification by flash chromatography on silica gel (CH₂Cl₂:hexanes 1:1) afforded 989.0 mg (1.94 mmol, 65%) of an orange solid. 

\[ \text{^1H NMR: } \delta = 6.34 \text{ (s, 2H), } 6.92 \text{ (dd, } J = 7.6 \text{ Hz, 7.5 Hz, 2H), } 7.00 \text{ (d, } J = 7.6 \text{ Hz, 2H), } 7.29 \text{ (dd, } J = 7.5 \text{ Hz 7.6 Hz, 2H), } 7.35-7.39 \text{ (m, 4H), } 7.45 \text{ (d, } J = 7.5 \text{ Hz, 2H), } 7.58-763 \text{ (m, 8H).} \]

\[ \text{^13C NMR (CDCl}_3\text{:DMSO-}d_6 \text{ 1:1, v/v) } \delta = 77.8, 84.2, 87.4, 109.9, 110.5, 115.3, 119.4, 122.9, 124.9, 125.7, 127.8, 130.1, 131.6, 131.7, 132.6, 157.9. \]

Anal. Calcd. C₃₈H₂₂O₂: C, 89.39; H, 4.34. Found: C, 89.72; H, 4.27.

3.5.3. Synthesis of 15

1,4-Bis(2-bromophenyl)buta-1,3-diyne, 16.

A solution of TMEDA (165.6 µL, 1.10 mmol) and CuI (105.2 mg, 0.55 mmol) was stirred in 10 mL of dichloromethane for 10 minutes. Then, 2-bromophenylacetylene (500 mg, 2.76 mmol) was added and the reaction mixture was stirred under air at room temperature for 12 hours. The mixture was quenched with water and extracted with dichloromethane. The combined organic layers were dried over MgSO₄ and concentrated in vacuo. Purification by flash chromatography on silica gel (CH₂Cl₂:hexanes 1:1) afforded 983 mg (2.73 mmol, 99% yield) of a white solid. 

\[ \text{^1H NMR } \delta = 7.21-7.31 \text{ (m, 4H), } 7.57-7.62 \text{ (m, 4H).} \]

\[ \text{^13C NMR } \delta = 77.8, 81.0, 124.0, 126.1, 127.1, 130.3, 132.5, 134.5. \]


1,4-Bis[2-(2-trimethylsilylethynyl)phenyl]buta-1,3-diyne, 17. A solution of 16 (983 mg, 2.73 mmol), CuI (52.0 mg, 0.27 mmol), Pd(PPh₃)₄ (315.5 mg, 0.27 mmol), and trimethylsilylacetylene (1.2 mL, 8.2 mmol) was stirred in 4 mL of an ACN:NEt₃ mixture (1:1 v/v) at 80 °C for 12 hours in a closed vessel. The mixture was quenched with water and extracted with dichloromethane. The combined organic layers were dried over MgSO₄ and concentrated in
vacuo. Purification by flash chromatography on silica gel (CH$_2$Cl$_2$:hexanes 1:4) afforded 1.06 g (2.67 mmol, 95%) of a red solid. $^1$H NMR $\delta$ = 0.30 (s, 18H), 7.27-7.32 (m, 4H), 7.46-7.50 (m, 4H). $^{13}$C NMR $\delta$ = 0.0, 77.9, 81.1, 99.6, 103.0, 125.2, 126.9, 128.2, 128.7, 132.0, 132.6. Anal. Calcd. C$_{26}$H$_{26}$Si$_2$: C, 79.13; H, 6.64. Found: C, 79.17; H, 6.69.

1,4-Bis(2-ethynylphenyl)buta-1,3-diyne, 18.

A solution of 17 (1.02 g, 2.59 mmol) and TBAF (1 M in THF, 13.0 mL, 13.0 mmol) was stirred in 10 mL of THF for 1 hour. The mixture was quenched with water and extracted with dichloromethane. The combined organic layers were dried over MgSO$_4$ and concentrated in vacuo. Purification by flash chromatography on silica gel (CH$_2$Cl$_2$:hexanes 1:4) afforded 589 mg (1.45 mmol, 75%) of a yellow solid. $^1$H NMR $\delta$ = 3.38 (s, 2H), 7.31-7.35 (m, 4H), 7.50-7.56 (m, 4H). $^{13}$C NMR $\delta$ = 77.6, 80.7, 81.5, 81.7, 124.8, 125.6, 128.4, 128.8, 132.6, 132.9. Anal. Calcd. C$_{20}$H$_{10}$: C, 95.97; H, 4.03. Found: C, 95.93; H, 4.07.

1,4-Bis[2(2-hydroxyphenylene)ethynyl]phenylene]buta-1,3-diyne, 15.

A solution of 18 (485.8 mg, 1.94 mmol), CuI (37.0 mg, 0.19 mmol), Pd(PPh$_3$)$_4$ (224.2 mg, 0.194 mmol), 2-iodophenol (657.7 mg, 5.82 mmol) and diisopropylamine (2.18 mL, 15.52 mmol) was stirred at room temperature in 10 mL of THF for 24 hours. The mixture was quenched with water and extracted with dichloromethane. The combined organic layers were dried over MgSO$_4$ and concentrated in vacuo. Purification by flash chromatography on silica gel (CH$_2$Cl$_2$:hexanes 1:1) afforded 505.7 mg (1.16 mmol, 60%) of an orange solid. $^1$H NMR $\delta$ = 6.24 (s, 2H), 6.84-6.91 (m, 4H), 7.21 (dd, $J$ = 8.7 Hz, 6.9 Hz, 2H), 7.33-7.45 (m, 6H), 7.57 (d, $J$ = 7.8 Hz, 2H), 7.65 (d, $J$ = 7.8 Hz, 2H). $^{13}$C NMR $\delta$ = 77.4, 82.7, 88.3, 94.7, 109.2, 114.9, 120.2, 123.8, 132.3, 129.2, 130.8, 131.4 131.5, 133.2, 157.1. Anal. Calcd. C$_{32}$H$_{18}$O$_2$: C, 88.46; H, 4.18. Found: C, 88.23; H, 4.16.
3.5.4. Enantioselective Sensing Experiments with 1

A stock solution of 1 (0.00375 M) in anhydrous CHCl₃ was prepared and 350 µL aliquots of this solution were placed in 4 mL vials. Then, solutions of the substrate (0.2828 M) in CHCl₃ were prepared. For each diimine formation, 10 µL of a substrate stock solution was placed in a vial containing the sensor solution over molecular sieves (4 Å, 8-12 mesh). The reactions were stirred at room temperature for 90 minutes. Prior to each use, the CD instrument was purged with nitrogen for 20 min at room temperature. CD spectra were collected with a standard sensitivity of 100 mdeg, a data pitch of 0.5 nm, a bandwidth of 1 nm, a scanning speed of 500 nm s⁻¹, and a response of 0.5 s using a quartz cuvette (1 cm path length). The data were baseline corrected and smoothed using a binomial equation. The CD analysis was conducted with sample concentrations of 9.38 x 10⁻⁵ M. Control experiments with 5-14 at the same concentration range showed that the free substrates are CD silent in the region of interest.

**Figure 3.12.** CD Spectra of various substrates with 1.

CD Spectra of the diimine obtained using 1 and (1R,2R)-5 (blue) and (1R,2R)-5 (red)
CD Spectra of the diimine obtained using 1 and (1R,2R)-6 (blue) and (1S,2S)-6 (red)

CD Spectra of the diimine obtained using 1 and (R)-7 (blue) and (S)-7 (red)

CD Spectra of the diimine obtained using 1 and (1R,2S)-8 (blue) and (1S,2R)-8 (red)
CD Spectra of the diimine obtained using 1 and (R)-9 (blue) and (S)-9 (red)

CD Spectra of the diimine obtained using 1 and (1R,2S)-10 (blue) and (1S,2R)-10 (red)

CD Spectra of the diimine obtained using 1 and (1R,2S)-11 (blue) and (1S,2R)-11 (red)
CD Spectra of the diimine obtained using 1 and (R)-12 (blue) and (S)-12 (red)

![CD Spectra of the diimine obtained using 1 and (R)-12 (blue) and (S)-12 (red)](image)

CD Spectra of the diimine obtained using 1 and (R)-13 (blue) and (S)-13 (red)

![CD Spectra of the diimine obtained using 1 and (R)-13 (blue) and (S)-13 (red)](image)

3.5.5. Calibration Curve and Ee Determination

A calibration curve was constructed using samples of 5 with varying ee. A stock solution of 1 (0.00375 M) in anhydrous CHCl₃ was prepared, and 350 µL aliquots of this solution were placed in 4 mL vials. Stock solutions of 5 (0.1313 M) with varying ee composition (+100.0, +80.0, +60.0, +20.0, 0.0, -20.0, -40.0, -60.0, -80.0, -100.0) were prepared in anhydrous CHCl₃. For each diimine formation, 10 µL of a substrate stock solution was placed in a vial containing the sensor solution, and molecular sieves were added. The reactions were stirred at room temperature for 90 minutes. Upon completion, the reaction solution was diluted to 9.38 x 10⁻⁵ M for CD analysis.
The data were baseline corrected and smoothed using a binomial equation. The CD amplitudes at 290 nm were plotted vs. %ee. The calibration curve shows a linear relationship (\(\text{mdeg} = 0.0813[\%\text{ee}] + 0.5761\)) with \(R^2 = 0.992\).

### 3.5.6. Enantioselective Sensing Experiments with 14 and 15

A stock solution of sensor 14 or 15 (0.006 M) in THF was prepared and portions of 0.5 mL were transferred to 4 mL vials. Solutions of substrates (0.15 M in THF) were prepared. To each vial containing 0.5 mL of stock solution was added either 1 equivalent (20 \(\mu\)L, 0.003 mmol) of a diamine or 2 equivalents (40 \(\mu\)L, 0.006 mmol) of an amino alcohol. To this solution was added Et\(_2\)Zn (1M in hexanes, 0.003 mmol), and the mixtures were allowed to stand for 5 minutes. The CD analysis was conducted with sample concentrations of 1.25 x 10\(^{-4}\) M in diethyl ether for sensor 14 and 1.25 x 10\(^{-4}\) M in THF for sensor 15. CD spectra were collected with a standard sensitivity of 100 mdeg, a data pitch of 0.5 nm, a bandwidth of 1 nm, a scanning speed of 500 nm s\(^{-1}\) and a response of 0.5 s using a quartz cuvette (1 cm path length). The data were baseline corrected and smoothed using a binomial equation. Control experiments with free substrates showed no CD signal in the region of interest.

**Figure 3.13.** CD Spectra of various substrates with 14 and 15.

CD Spectra obtained using 14, Et\(_2\)Zn, and (1\(R\),2\(R\))-5 (blue) or (1\(S\),2\(S\))-5 (red)
CD Spectra obtained using $14$, Et$_2$Zn, and $(R)$-7 (blue) or $(S)$-7 (red)

CD Spectra obtained using $14$, Et$_2$Zn, and $(R)$-12 (blue) or $(S)$-12 (red)

CD Spectra obtained using $14$, Et$_2$Zn, and $(R)$-13 (blue) or $(S)$-13 (red)
CD Spectra obtained using $\textbf{14}$, $\text{Et}_2\text{Zn}$, and $(R)$-$\textbf{19}$ (blue) or $(S)$-$\textbf{19}$ (red)

CD Spectra obtained using $\textbf{14}$, $\text{Et}_2\text{Zn}$, and $(1R,2R)$-$\textbf{20}$ (blue) or $(1S,2S)$-$\textbf{20}$ (red)

CD Spectra obtained using $\textbf{14}$, $\text{Et}_2\text{Zn}$, and $(1R,2R)$-$\textbf{21}$ (blue) or $(1S,2S)$-$\textbf{21}$ (red)
CD Spectra obtained using $\mathbf{15}$, Et$_2$Zn, and $(1R,2R)$-$\mathbf{5}$ (blue) or $(1S,2S)$-$\mathbf{5}$ (red)

CD Spectra obtained using $\mathbf{15}$, Et$_2$Zn, and $(R)$-$\mathbf{7}$ (blue) or $(S)$-$\mathbf{7}$ (red)

CD Spectra obtained using $\mathbf{15}$, Et$_2$Zn, and $(1R,2S)$-$\mathbf{10}$ (blue) or $(1S,2R)$-$\mathbf{10}$ (red)
CD Spectra obtained using $\textbf{15}$, Et$_2$Zn, and $(R)$-$\textbf{12}$ (blue) or $(S)$-$\textbf{12}$ (red)

![CD Spectra graph](image1)

CD Spectra obtained using $\textbf{15}$, Et$_2$Zn, and $(R)$-$\textbf{13}$ (blue) or $(S)$-$\textbf{13}$ (red)

![CD Spectra graph](image2)

CD Spectra obtained using $\textbf{15}$, Et$_2$Zn, and $(R)$-$\textbf{19}$ (blue) or $(S)$-$\textbf{19}$ (red)

![CD Spectra graph](image3)
CD Spectra obtained using 15, Et₂Zn, and (1R,2R)-20 (blue) or (1S,2S)-20 (red)

CD Spectra obtained using 15, Et₂Zn, and (1R,2R)-21 (blue) or (1S,2S)-21 (red)

3.5.7. MS Analysis of the Complex Formation
A solution of 15 (1.57 mg, 0.005 mmol) and 20 (0.90 mg, 0.005 mmol) in 1 mL of a dry THF:MeOH mixture (1:1 v/v) was prepared. Then, Et₂Zn (5 µL, 0.005 mmol, 1M in hexanes) was added and the mixture was stirred for 10 minutes. Electrospray mass spectrometry (positive ion mode) showed the presence of two species, one with a stoichiometry of 1:1:1 15:Zn:20 and the other with a stoichiometry of 2:2:2 [15:Zn:20]₂.
Figure 3.14. ESI-MS: m/z = 708.2 (M⁺1) (1:1:1); m/z = 1416.4 (M⁺1) (2:2:2)

3.5.8. Calibration Curve and Ee Determination with 14 and 20

A calibration curve was constructed using samples of the Zn complex derived from 14 and 20 at varying ee. A stock solution of 14 (0.001 M in THF) was prepared and separated into 0.5 mL portions. Another stock solution of 20 was prepared (0.015 M in THF). Portions of 20 were titrated into the stock solutions or 14 to generate samples with varying %ee (+100, +80, +60, +40, +20, 0, -20, -40, -60, -80, -100). To these solutions was added Et₂Zn (1 µL, 1 M in hexanes, 0.001 mmol). After 5 minutes, CD analysis was carried out as described in section 2.5.6 at 1.25 x 10⁻⁴ M in anhydrous THF. The Cotton effect amplitudes at 404 nm were plotted against the enantiomeric excess of 20 as shown in Figure 3.11.
3.5.9. Crystallography

A single crystal of 14 was obtained by slow evaporation of a concentrated chloroform solution. Single crystal X-ray analysis was performed at 100 K using a Siemens platform diffractometer with graphite monochromated Mo-Kα radiation (λ = 0.71073 Å). Data were integrated and corrected using the Apex 2 program. The structures were solved by direct methods and refined with full-matrix least-square analysis using SHELX-97-2 software. Non-hydrogen atoms were refined with anisotropic displacement parameters. Formula: C$_{32}$H$_{18}$O$_2$, M = 580.48, crystal dimensions 0.12 x 0.14 x 0.11 mm, primitive, space group P21/n, $a = 6.1914(9)$ Å, $b = 9.5908(13)$ Å, $c = 18.537(3)$ Å, $α = 90.0°$, $β = 94.561(2)°$, $γ = 90.0°$, $V = 1097.2$ Å$^3$, $Z = 2$, $\rho_{\text{calcd}} = 1.315$ g cm$^{-3}$.

![Figure 3.15. Crystal structure of 14.](image)

A single crystal 17 was obtained by slow evaporation of a concentrated chloroform solution. Formula: C$_{26}$H$_{26}$Si$_2$, M = 394.65, crystal dimensions 0.32 x 0.26 x 0.11 mm, primitive, space group P21/c, $a = 11.7792(2)$ Å, $b = 9.2719(2)$ Å, $c = 12.4925(2)$ Å, $α = 90.0°$, $β = 115.3720(10)°$, $γ = 90.0°$, $V = 1232.77(4)$ Å$^3$, $Z = 2$, $\rho_{\text{calcd}} = 1.063$ g cm$^{-3}$.
A single crystal 18 was obtained by slow evaporation of a concentrated chloroform solution. Formula: C\textsubscript{20}H\textsubscript{10}, M = 250.28, crystal dimensions 0.21 x 0.15 x 0.11 mm, primitive, space group P-1, \(a = 6.2784(6)\) Å, \(b = 7.4159(5)\) Å, \(c = 7.4756(6)\) Å, \(\alpha = 74.904(5)^\circ\), \(\beta = 65.602(5)^\circ\), \(\gamma = 74.157(5)^\circ\), \(V = 348.45(5)\) Å\(^3\), \(Z = 1\), \(\rho_{\text{calc}} = 1.193\) g cm\(^{-3}\).

3.6. References


5 Iwaniuk, D. P.; Bentley, K. W.; Wolf, C. Chirality 2012, 24, 584.

6 Bentley, K. W.; De los Santos, Z. A.; Weiss, M. J.; Wolf, C. Chirality, 2015, Accepted.
Chapter IV. Stereodynamic 1,8-Diarylnaphthalene Probes for the Determination of Absolute Configuration, Enantiomeric Excess, and Concentration of Chiral Amines, Amino Alcohols, and Amino Acids

4.1 Introduction

As automated parallel synthesis allows hundreds of reactions to be run at the same time, it is imperative that the analysis of the product mixtures be fast and accurate. Enantioselective sensing using optical chemosensors can be a viable alternative to established methods, for example chiral HPLC, if the chiral recognition event between the sensor and the substrate is fast and quantitative. Many current systems utilize dynamic covalent chemistry to achieve these goals. A stereodynamic dialdehyde probe that utilizes reversible imine formation for the enantioselective sensing of chiral amino alcohols and amino acids was developed by Ghosn and Wolf (Figure 4.1). In this design, two salicylaldehyde moieties are anchored to a rigid naphthalene framework. The sensor is racemic at room temperature due to facile rotation about the chiral aryl-aryl axes. Imine formation with chiral amine substrates slows this rotation and generates a CD active product. A preferred chiral conformation is stabilized by intramolecular hydrogen bonds between the sensor and the bound substrate. This locks the sensor into a well defined chiral conformation with a characteristic CD readout. The CD analysis then allows determination of the absolute configuration and enantiomeric excess of chiral amine substrates that contain a hydrogen bond donor, such as amino alcohols and amino acids.

While this particular system proved useful for the accurate determination of the absolute configuration and ee of a variety of substrates by CD, it was not suitable for concentration analysis. Asymmetric reaction analysis, however, requires determination of the yield as well as its stereochemical outcome. It was proposed that substitution of one salicylaldehyde unit for a non-reactive chromophore would allow concentration analysis in addition to absolute configuration and ee determination (Figure 4.2). As discussed for the dialdehyde probe, the binding of a substrate would affect the conformational equilibrium of such a sensor and favor an axially chiral isomer with a distinct CD signal. Communication between the salicylaldehyde unit and the adjacent chromophore would then cause a fluorescence change that can be correlated to the amount of the bound substrate. This would allow for the calculation of the absolute configuration, enantiomeric excess and concentration of a chiral substrate by two fast optical measurements.

Figure 4.2. Sensing strategy for determining enantiomeric excess and concentration simultaneously.
4.2. First Generation Probe\(^4\)

The first sensor design shows one salicylaldehyde moiety substituted with anthracene which is a strong fluorophore. The synthesis of \(1\) proved to be quite challenging (Scheme 4.1). First, mono-Suzuki coupling with 1,8-dibromonaphthalene was used to install the stereodynamic salicylaldehyde unit in \(4\). An additional Suzuki coupling with 9-anthraceneboronic acid gave \(5\). The difficulty of this coupling, and thus the moderate yield, can be understood by studying the crystal structures of the intermediates. Access to bromide \(4\) is sterically hindered by the presence of the salicylaldehyde unit. Intermediate \(5\) also shows a large splay angle between the two chromophores which underscores the steric bulk at the second Suzuki coupling site. The methoxy group in \(5\) is sterically shielded by the anthracene ring, which contributes to the difficulty of demethylation. In fact, the final deprotection did not occur using standard \(\text{BBr}_3\) conditions. After extensive screening of conditions, \(\text{LiCl}\) in refluxing DMF for three days finally afforded \(1\).

![Scheme 4.1. Synthesis of \(1\) with crystal structures of the intermediates.](image)

The barrier to rotation about the chiral aryl-aryl axis was investigated by dynamic HPLC. Unfortunately, the enantiomers of \(1\) could not be separated using a variety of chiral columns and conditions. However, the enantiomers of precursor \(5\) were separated on a Whelk-O 1 chiral stationary phase using dichloromethane/hexane (1:1) as mobile phase. The elution profiles of the two enantiomers at four different temperatures were collected and then simulated, providing the
enantiomerization rates based on reversible first order kinetics (Figure 4.3). Eyring plot analysis allowed for the calculation of the activation enthalpy $\Delta H^\ddagger$ and entropy $\Delta S^\ddagger$. The fairly negative entropy (-120.5 J mol$^{-1}$K$^{-1}$) corresponds well to the expected T-shaped transition state, with the salicylaldehyde moiety positioned perpendicular to the anthracene. The energy barrier to rotation, $\Delta G^\ddagger$, was calculated to be 85.5 kJ/mol, lower than the approximately 100 kJ/mol barrier necessary for isolation of the enantiomers at room temperature.

**Figure 4.3.** Top: HPLC readout for the enantiomers of 1 at four different temperatures. The enantiomers were separated using the (S,S)-Whelk-O 1 stationary phase with a flow rate of 1 mL/min using dichloromethane:hexane (1:1) as mobile phase. Middle: Simulated HPLC elution profiles with the corresponding calculated $\Delta G^\ddagger$ values. Bottom: Eyring plot analysis.
Imine formation from sensor 1 and a chiral amine was expected to be promoted by the phenol group and result in a CD active compound (Scheme 4.2). Steric interactions between the anthracene and the chiral substrate would slow the rotation about the chiral axis and favor population of a preferred chiral conformation. The absolute configuration of the amine should thus dictate the sign of the CD signal through an asymmetric transformation of the first kind leading to either (S,M) or the (R,P) product, and enantiomers of a given amine therefore give opposite CD spectra.

Scheme 4.2. Asymmetric induction process for sensor 1.

The reaction between 1 and a chiral amino alcohol was surprisingly slow. Despite the presence of the phenol in 1, the imine reaction required 24 hours for full conversion. This is attributed to the steric bulk of the anthracene fluorophore. With the addition of 10 mol% of trifluoroacetic acid, the reaction is complete in only 2 hours. The reaction progress was monitored by in-situ IR, with the aldehyde stretching at 1668 cm\(^{-1}\) gradually disappearing while the imine stretching at 1635 cm\(^{-1}\) steadily increases (Figure 4.4).

Figure 4.4. In-situ IR analysis of the imine formation reaction between 1 and 7.
When 1 was treated with a variety of chiral amines, amino alcohols, and amino acids, strong CD signals were observed (Figure 4.5). The signals are generated at high wavelength, whereas the free chiral substrates are CD silent. The sign of the curve can be correlated to the absolute configuration of the substrate, with the \( R \) enantiomer always exhibiting a negative maximum at 270 nm, while the \( S \) enantiomer is inducing a positive CD response. The CD spectra were collected at micromolar concentration and the most intense signals were observed in alcoholic solvents.

**Figure 4.5.** Top: Substrates tested for sensor 1. Bottom: a) CD spectra of the imines obtained from 1 and (\( R \))-7 (blue) and (\( S \))-7 (red). b) CD spectra of the imines obtained from 1 and (\( R \))-11 (blue) and (\( S \))-11 (red). c) CD spectra of the imines obtained from 1 and (\( R \))-16 (blue) and (\( S \))-16 (red). All spectra collected at \( 7.5 \times 10^{-5} \) M in methanol.

Because of the \( \pi \)-stacking between the salicylaldehyde and the anthracene, it was expected that the fluorescence would change upon binding of a substrate, and that this change
would be directly proportional to the amount of bound substrate. This would allow for the
calculation of the concentration of a substrate in addition to the absolute configuration and
enantiomeric excess. Unfortunately, the changes in both the UV and fluorescence were not
significant enough for concentration analysis (see Experimental Section).

4.3. Second Generation Probe

In an attempt to develop a sensor with the ability to determine concentration as well as
the chiral information of amine substrates, the anthracene moiety was replaced with isoquinoline
\(N\)-oxide to give sensor structure 2. The \(N\)-oxide would serve as a hydrogen bond acceptor for
bound amino alcohols and amino acids, and this interaction was expected to significantly alter
the fluorescent properties of the quinoline ring.

The synthesis of 2 proceeded much more smoothly than that of 1 (Scheme 4.3). A mono-
Suzuki coupling between 1,8-dibromonaphthalene and 4-isoquinolineboronic acid yielded 18,
which was then oxidized with \(m\)-CPBA to 19. A second Suzuki coupling afforded 20, which was
demethylated with BBr\(_3\) to give 2.

![Scheme 4.3. Synthesis of 2 with a crystal structure of the intermediate 18.](image)

The reaction of 2 with amino alcohol 7 was monitored by in-situ IR analysis (Figure 4.6).
The reaction proceeded much faster compared to sensor 1 and did not require an additional acid
catalyst. The disappearance of the formyl stretching at 1680 cm\(^{-1}\) was accompanied by the rapid
formation of the imine stretching at 1640 cm\(^{-1}\). The reaction was complete within 20 minutes according IR and \(^1\)H NMR spectroscopy. Notably, the reaction between 2 and 7 proceeded more rapidly than the corresponding reaction between salicylaldehyde and 7 (see Experimental Section).

**Figure 4.6.** In-situ IR analysis of the imine formation reaction between 2 and 7.

Sensor 2 was treated with several amino alcohols and amino acids, and the CD spectra were collected (Figure 4.7). As opposed to sensor 1, the strongest CD signals were generated in apolar solvents such as hexane, while methanol produced very poor signals. This supports the assumption that intramolecular hydrogen bonding occurs between the substrate and the \(N\)-oxide of the isoquinoline. Additionally, the absolute configuration of all substrates can be determined by the sign of the CD signal at 260 nm, with the \(R\) enantiomer generating a positive CD response and the \(S\) enantiomer generating a negative response.
Figure 4.7. Top: a) CD Spectra of the imines obtained with 2 and (R)-8 (blue) and (S)-8 (red). b) CD Spectra of the imines obtained with 2 and (R)-15 (blue) and (S)-15 (red). All CD spectra obtained at 7.5 x 10^{-5} M in hexane. Bottom: Structures of the substrates tested.

In order to determine the usefulness of 2 for enantioselective sensing, CD spectra were collected of the imines obtained with amino alcohol 7 at varying ee values (Figure 4.8). A linear relationship was observed between the ee of 7 and the CD intensity at three different wavelengths. Using the linear regression equation derived from the calibration curve, the ee values of four unknown samples were calculated at each wavelength. The average calculated values correlated well with the actual ee (Table 4.1). A similar calibration curve was also generated for tryptophan, with the calculated ee values of 4 unknowns also correlating closely to the actual values.

With the success of 2 for absolute configuration and ee analysis, the fluorescence properties of the sensor were examined to determine its suitability for concentration analysis.
(Figure 4.8). As the molar ratio of 7 to 2 was increased from 0 to 1.0, a fluorescence enhancement was observed. When additional equivalents of 7 were added, no change in the fluorescence output occurred. A calibration curve was generated by plotting the molar ratio against the fluorescence maxima at 515 nm, allowing for the accurate concentration determination of 4 unknown samples (Table 4.1).

**Figure 4.8.** Top left: Calibration curves generated from plotting the maxima of the CD spectra of 2 with 7 at 275 nm (blue), 295 nm (red), and 325 nm (green) and 15 (right). Top right: Calibration curves generated from plotting the maxima of the CD spectra of 2 with 15 at 275 nm (blue) and 295 nm (red). Bottom left: Fluorescence spectra of 2 at various molar ratios of 7 from 0 – 1.2 eq. Bottom right: Calibration curve generated from plotting the fluorescence maxima at 515 nm against the molar ratio of [2]/[7].
Table 4.1. Chemosensing Results for 2.

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When comparing the CD spectra of sensors 1 and 2, it is clear that the imines derived from 1 generate much stronger CD intensities. This is due to the presence of an additional chiral axis in 2 (Scheme 4.4). Upon imine formation, 2 is expected to populate a preferred chiral conformation that includes an intramolecular hydrogen bonding motif with the amino alcohol or amino acid. Because of the presence of two chiral axes, additional stereoisomers with individual and possibly opposite CD responses co-exist. For this reason, the CD responses for 2 are significantly diminished. While the syn conformer that includes the intramolecular hydrogen bonding mechanism is expected to predominate in solution, the crystal structure of 2 with substrate 6 shows that the anti conformer prevails in the solid state (Figure 4.9).

Scheme 4.4. Asymmetric induction process for sensor 2. The structures shown in blue are expected to be thermodynamically favored in solution.
Figure 4.9. Front view (left) and side view (right) of the X-ray structures of the imine obtained with 2 and 6.

4.4. Third Generation Probe

While sensor 2 exhibited moderate CD signals for a variety of chiral amino alcohols and amino acids, it was postulated that removal of the second chiral axis would improve the CD readouts by eliminating the possible number of stereoisomers of the imines formed. Therefore, the isoquinoline N-oxide was replaced with pyridine N-oxide (Scheme 4.5). The synthetic procedure is nearly identical as that for sensor 2. A mono-Suzuki coupling between 1,8-dibromonaphthalene and 4-pyridylboronic acid gave 25, which was then oxidized by m-CPBA to 26. A subsequent Suzuki coupling installed the salicylaldehyde in 27, and BBr₃ demethylation afforded the final sensor 3.

Scheme 4.5. Synthesis of 3.
As before, the imine formation was monitored by in-situ IR spectroscopy for the reaction of 1 with amino alcohol 7 (Figure 4.10). The reaction proceeded quickly without an additional catalyst, with full conversion being achieved within 15 minutes.

Figure 4.10. In-situ IR analysis of the imine formation reaction between 3 and 7.

When 3 was treated with several amino alcohols and amino acids and the CD spectra collected, the intensities were indeed very strong (Figure 4.11). For amino alcohols, a positive CD signal was observed for the bound \textit{R} enantiomer at 330 nm, while the opposite CD response was observed for the \textit{S} enantiomer. Amino acids also showed positive CD signals for the \textit{R} enantiomer, in this case at 260 nm, with the \textit{S} enantiomer inducing a negative CD response of 3. The chiroptical responses of all three sensors are listed in Table 4.2.
Scheme 4.6. Asymmetric induction process for sensor 3. The structures in blue are expected to be favored.

Figure 4.11. Top: a) CD Spectra of the imines obtained with 3 and (1R,2S)-6 (blue) and (1S,2R)-6 (red). b) CD Spectra of the imines obtained with 3 and (R)-16 (blue) and (S)-16 (red). All CD spectra collected at 7.5 x 10^{-5} M in hexane. Bottom: Structures of the substrates tested.
Table 4.2. Sensing results for sensors 1, 2, and 3.

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<td>AA</td>
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<td>+20</td>
<td>+</td>
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<td>+20</td>
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<td>+</td>
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<td>3</td>
<td>AC</td>
<td>(R)-29</td>
<td>+11</td>
<td>+</td>
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<td>AC</td>
<td>(S)-29</td>
<td>-11</td>
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$^a$CD output at 270 nm for sensor 1 and 260 nm for sensors 2 and 3. The CD response to 29 was measured at 280 nm. $^b$Predicted CD sign at 270 nm for sensor 1, where R is negative and S is positive. Analysis of the CD readout at 260 nm for sensors 2 and 3 shows R enantiomers give a positive sign and S substrates give a negative CD response for all substrates. MA = monoamine, AA = amino alcohol, AC = amino acid.

As with 2, the ability of sensor 3 to accurately determine ee and concentration was determined through CD and fluorescence spectroscopy. The imines from 3 and amino alcohol 6 at varying ee values were formed and the CD spectra collected (Figure 4.12). A linear correlation
exists between the ee and the CD output at various wavelengths, and the ee of unknown samples were determined from the linear regression equations derived from the calibration curve (see Experimental Section) A fluorescence enhancement occurred when the molar ratio of 6 to 3 was increased from 0 – 1.0 equivalent. Interestingly, quenching of the fluorescence was observed when additional equivalents of the amino alcohol were added.

Figure 4.12. Top left: CD Spectra of the imines obtained with 3 and varying ee of 6. Top right: Linear relationship between the CD output and ee at 260 nm (blue), 290 nm (red), and 340 nm (green). Bottom left: Fluorescence spectra of the imines obtained with 3 and varying molar ratio of 6 from 0-1 (blue) and from 1.2-2 (red). Bottom right: Plot of the fluorescence intensity at 515 nm vs the molar ratio of [6]/[3].
A single crystal of the imine obtained with 3 and amino alcohol 6 was obtained by slow diffusion of hexanes into a concentrated chloroform solution (Figure 4.13). The asymmetric unit showed four imine structures. Three of the imines contained the predicted intramolecular hydrogen bonding network between the hydroxy group of the amino alcohol and the N-oxide of the sensor. The fourth structure showed the open conformation devoid of the hydrogen bonding motif. As a result, the splaying angle between the adjacent phenyl and pyridyl rings was significantly altered. It is possible that when additional equivalents of the substrate are added, a disruption in the intramolecular hydrogen bonding network occurs in solution. Because the open conformation has significant splaying between the peri substituents, the fluorescence may be quenched when additional equivalents of amino alcohol are present (Figure 4.12).

**Figure 4.13.** Left: Crystal structure of the imine obtained from 3 and 6 with the intramolecular hydrogen bond shown with the dashed line. Right: Crystal structure of the same imine devoid of the intramolecular hydrogen bond.

### 4.5. Conclusions

Three new 1,8-diarylnaphthalene probes were developed. These sensors include a stereodynamic salicylaldehyde unit for imine formation with chiral amines, amino alcohols, and amino acids. A fluorophore was introduced peri to the salicylaldehyde as a reporter for substrate
concentration. When anthracene was utilized, CD spectra could be obtained for amines, amino acids, and amino alcohols, though concentration analysis was not possible. For the second generation probe, isoquinoline N-oxide served as the fluorescence reporter. CD spectra were obtained for amino alcohols and amino acids, and the sensor was successfully used for concentration analysis. However, the CD intensities were low due to the presence of an additional chiral axis, leading to complex conformational equilibria. This additional axis was eliminated by using pyridine N-oxide as the fluorophore. Strong CD signals were observed upon binding of amino alcohols and amino acids. Absolute configuration, ee, and concentration analysis was possible with this sensor design.

4.6. Experimental Section

4.6.1. Synthesis of 1

1-(3’-Formyl-4’-methoxyphenyl)-8-bromonaphthalene, 4

A solution of 1,8-dibromonaphthalene (500 mg, 1.7 mmol), 3-formyl-4-methoxyphenylboronic acid (472.0 mg, 2.6 mmol), Pd(PPh₃)₄ (151.5 mg, 0.13 mmol), and K₃PO₄ (927.7 mg, 4.4 mmol) in 18 mL of toluene:ethanol:water (3:2:1 v/v) was stirred at 80 °C for 4 hours. The resulting mixture was allowed to cool to room temperature, quenched with water, and extracted with CH₂Cl₂. The combined organic layers were dried over MgSO₄ and concentrated in vacuo. Purification by flash chromatography on silica gel (CH₂Cl₂:hexanes 4:1) afforded 417 mg (1.2 mmol, 70% yield) of a yellow solid.

¹H NMR δ = 4.02 (s, 3H), 7.12 (d, J = 8.5 Hz, 1H), 7.39-7.50 (m, 3H), 7.68 (d, J = 8.2 Hz, 1H), 7.81 (dd, J = 8.4 Hz, 8.2 Hz, 2H), 7.90 (d, J = 8.0 Hz, 1H), 7.98 (s, 1H), 10.56 (s, 1H). ¹³C NMR: δ = 55.8, 110.7, 119.8, 124.0, 125.3, 126.1, 129.0, 129.1, 129.5, 129.8, 131.4, 133.8,
135.3, 136.1, 137.4, 138.6, 161.1, 190.0. Anal. Calcd. C$_{18}$H$_{13}$BrO$_2$: C, 63.36; H 3.84; Found: C, 63.18; H, 4.06.

1-(3’-Formyl-4’-methoxyphenyl)-8-(9’-anthryl)naphthalene, 5

A solution of 3 (400 mg, 1.2 mmol), anthracene-9-boronic acid (390 mg, 1.8 mmol), Pd(PPh$_3$)$_4$ (208 mg, 0.2 mmol), and K$_3$PO$_4$ (636.8 mg, 3.0 mmol) in 15 mL of toluene was stirred at 120 °C for 18 hours. The resulting mixture was allowed to cool to room temperature, quenched with water, and extracted with CH$_2$Cl$_2$. The combined organic layers were dried over MgSO$_4$ and concentrated in vacuo. Purification by flash chromatography on silica gel (CH$_2$Cl$_2$:hexanes 4:1) afforded 206 mg (0.5 mmol, 40% yield) of a yellow solid.

$^1$H NMR: δ = 3.61 (s, 3H), 5.53 (d, J = 8.5 Hz, 1H), 6.30 (dd, J = 8.5 Hz, 2.2 Hz, 1H), 6.63 (d, J = 2.1 Hz, 1H), 7.08 (d, J = 7.0 Hz, 1H), 7.20-7.41 (m, 7H), 7.49 (dd, J = 7.7 Hz, 7.5 Hz, 1H), 7.63 (dd, J = 7.8 Hz, 7.4 Hz, 1H), 7.78 (d, J = 8.5 Hz, 1H), 7.84 (d, J = 8.5 Hz, 1H), 8.05-8.08 (m, 2H), 8.11 (d, J = 8.2 Hz, 1H), 9.63 (s, 1H). $^{13}$C NMR: δ = 55.3, 108.0, 121.4, 124.7, 125.0, 125.1, 125.3, 125.4, 125.7, 125.9, 126.9, 127.1, 127.7, 127.8, 127.9, 129.2, 129.4, 130.0, 130.7, 130.9, 131.2, 131.3, 131.8, 132.0, 133.8, 134.7, 135.0, 135.6, 137.5, 139.1, 158.8, 188.4. Anal. Calcd. C$_{32}$H$_{22}$O$_2$: C, 87.65; H, 5.06; Found: C, 87.85; H, 5.27.

1-(3’-Formyl-4’-hydroxyphenyl)-8-(9’-anthryl)naphthalene, 1

A solution of 4 (200 mg, 0.46 mmol) and LiCl (193 mg, 4.6 mmol) in 5 mL of DMF was stirred at 150 °C for 12 hours. The resulting mixture was allowed to cool to room temperature, quenched with water and extracted with CH$_2$Cl$_2$. The combined organic layers were washed with brine, dried over MgSO$_4$ and concentrated in vacuo. Purification by flash chromatography on silica gel (CH$_2$Cl$_2$:hexane 2:1) afforded 87.1 mg (0.2 mmol, 60% yield) of a yellow solid.
$^1$H NMR: $\delta = 5.65$ (d, $J = 8.4$ Hz, 1H), 6.26 (d, $J = 2.2$ Hz, 1H), 6.30 (dd, $J = 8.4$ Hz, 2.3 Hz, 1H), 7.07 (d, $J = 7.0$ Hz, 1H), 7.19-7.38 (m, 5H), 7.44 (d, $J = 8.3$ Hz, 1H), 7.48-7.53 (m, 2H), 7.66 (dd, $J = 8.1$ Hz, 8.0 Hz, 1H), 7.81 (ddd, $J = 8.6$ Hz, 8.5 Hz, 2.9 Hz, 2H), 8.06 (d, $J = 8.3$ Hz, 1H), 8.11-8.14 (m, 2H), 8.56 (s, 1H), 10.42 (s, 1H). $^{13}$C NMR: $\delta = 113.7$, 117.2, 124.8, 124.9, 125.0, 125.2, 125.4, 125.5, 126.0, 126.7, 127.1, 128.4, 128.5, 129.4, 129.5, 130.2, 130.8, 130.9, 131.2, 131.3, 131.8, 132.1, 132.3, 132.9, 135.0, 135.1, 135.5, 137.4, 138.8, 158.9, 195.6. Anal. Calcd. C$_{31}$H$_{20}$O$_2$: C, 87.71; H, 4.75; Found: C, 87.97; H, 5.08.

4.6.2. Synthesis of 2

1-Isoquinolyl-8-bromonaphthalene, 18

A solution of 1,8-dibromonaphthalene (500 mg, 1.7 mmol), 4-isoquinolineboronic acid (453.7 mg, 2.6 mmol), Pd(PPh$_3$)$_4$ (151.5 mg, 0.13 mmol), and K$_3$PO$_4$ (927.7 mg, 4.4 mmol) in 18 mL of toluene:ethanol:water (3:2:1 v/v) was stirred at 80 °C for 4 hours. The resulting mixture was allowed to cool to room temperature, quenched with water, and extracted with CH$_2$Cl$_2$. The combined organic layers were dried over MgSO$_4$ and concentrated in vacuo. Purification by flash chromatography on silica gel (CH$_2$Cl$_2$:EtOAc 2:1) afforded 470 mg (1.4 mmol, 80% yield) of a yellow solid.

$^1$H NMR: $\delta = 7.26$-7.36 (m, 2H), 7.51-7.61 (m, 4H), 7.71 (d, $J = 7.4$ Hz, 1H), 7.95 (d, $J = 8.0$ Hz, 1H), 8.01 (dd, $J = 9.3$ Hz, 9.3 Hz, 2H), 8.48 (s, 1H), 9.33 (s, 1H). $^{13}$C NMR: $\delta = 119.7$, 125.2, 125.5, 126.4, 127.0, 127.5, 127.8, 129.2, 130.1, 130.3, 130.6, 132.1, 133.9, 134.0, 134.2, 136.0, 136.6, 143.2, 151.7. Anal. Calcd. C$_{19}$H$_{12}$BrN: C, 68.28; H, 3.62; N, 4.19; Found: C, 68.07; H, 3.62; N, 4.13.
1-(4'-Isoquinolyl)-8-bromonaphthalene N-oxide, 19

A solution of 18 (470 mg, 1.4 mmol) and m-CBPA (728 mg, 4.2 mmol) in 15 mL of CH₂Cl₂ was stirred at room temperature for 12 hours. The mixture was washed with 2M NaOH, dried over MgSO₄, and concentrated in vacuo. Purification by flash chromatography on silica gel (CH₂Cl₂:MeOH 20:1) afforded 441 mg (1.26 mmol, 90% yield) of a light brown solid.

¹H NMR: δ = 7.14 (d, J = 8.5 Hz, 1H), 7.34-7.42 (m, 2H), 7.48 (d, J = 7.1 Hz, 1H), 7.56-7.62 (m, 2H), 7.75 (d, J = 7.6 Hz, 1H), 7.77 (d, J = 8.4 Hz, 1H), 7.96 (d, J = 8.6 Hz, 1H), 8.05 (d, J = 8.9 Hz, 1H), 8.16 (s, 1H), 8.85 (s, 1H).

¹³C NMR: δ = 119.2, 125.0, 125.5, 126.8, 128.9, 128.9, 129.2, 129.3, 130.1, 130.9, 131.1, 131.1, 131.9, 134.2, 135.3, 135.9, 136.9, 138.8. Anal. Calcd. C₁₉H₁₂BrNO: C, 65.16; H, 3.45; N, 4.00; Found: C, 65.14; H, 3.75; N, 3.84.

1-(4'-Isoquinolyl)-8-(3'-formyl-4'-methoxyphenyl)naphthalene N-oxide, 20

A solution of 19 (440 mg, 1.3 mmol), 3-formyl-4-methoxyphenylboronic acid (339.2 mg, 1.9 mmol), Pd(PPh₃)₄ (109 mg, 0.1 mmol) and K₃PO₄ (669 mg, 3.2 mmol) in 18 mL of toluene:ethanol:water (3:2:1 v/v) was stirred at 100 °C for 12 hours. The resulting mixture was allowed to cool to room temperature, quenched with water, and extracted with CH₂Cl₂. The combined organic layers were dried over MgSO₄ and concentrated in vacuo. Purification by flash chromatography on silica gel (CH₂Cl₂:MeOH 20:1) afforded 357.6 mg (0.88 mmol, 70% yield) of a light brown solid. NMR analysis showed a mixture of syn and anti isomers with a ratio of 80:20.

¹H NMR: δ = 3.71 (s, 0.6H), 3.89 (s, 2.4H), 6.01 (d, J = 8.8 Hz, 0.2H), 6.64 (d, J = 7.7 Hz, 0.2H), 6.70 (d, J = 8.8 Hz, 0.8H), 6.90 (s, 0.8H), 6.99 (d, J = 8.0 Hz, 1H), 7.10 (d, J = 7.7 Hz, 0.8H), 7.27-7.31 (m, 2H), 7.39-7.48 (m, 3.2H), 7.56-7.65 (m, 2H), 7.94 (s, 1H), 8.02 (d, J = 7.7 Hz, 1H), 8.11 (d, J = 7.7 Hz, 1H), 8.37 (s, 1H), 9.92 (s, 0.8H), 10.36 (s, 0.2H). ¹³C NMR: δ =
A solution of 20 (350 mg, 0.86 mmol) and BBr$_3$ (1M in CH$_2$Cl$_2$, 2.6 mL, 2.6 mmol) in 10 mL of CH$_2$Cl$_2$ was stirred at room temperature for 2 hours. The resulting mixture was quenched with 2-propanol, washed with water, dried over MgSO$_4$, and concentrated in vacuo. Purification by flash chromatography on silica gel (CH$_2$Cl$_2$:MeOH 20:1) afforded 253 mg (0.65 mmol, 75% yield) of a white solid. NMR analysis showed a mixture of syn and anti isomers with a ratio of 70:30.

$^1$H NMR: δ = 5.96 (d, $J = 8.4$ Hz, 0.3H), 6.59 (s, 1H), 6.69 (d, $J = 8.4$ Hz, 0.7H), 7.06-7.17 (m, 2H), 7.27-7.48 (m, 2H), 7.66-7.87 (m, 5H), 7.89-7.92 (m, 1H), 8.04 (d, $J=8.10$ Hz, 1H), 8.12 (d, $J = 8.1$ Hz, 1H), 8.34 (s, 0.3H), 8.44 (s, 0.7H), 9.08 (s, 0.7H), 9.82 (s, 0.3H), 10.60 (s, 0.7H), 10.98 (s, 0.3H). $^{13}$C NMR: δ = 114.7, 115.2, 117.9, 124.9, 125.3, 125.6, 125.7, 126.0, 128.3, 128.7, 128.9, 129.0, 129.3, 129.4, 129.4, 130.7, 130.8, 130.9, 131.0, 131.0, 132.9, 133.0, 134.2, 134.7, 134.9, 136.4, 136.8, 137.0, 137.8, 137.8, 139.2, 139.2, 159.2, 159.8, 195.2, 196.0.

Anal. Calcd. C$_{26}$H$_{17}$NO$_3$: C, 79.78; H, 4.38; N, 3.58; Found: C, 79.81; H, 4.72; N, 3.40.

4.6.3. Synthesis of 3

1-(4'-Pyridyl)-8-bromonaphthalene, 25

A solution of 1,8-dibromonaphthalene (500 mg, 1.7 mmol), 4-pyridineboronic acid (322 mg, 2.6 mmol), Pd(PPh$_3$)$_4$ (151.5 mg, 0.13 mmol), and K$_3$PO$_4$ (927.7 mg, 4.4 mmol) in 18 mL of toluene:EtOH:water (3:2:1 v/v) was stirred at 90 °C for 6 hours. The resulting mixture was allowed to cool to room temperature, quenched with water, and extracted with CH$_2$Cl$_2$. The
combined organic layers were dried over MgSO\(_4\) and concentrated in vacuo. Purification by flash chromatography on silica gel (CH\(_2\)Cl\(_2\):EtOAc 2:1) afforded 360 mg (1.3 mmol, 75% yield) of a yellow solid.

\(^1\)H NMR:  δ = 7.31-7.38 (m, 4H), 7.50 (dd,  J = 7.3, Hz, 8.0 Hz, 1H), 7.79 (d,  J = 6.6 Hz, 1H), 7.90 (dd,  J = 8.3 Hz, 8.3 Hz, 2H), 8.63 (d,  J = 5.7 Hz, 2H).  \(^{13}\)C NMR:  δ = 119.6, 125.3, 125.4, 126.5, 129.0, 129.9, 131.0, 134.0, 136.0, 137.5, 148.6, 151.4.  Anal. Calcd. C\(_{15}\)H\(_{10}\)BrN:  C, 63.40; H, 3.55; N, 4.93; Found: C, 63.39; H, 3.52; N, 4.82.

1-(4’-Pyridyl)-8-bromonaphthalene  N-oxide, 26

A solution of 25 (400 mg, 1.4 mmol) and \(m\)-CPBA (729 mg, 4.2 mmol) in 10 mL of CH\(_2\)Cl\(_2\) was stirred at room temperature for 8 hours. The mixture was washed with 2M NaOH, dried over MgSO\(_4\), and concentrated in vacuo. Purification by flash chromatography on silica gel (CH\(_2\)Cl\(_2\):EtOH 20:1) and recrystallization from CHCl\(_3\) and hexanes (1:1 v/v) afforded 357 mg (1.2 mmol, 85% yield) of a light brown solid containing 33% of chloroform based on NMR analysis.

\(^1\)H NMR:  δ = 7.29 (d,  J = 6.3 Hz, 2H), 7.35-7.41 (m, 2H), 7.53 (dd,  J = 7.6 Hz, 7.7 Hz, 1H), 7.82 (d,  J = 7.3 Hz, 1H), 7.92-7.97 (m, 2H), 8.30 (d,  J = 6.3 Hz, 2H).  \(^{13}\)C NMR:  δ = 119.2, 125.4, 126.8, 127.4, 128.9, 129.2, 130.5, 140.0, 134.2, 135.6, 136.1, 138.1, 142.4.  Anal. Calcd. C\(_{15}\)H\(_{10}\)BrNO \((\text{CHCl}_3)_{1/3}\):  C, 54.18; H, 3.06; N, 4.12; Found: C, 54.20; H, 3.44; N, 4.10.

1-(4’-Pyridyl)-8-(3’-formyl-4’-methoxyphenyl)naphthalene  N-oxide, 27

A solution of 26 (200 mg, 0.7 mmol), 3-formyl-4-methoxyphenylboronic acid (180 mg, 1.0 mmol), Pd(PPh\(_3\))\(_4\) (58.0 mg 0.05 mmol), and K\(_2\)PO\(_4\) (353.4 mg, 1.7 mmol) in 12 mL of toluene:EtOH:water (3:2:1 v/v) was stirred at 100 °C for 12 hours. The resulting mixture was allowed to cool to room temperature, quenched with water, and extracted with CH\(_2\)Cl\(_2\). The
combined organic layers were dried over MgSO₄ and concentrated in vacuo. Purification by flash chromatography on silica gel (CH₂Cl₂:EtOH 20:1) and recrystallization from CH₂Cl₂ and hexanes (1:1 v/v) afforded 186 mg (0.53 mmol, 75% yield) of a brown solid containing 33% of dichloromethane based on NMR analysis.

¹H NMR: δ = 3.93 (s, 3H), 6.75-6.85 (m, 3H), 7.24 (m, 1H), 7.36 (d, J = 7.9 Hz, 1H), 7.43-7.46 (m, 2H), 7.55-7.61 (m, 2H), 7.74-7.78 (m, 2H), 7.96 (dd, J = 8.1 Hz, 8.2 Hz, 2H), 10.39 (s, 1H).

¹³C NMR: δ = 56.2, 111.5, 123.7, 125.2, 125.8, 126.7, 128.7, 129.1, 129.6, 130.3, 130.6, 131.0, 135.0, 135.2, 135.4, 136.6, 137.4, 137.6, 141.5, 161.0, 189.3. Anal. Calcd. C₂₃H₁₇NO₅•(CH₂Cl₂)₁/₃: C, 73.04; H, 4.64; N, 3.65; Found: C, 73.10; H, 5.01; N, 3.60.

1-(4'-Pyridyl)-8-(3'-formyl-4'-hydroxyphenyl)naphthalene N-oxide, 3

A solution of 27 (200 mg, 0.6 mmol) and BBr₃ (1M in CH₂Cl₂, 1.7 ml, 1.7 mmol) in 10 mL of CH₂Cl₂ was stirred at room temperature for 2 hours. The resulting mixture was quenched with 2-propanol, washed with water, dried over MgSO₄, and concentrated in vacuo. Purification by flash chromatography on silica gel (CH₂Cl₂:EtOH 20:1) and recrystallization from CH₂Cl₂ and hexanes (1:1 v/v) afforded 184 mg (0.54 mmol, 90% yield) of a yellow solid containing 66% of dichloromethane based on NMR analysis.

¹H NMR: δ = 6.78 (d, J = 8.3 Hz, 1H), 6.91 (m, 2H), 7.21-7.26 (m, 2H), 7.40 (d, J = 6.0 Hz, 1H), 7.46 (d, J = 7.0 Hz, 1H), 7.58-7.65 (m, 2H), 7.87-7.95 (m, 2H), 8.00 (dd, J = 7.1 Hz, 7.3 Hz, 2H), 9.78 (s, 1H), 10.84 (s, 1H). ¹³C NMR: δ = 117.5, 119.7, 125.4, 126.0, 128.7, 129.2, 130.4, 131.0, 134.3, 134.5, 135.3, 135.6, 137.4, 138.0, 141.2, 160.6, 195.6. Anal. Calcd. C₂₂H₁₅NO₅•(CH₂Cl₂)₂/₃: C, 68.41; H, 4.14; N, 3.52; Found: C, 68.29; H, 4.17; N, 3.47.
4.6.4. Enantioselective Sensing Experiments

General procedure for chemosensing of amines and amino alcohols

A stock solution of sensor 1, 2, or 3 (0.00375 M) in CHCl$_3$ was prepared and portions of 350 µL were transferred to 4 mL vials. Solutions of the substrates (0.026 M in CHCl$_3$) were prepared. To each vial containing 350 µL of stock solution was added 1 equivalent (50 µL, 0.0013 mmol) of the substrate. The reactions were stirred overnight for sensor 1 and 15 minutes for sensors 2 and 3. The reaction times can be reduced to 5 hours for sensor 1 by addition of 10 mol% of trifluoroacetic acid or $p$-toluenesulfonic acid. The CD analysis was conducted with sample concentrations of 7.50 x 10$^{-5}$ M in MeOH for sensor 1 and in hexanes for sensors 2 and 3. CD spectra were collected with a standard sensitivity of 100 mdeg, a data pitch of 0.5 nm, a bandwidth of 1 nm, a scanning speed of 500 nm s$^{-1}$ and a response of 0.5 s using a quartz cuvette (1 cm path length). The data were baseline corrected and smoothed using a binomial equation. Control experiments with free substrates showed no CD signal in the region of interest.

Figure 4.14. CD Spectra of various substrates with 1, 2, and 3.

CD Spectra of the imine obtained from 1 and (1R,2S)-6 (blue) and (1S,2R)-6 (red)
CD Spectra of the imine obtained from 1 and (R)-7 (blue) and (S)-7 (red)

CD spectra of the imine obtained from 1 and (1R,2R)-8 (blue) and (1S,2S)-8 (red)

CD Spectra of the imine obtained from 1 and (R)-9 (blue) and (S)-9 (red)
CD Spectra of the imine obtained from 1 and (R)-10 (blue) and (S)-10 (red)

CD Spectra of the imine obtained from 1 and (R)-11 (blue) and (S)-11 (red)

CD Spectra of the imine obtained from 1 and (R)-12 (blue) and (S)-12 (red)
CD Spectra of the imine obtained from 1 and (R)-13 (blue) and (S)-13 (red)

CD Spectra of the imine obtained from 1 and (R)-14 (blue) and (S)-14 (red)

CD Spectra of the imine obtained from 1 and (R)-15 (blue) and (S)-15 (red)
CD Spectra of the imine obtained from 1 and (R)-16 (blue) and (S)-16 (red)

CD Spectra of the imine obtained from 1 and (R)-17 (blue) and (S)-17 (red)

CD Spectra of the imine obtained from 2 and (1R,2S)-6 (blue) and (1S,2R)-6 (red)
CD Spectra of the imine obtained from 2 and (R)-7 (blue) and (S)-7 (red)

CD Spectra of the imine obtained from 2 and (1R,2R)-8 (red) and (1S,2S)-8 (red)

CD Spectra of the imine obtained from 2 and (1S,2R)-9 (blue) and (1R,2S)-9 (red)
CD Spectra of the imine obtained from 2 and (R)-21 (blue) and (S)-21 (red)

CD Spectra of the imine obtained from 2 and (R)-22 (blue) and (S)-22 (red)

CD Spectra of the imine obtained from 2 and (R)-23 (blue) and (S)-23 (red)
CD Spectra of the imine obtained from 2 and (R)-24 (blue) and (S)-24 (red)

CD Spectra of the imine obtained from 2 and (R)-14 (blue) and (S)-14 (red)

CD Spectra of the imine obtained from 2 and (R)-15 (blue) and (S)-15 (red)
CD Spectra of the imine obtained from 2 and (R)-16 (blue) and (S)-16 (red)

CD Spectra of the imine obtained from 2 and (R)-17 (blue) and (S)-17 (red)

CD Spectra of the imine obtained from 3 and (1R,2S)-6 (blue) and (1S,2R)-6 (red)
CD Spectra of the imine obtained from 3 and (R)-7 (blue) and (S)-7 (red)

CD Spectra of the imine obtained from 3 and (1R,2S)-8 (blue) and (1S,2R)-8 (red)

CD Spectra of the imine obtained from 3 and (1R,2S)-9 (blue) and (1S,2R)-9 (red)
CD Spectra of the imine obtained from 3 and (R)-21 (blue) and (S)-21 (red)

CD Spectra of the imine obtained from 3 and (R)-22 (blue) and (S)-22 (red)

CD Spectra of the imine obtained from 3 and (R)-23 (blue) and (S)-23 (red)
CD Spectra of the imine obtained from 3 and \((R)-24\) (blue) and \((S)-24\) (red)

CD Spectra of the imine obtained from 3 and \((1S,2S)-28\) (blue) and \((1R,2R)-28\) (red)

CD Spectra of the imine obtained from 3 and \((R)-14\) (blue) and \((S)-14\) (red)
CD Spectra of the imine obtained from 3 and (R)-15 (blue) and (S)-15 (red)

CD Spectra of the imine obtained from 3 and (R)-16 (blue) and (S)-16 (red)

CD Spectra of the imine obtained from 3 and (R)-29 (blue) and (S)-29 (red)
4.6.5. Calibration Curve and Ee Determination with Sensor 2 and Amino Alcohol 7
A calibration curve was constructed using samples of 7 with varying ee. Stock solutions of 2 (0.00375 M in CHCl₃) with varying enantiomeric composition (+100, +80, +60, +40, +20, 0, -20, -40, -60, -80, -100 ee) were prepared and the condensation reaction was carried out as described in section 3.6.4. The CD amplitudes measured at 275, 295, and 325 nm were plotted against % ee.

4.6.6. Calibration Curve and Ee Determination with Sensor 2 and Amino Acid 15
A calibration curve was constructed using samples of 15 with varying ee. Stock solutions of 2 (0.00375 M in DMSO) with varying enantiomeric composition (+100, +80, +60, +40, +20, 0, -20, -40, -60, -80, -100 ee) were prepared and the condensation reaction was carried out as described above for amino acids. A full equivalent of HCl (1.3 µL, 0.0013 mmol) was added to each vial and CD spectra were obtained as described in section 3.6.4. The CD amplitudes measured at 260 and 290 nm were plotted against % ee.

4.6.7. Calibration Curve and Ee Determination with Sensor 3 and Amino Alcohol 6
A calibration curve was constructed using samples of 6 with varying ee. Stock solutions of 6 with varying ee composition (+100.0, +80.0, +60.0, +40.0, +20.0, 0.0, -20.0, -40.0, -60.0, -80.0, -100.0) were added to 0.00375 M solutions of 3 and the condensation reaction and CD analysis were carried out as described above. The Cotton effect amplitudes measured at 260 nm were plotted against % ee.

4.6.8. Calibration Curve and Ee Determination with Sensor 3 and Amino Acid 16
A calibration curve was constructed using samples of 16 with varying ee. Stock solutions of 3 (0.00375 M in DMSO) with varying enantiomeric composition (+100, +80, +60, +40, +20, 0, -20, -40, -60, -80, -100 ee) were prepared and the condensation reaction was carried out as described above for amino acids. One equivalent of HCl (1.3 µL, 0.0013 mmol) was added to
each vial and CD spectra were obtained as described above. The CD amplitudes measured at
274, 303, and 335 nm were plotted against % ee.

**Figure 4.15.** CD Spectra of the imine obtained from 3 and varying ee compositions of 16

**Figure 4.16.** Linear relationship between the CD amplitude at 260 nm (blue) and 290 nm (red) nm and the enantiomeric excess of 16
**Table 4.3.** Experimentally determined ee’s of four scalemic samples of 16 using the CD maxima at 274, 303 and 335 nm

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<th>Actual % ee (R)</th>
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<th>Calculated % ee at 303 nm (R)</th>
<th>Calculated % ee at 335 nm (R)</th>
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4.6.9. **Determination of the Concentration of 7 Using the Imine Obtained from 2**

The change in the fluorescence of the sensor upon imine formation was analyzed. A calibration curve was constructed using samples containing various amounts of 7. First, 350 µL solutions of 2 (0.00375 M in CHCl₃) were placed in 16 vials. To each vial was then transferred a solution of 7 (0.065 M) in varying amounts (0, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, and 120 mol%) and the condensation reaction was carried out as described above. Fluorescence spectra were collected using an excitation wavelength of 340 nm with slit widths of 3 nm and 6 nm and a quartz cuvette (1 cm path length). The fluorescence intensity at 515 nm increased as the concentration of 7 increased from 0 to 100 mol%. When the concentration of 7 was in excess of 100 mol%, the intensity remained constant. Plotting and curve fitting of the fluorescence intensity (I) at 515 nm against the concentration (c) of 7 ranging from 0 to 100 mol% gave a polynomial equation \( I = -762.79(c)^2 + 1773.5(c) + 180.29 \) with \( R^2 = 0.99415 \).
4.6.10. Determination of the Concentration of 6 Using the Imine Obtained from 3

The change in the fluorescence of the sensor upon imine formation was analyzed. A calibration curve was constructed using samples containing various amounts of 6. First, 350 µL solutions of 3 (0.00375 M in CHCl₃) were added to 16 vials. To each vial was then transferred a solution of 6 (0.13 M, 10 µl) in varying amounts (0, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 120, 140, 160, 180 and 200 mol%) and the condensation reaction was carried out as described above. Fluorescence spectra were collected using an excitation wavelength of 340 nm with slit widths of 3 nm and 6 nm and a quartz cuvette (1 cm path length). The fluorescence intensity at 515 nm increased as the concentration of 6 increased from 0 to 100 mol%, followed by quenching in the presence of excess of 6. Plotting and curve fitting of the fluorescence intensity (I) at 515 nm against the concentration (c) of 6 ranging from 0 to 100 mol% gave a polynomial equation (I = -993.63(c)^2 + 2406.8(c) + 127.41) with R² = 0.99511.

4.6.11. Determination of the Concentration of 16 Using the Imine Obtained from 3

The change in the fluorescence of the sensor upon imine formation was analyzed. A calibration curve was constructed using samples containing various amounts of 16. First, 350 µL solutions
of 3 (0.00375 M in DMSO) were placed in 16 vials. To each vial was then transferred a solution of 16 (0.065 M in DMSO) in varying amounts (0, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 140, 160, 180, and 200 mol%) and the condensation reaction was carried out as described above for amino acids. Fluorescence spectra were collected using an excitation wavelength of 350 nm with slit widths of 3 nm and 6 nm and a quartz cuvette (1 cm path length). The fluorescence intensity at 450 nm decreased as the concentration of 16 increased from 0 to 100 mol%. When the concentration of 16 was in excess of 100 mol%, the intensity remained constant. Plotting and curve fitting of the fluorescence intensity (I) at 450 nm against the concentration (c) of 16 ranging from 0 to 100 mol% gave a polynomial equation (I = 71052 (c)^2 - 246472(c) + 236004) with R^2 = 0.99397.

**Figure 4.18.** Fluorescence spectra obtained for the imine formed from 3 and varying concentrations of 16 from 0-100 mol% (blue) and 120-200 mol% (red).
Figure 4.19. Fluorescence intensity (I) measured at 450 nm plotted against equivalents of 16

![Graph showing fluorescence intensity vs. ratio (10)/(1)](image)

Figure 4.20. Curve fitting of the fluorescence emission at 450 nm

![Graph showing regression equation](image)

Five solutions of sensor 3 were prepared and added to solutions of varying concentrations of 16 as described above. Using the regression equation obtained from the calibration curve and the measured fluorescence intensity at 450 nm, the concentration of these samples was determined with high accuracy.
Table 4.4. Experimentally determined concentrations of five samples of varying concentration of 16 using the fluorescence response at 450 nm.

<table>
<thead>
<tr>
<th>Actual Concentration (mM)</th>
<th>Calculated Concentration (mM)</th>
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</thead>
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<tr>
<td>2.93</td>
<td>2.97</td>
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4.6.12. Attempts to Determine the Concentration of 7 Using the Imine Obtained from 1

The change in the UV and fluorescence of sensor 1 upon imine formation with 7 was analyzed. First, 350 µL solutions of 1 (0.00375 M in CHCl₃) were placed in 16 vials. To each vial was then transferred a solution of 7 (0.065 M in CHCl₃) in varying amounts (0, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 140, 160, 180, and 200 mol%) and the condensation reaction was carried out as described above for amino acids. Fluorescence spectra were collected using an excitation wavelength of 400 nm with slit widths of 3 nm and 6 nm and a quartz cuvette (1 cm path length). The fluorescence intensity at 440 nm increased at low substrate concentration (up to 30 mol% of 7) and then remained constant. UV spectra were collected in CHCl₃ (3.5 x 10⁻⁵ M). The UV absorption increased upon imine formation but the changes were too small for quantitative purposes.
Figure 4.21. UV spectra of the imine obtained from 1 and 7.

Figure 4.22. Fluorescence spectra of the imine obtained from 1 and 7 with the ratio of [7]/[1] = 0 (blue), 0.3 (red), 0.5 (orange), and 1.0 (green)

4.6.13. Determination of the Rotational Energy Barrier of Sensor 1 by Dynamic HPLC

The barrier to rotation ($\Delta G^{\ddagger}$) of the 3'-formyl-4'-methoxyphenyl unit of sensor precursor 5 was determined by DHPLC. Compound 5 (1 mg, 0.002 mmol) was dissolved in 1.5 mL of CH$_2$Cl$_2$:hexanes (1:1 v/v). HPLC data were collected using 1:1 CH$_2$Cl$_2$:hexanes as mobile phase, a flow rate of 1 mL/min, an injection volume of 20 µL and the (S,S)-Whelk-O 1 column at various temperatures. The rotational barrier was determined by simulation of the elution profiles obtained at -4.8, -10.4, -14.9, and -20.2 °C with the computer program Mimesis 3.1. The rate
constant of enantiomerization was optimized until the simulated and experimentally obtained elution profiles were superimposable.

4.6.14. Comparison of CD Output Obtained with the Protonated and Deprotonated Form of the Imine Obtained from Sensors 1, 2, and 3 and Amino Acids

Imine formation with sensor 3 and amino acids 14, 15, 16, and 29 was conducted in the presence of TBAOH as described above. After the condensation was complete, 1 equivalent of HCl (1.25 M in EtOH, 4 µL) was added, changing the color from dark to light yellow (Scheme 4.7). CD spectra were collected as described above.

Scheme 4.7. Condensation of 3 with amino acid 21 in the presence of TBAOH, followed by addition of 1 equivalent of HCl.

Figure 4.23. Comparison of the CD spectra of 3 at different pH.

CD Spectra of the imine obtained from 3, TBAOH and (R)-14 (solid blue) and (S)-14 (solid red). CD response of the imine obtained from 3 and (R)-14 (dashed blue) and (S)-14 (dashed red) upon addition of HCl.
CD Spectra of the imine obtained from 3, TBAOH and (R)-15 (solid blue) and (S)-15 (solid red). CD response of the imine obtained from 3 and (R)-15 (dashed blue) and (S)-15 (dashed red) upon addition of HCl.

CD Spectra of the imine obtained from 3, TBAOH and (R)-16 (solid blue) and (S)-16 (solid red). CD response of the imine obtained from 3 and (R)-16 (dashed blue) and (S)-16 (dashed red) upon addition of HCl.
CD Spectra of the imine obtained from 3, TBAOH and (R)-29 (solid blue) and (S)-29 (solid red).

CD response of the imine obtained from 3 and (R)-29 (dashed blue) and (S)-29 (dashed red) upon addition of HCl.

CD Spectra of the imine obtained from 2, TBAOH and (R)-15 (solid blue) and (S)-15 (solid red).

CD response of the imine obtained from 2 and (R)-15 (dashed blue) and (S)-15 (dashed red) upon addition of HCl.
CD Spectra of the imine obtained from 1, TBAOH and (R)-17 (solid blue) and (S)-17 (solid red). CD response of the imine obtained from 1 and (R)-17 (dashed blue) and (S)-17 (dashed red) upon addition of HCl.

4.6.15. Crystallography

A single crystal of the imine formed from 2 and (1S,2R)-6 was obtained by slow diffusion of hexanes into a concentrated chloroform solution. Crystallographic analysis was performed at 100 K using a Siemens platform diffractometer with graphite monochromated Mo-Kα radiation (λ = 0.71073 Å). Data were integrated and corrected using the Apex 2 program. The structure was solved by direct methods and refined with full-matrix least-square analysis using SHELX-97-2 software. Non-hydrogen atoms were refined with anisotropic displacement parameters. The asymmetric unit contains one imine molecule having (1S,2R,M,M) configuration and one chloroform molecule. Crystal structure data: Formula C₄₀H₃₀N₂O₃, M = 586.23, crystal dimensions 0.5 x 0.3 x 0.1 mm, orthorhombic, space group P2₁2₁2₁, a = 12.362(3) Å, b = 14.611(3) Å, c = 19.273(4) Å, α = 90.0°, β = 90.0°, γ = 90.0°, V = 3481.0 Å³, Z = 4, ρcalc = 1.347 g cm⁻³.
A single crystal of compound 4 was obtained by slow evaporation of a concentrated chloroform solution. Crystallographic analysis was performed with identical parameters as listed above. The asymmetric unit contains one molecule of 4. Crystal structure data: Formula C_{18}H_{13}O₂Br, M = 340.19, crystal dimensions 0.4 x 0.2 x 0.1 mm, monoclinic, space group C2/c, \( a = 21.461(2) \) Å, \( b = 7.9205(8) \) Å, \( c = 16.9348(16) \) Å, \( \alpha = 90.0^\circ \), \( \beta = 103.40^\circ \), \( \gamma = 90.0^\circ \), \( V = 2800.2(5) \) Å³, \( Z = 8 \), \( \rho_{\text{calcld}} = 1.614 \text{ g cm}^{-3} \).

Figure 4.25. 1-(3’-Formyl-4’-methoxyphenyl)-8-bromonaphthalene (4): view from the front (left) and the side (right)
A single crystal of compound 5 was obtained by slow evaporation of a concentrated chloroform solution. Crystallographic analysis was performed with identical parameters as listed above. The asymmetric unit contains one molecule of 5. Crystal structure data: Formula C$_{32}$H$_{22}$O$_2$, M = 438.50, crystal dimensions 0.22 x 0.21 x 0.12 mm, orthorhombic, space group P2$_1$2$_1$2$_1$, $a = 9.3196(8)$ Å, $b = 14.6659(12)$ Å, $c = 15.9831(13)$ Å, $\alpha = 90.0^\circ$, $\beta = 90.0^\circ$, $\gamma = 90.0^\circ$, $V = 2184.6(3)$ Å$^3$, $Z = 4$, $\rho_{\text{calc}} = 1.333$ g cm$^{-3}$.

**Figure 4.26.** 1-(3'-Formyl-4'-methoxyphenyl)-8-(9'-anthryl)naphthalene (5): view from the front (left) and the side (right)

A single crystal of compound 6 was obtained by slow evaporation of a concentrated chloroform solution. Crystallographic analysis was performed with identical parameters as listed above. The asymmetric unit contains one molecule of 6. Crystal structure data: Formula C$_{19}$H$_{12}$NBr, M = 334.21, crystal dimensions 0.35 x 0.25 x 0.16 mm, monoclinic, space group P2$_1$/c, $a = 7.9306(13)$ Å, $b = 15.123(2)$ Å, $c = 12.1926(19)$ Å, $\alpha = 90.0^\circ$, $\beta = 105.512(2)^\circ$, $\gamma = 90.0^\circ$, $V = 1409.1(4)$ Å$^3$, $Z = 4$, $\rho_{\text{calc}} = 1.575$ g cm$^{-3}$.
Figure 4.27. 1-(4'-Isoquinolyl)-8-bromonaphthalene (18): view from the front (left) and the side (right)

A single crystal of the imine formed from 3 and (1S,2R)-6 was obtained by slow diffusion of hexanes into a concentrated chloroform solution of the imine. The asymmetric unit contains four unique imine molecules with (1S,2R,M) configuration and three chloroform molecules. The imines A, C and D show intramolecular hydrogen bonding between the alcohol moiety of 6 and the N-oxide group of the sensor. Crystal structure data: Formula C\(_{36}\)H\(_{28}\)N\(_2\)O\(_3\), M = 536.63, crystal dimensions 0.6 x 0.2 x 0.1 mm, monoclinic, space group P2\(_1\), \(a = 14.036(1)\) Å, \(b = 9.731(5)\) Å, \(c = 44.837(1)\) Å, \(\alpha = 90.0^\circ\), \(\beta = 96.093^\circ\), \(\gamma = 90.0^\circ\), \(V = 6089.81\) Å\(^3\), \(Z = 8\), \(\rho_{\text{calc}} = 1.3668\) g cm\(^{-3}\).
Figure 4.28. View facing the naphthalene ring (left) and along the naphthalene ring (right)
4.7. References


Chapter V. A Stereodynamic Binaphthol Ligand for Sensing of Chiral Compounds*

5.1. Introduction

The use of biphenol ligands for chiral amplification of metal complexes is well documented. Particularly, Kwit and Gawronski reported the use of stereodynamic biphenol ligands to increase the efficiency of asymmetric reactions. They found that addition of biphenol to a chiral diamine-zinc complex increases the yield and ee of the asymmetric hydrosilylation of ketones. When biphenol binds to the chiral zinc complex, it populates a preferred chiral conformation. This extends the chiral information around the zinc coordination sphere, which in turn increases the asymmetric induction of the hydrosilylation reaction. It was also shown that these complexes have characteristic CD signals, indicating effective asymmetric transformation of the first kind.

The goal of this project was to test the usefulness of metal complexes with stereodynamic biphenol or binaphthol ligands 1 and 2 for chirality sensing of several classes of substrates (Scheme 5.1). These ligands were expected to rapidly bind to a variety of metals and to form stable coordination complexes. Subsequent coordination of a chiral substrate would then generate a conformational bias in the reporter ligand 1 and 2, respectively, and thus produce a strong CD signal, which could be exploited for HTS purposes.

Scheme 5.1. Asymmetric induction process with metal complexes carrying ligand 1 or 2.

5.2. Results and Discussion

As discussed above, biphenol 1 has been used to enhance the asymmetric reaction environment of catalytically active metal complexes due to the facile rotation about the chiral aryl-aryl axis and instant population of a thermodynamically favored chiral conformation. At the beginning of this study, the experimental racemization data for biphenol and stereodynamic binaphthol ligands were not reported, while limited information was available for other tropos ligands. The barrier to enantioconversion for several biphep (2,2'-bis(diphenylphosphino)-1,1'-biphenyl) ligands, however, was determined by Maier and Trapp utilizing dynamic HPLC. While these ligands racemize at room temperature, it is possible they become conformationally stable upon coordination to a metal. Gagné determined that coordination of biphep to Pt increases the rotational energy barrier by nearly 30%.

In order to better understand the racemization kinetics of 1, dynamic HPLC was attempted at low temperature. However, after screening several chiral stationary phases and conditions, the enantiomers could not be separated. Instead, 1 was derivatized to 3 with
isobutyryl chloride to introduce diastereotopic methyl protons for variable temperature NMR analysis. The coalescence of the methyl shift allowed for the determination of the rotational barrier, $\Delta G^\ddagger$, as 52.6 kJ/mol (Figure 5.1). Fujimura calculated the value using DFT as 48.1 kJ/mol, which is in good agreement with the experimentally determined value. The fused benzene ring in 2 is not expected to significantly increase the rotational energy barrier and it should have a similar racemization rate constant. Considering the study with biphep by Gagné, one would therefore expect that both 1 and 2 undergo facile enantioconversion even upon formation of a coordination complex.

**Figure 5.1.** Left: Variable-temperature NMR analysis of the enantioconversion of 3 (only the methyl signals are shown). Right: Schematic representation of the enantioconversion of 3.

Biphenol 1 was treated with diethyl zinc and enantiopure 1,2-diphenyl-1,2-diaminoethane, 8, in order to determine its usefulness for chirality sensing. A weak CD response was observed above 300 nm at micromolar concentration, however the complex was unstable under air and quickly decomposed. In an effort to improve the CD response and stability, ligand
2 was synthesized. It was expected that the larger chromophores would enhance the chiral amplification and shift the CD signals to higher wavelengths.

Binaphthol 2 was obtained in several steps (Scheme 5.2). First, ortho-bromination of 1-naphthol was achieved with high selectivity to give 4. Protection of the naphthol with MeI gave 5, which was converted to the boronic acid 6 with n-BuLi and B(OMe)₃. Suzuki coupling with 4 gave the protected binaphthene 7, which was demethylated with BBr₃ to yield 2.

![Scheme 5.2. Synthesis and crystal structure of binaphthol 2.](image)

When 2 was treated with Et₂Zn and 8, the CD signal that was generated was much stronger than the corresponding signal with 1, while the wavelength was significantly red-shifted (Figure 5.2). Strong CD signals were also observed with other substrates including monoamines 9-13 and primary and tertiary amino alcohols 14-20. Large Cotton effects were observed for both aliphatic and aromatic substrates, with a maximum near 350 nm. CD signals were observed immediately upon mixing of the components, and the maximum signal was obtained after 5 minutes. The absolute configuration can be correlated to the sign of the CD amplitude. For amines, a positive CD signal was observed for the S enantiomer, while R amines gave a negative response. Amino alcohols with a single chiral center gave a positive signal for the R enantiomer and a negative signal for the S enantiomer, while the opposite was true for amino alcohols.
containing two chiral centers (Table 5.1). Several other metals, such as Mg(OtBu)$_2$, Zn(OTf)$_2$, and Al(OiPr)$_3$ also gave a CD signal in the presence of 2 and 8, however, none was as intense as with Et$_2$Zn.

**Figure 5.2.** Top: a) CD spectra of the Zn complexes derived from 2 and (1R,2R)-8 (solid blue) or (1S,2S)-8 (solid red) and from 1 and (1R,2R)-8 (dashed blue) or (1S,2S)-8 (dashed red). b) CD spectra of the Zn complexes derived from 2 and (1R,2S)-17 (blue) or (1S,2R)-17 (red). Bottom: Structures of substrates tested with 2 and Et$_2$Zn.
Table 5.1. Sensing results obtained with metal complexes of 2.

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<th>Predicted Cotton Effect$^b$</th>
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$^a$CD measurement at 3.0 x 10^{-3}\text{M} \\

$^b$Predicted sign at 350 nm for mono-amines: $R$ is negative, $S$ is positive; amino alcohols with one chiral center: $R$ is negative, $S$ is positive; chiral amino alcohols with two chiral centers: $R$ is positive, $S$ is negative; $\alpha$-hydroxy acids: $R$ is negative, $S$ is positive; amino acids: $R$ is positive, $S$ is negative.

Analysis of the Zn complex with 2 and diamine 8 by mass spectrometry revealed a bimetallic species with a stoichiometry of 2:2:2 (2:Zn:8)$_2$. The zinc complex of 2 and amino alcohol 9 also showed a bimetallic species but with a stoichiometry of 2:2:4 (2:Zn:9)$_2$. Very little is known about the structures of zinc complexes carrying a binaphtholate and diamine, despite several reports of their use in asymmetric catalysis. Walsh et al. determined the X-ray structure of a zinc complex derived from a BINOL derivative and a bulky secondary diamine.
with a 1:1:1 stoichiometry and thus tetrahedral Zn center. A single crystal of 2 bound to Zn also
carrying diamine 8 was grown by slow diffusion of diethyl ether into a concentrated chloroform
solution. Importantly, X-ray analysis supports the (2:2:2) stoichiometry determined by MS
analysis (Figure 5.3). The structure exhibits a four-membered µ-oxo ring that consists of two Zn
centers bridged by one oxygen from each of the binaphtholate ligands. One molecule of 8 is also
coordinated to each metal center, contributing to distorted bipyramidal Zn centers. The two
binaphthol ligands display opposite stereochemistry to give an overall (1S,2S,P,M) configuration.

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**Figure 5.3:** Top: Crystal structures of bimetallic Zn complexes obtained with 2 and (1S,2S)-8. A
stoichiometry of 2:2:2 is observed, and each Zn atom has a distorted trigonal bipyramidal
geometry. Bottom: Selected crystallographic distances [Å] and angles [°].
In order to increase the substrate scope, a completely unrelated class of chiral compounds was tested. Riguera and colleagues reported an effective NMR method for determining the absolute configuration of $\alpha$- and $\beta$-hydroxy acids using BINOL-borate complexes.\(^9\) It was hypothesized that ligand 2 would show strong CD signals when treated with chiral $\alpha$-hydroxy acids and B(OMe)$_3$. Comparison of the borate complexes obtained from 1 and 2 with acid 21 showed that 1 gave no CD signal above 300 nm even at elevated concentrations (Figure 5.4). In contrast, borate complexes of 2 and substrates 21-24 produced characteristic CD amplitudes. The expected (binaphtholate)boron($\alpha$-alkoxy carboxylate) complex having a 1:1:1 stoichiometry was observed by MS. As before, complex formation was fast and CD measurements were taken within 5 minutes. The absolute configuration of the analytes was determined by observing the sign of the CD output at 320 nm, with the $R$ enantiomer displaying a negative CD and the $S$ a positive one. In addition to $\alpha$-hydroxy acids, amino acids also generated CD signals in the presence of 2 and B(OMe)$_3$. A positive CD maximum at 350 nm was observed for all $R$ enantiomers, while the $S$ enantiomers generated a negative signal.
Figure 5.4. Top: a) CD Spectra of the boron complexes derived from 2 and (R)-22 (solid blue) or (S)-22 (solid red) and from 1 and (R)-22 (dashed blue). b) CD spectra of the boron complexes derived from 2 and (R)-27 (blue) or (S)-27 (red). Bottom: Structures of the substrates tested with 2 and B(OMe)₃.

A recent report by Anslyn, James, and Bull described the use of a three-component assembly for the ee analysis of chiral primary amines. In that study, atropos BINOL and 2-formylphenylboronic acid were treated with a primary amine, which formed a tetrahedral boron complex upon imine formation. Using similar conditions, both ligands 1 and 2 were treated with 4-methoxy-2-formylphenylboronic acid 31 and amines 32 and 33 (Figure 5.5). A weak CD signal was observed for 1, while a much stronger, red-shifted signal was observed with ligand 2. The chiral amplification relies solely on the central-to-axial chirality induction from the chiral amine substrate to stereolabile 2 and eliminates the need for a chiral BINOL ligand. However,
this approach is only applicable to primary amines, in contrast to the chirality sensing with stereodynamic zinc complexes of 2, which included a tertiary amino alcohol.

![Chemical structure and diagram]

**Figure 5.5.** Top: Chirality sensing using 2 and 31. Bottom left: CD spectra of the reaction products obtained using 2, 31, and (R)-32 (solid blue) or (S)-32 (solid red). The dashed lines correspond to the spectra obtained with 31 and (R)-32 (dashed blue) or (S)-32 (dashed red) in the absence of 2. Bottom right: The same comparison with 33. All CD collected at 3.75 x 10^{-5} M in CHCl₃.

The possibility of quantitative ee analysis was tested by collecting the CD spectra of the Zn complexes derived from 2, Et₂Zn, and nonracemic mixtures of 8. A nonlinear trend was observed when plotting the CD maxima at 360 nm against substrate ee (Figure 5.6). This indicates the presence of homo- and heterochiral (2:Zn:8)₂ adducts. This result matches well with the presence of a bimetallic species observed in the solid state and by MS analysis in solution. The ee of unknown samples were calculated with high accuracy using the regression equation derived from the calibration curve. This analysis was successfully repeated with amino alcohol 18 (Table 5.2). A red shift in the UV signature of the Zn complex with 2 was observed when an
equivalent of 8 was added, which shows the potential of 2 for concentration analysis (see Experimental Section).

Figure 5.6. Top left: CD spectra of the Zn complex obtained with 2 and non-racemic samples of 8 at 3.0 x 10^{-5} M in diethyl ether. Top right: Plot of the CD maxima at 360 nm vs ee of 8. Bottom left: CD spectra of the Zn complex obtained with 2 and non-racemic samples of 18 at 3.0 x 10^{-4} M in diethyl ether. Bottom right: Plot of the CD maxima at 360 nm vs ee of 18.

Table 5.2. Quantitative sensing results.

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5.3. Conclusions

Metal complexes derived from tropos binaphthol ligand 2 were introduced to chirality sensing of monoamines, diamines, amino alcohols, amino acids, and α-hydroxy acids. Stronger CD signals were observed with 2 when compared with commercially available 1. The CD signals originate from an asymmetric transformation of the first kind of the stereodynamic zinc and boron binaphtholates. Complex formation is fast, and the CD signals generated were successfully correlated to the absolute configuration and ee of the chiral analytes tested.

5.4. Experimental Section

5.4.1. Synthesis of 2

2-Bromo-1-naphthol, 4

1-Naphthol (500 mg, 3.5 mmol) and diisopropylamine (49 µl, 0.35 mmol) were dissolved in 10 mL of dichloromethane. N-Bromosuccinimide (679.0 mg, 3.8 mmol) was carefully added and the reaction mixture was stirred at 40 °C for 8 hours. The resulting mixture was allowed to cool to room temperature, quenched with 2N H₂SO₄, and extracted with dichloromethane. The combined organic layers were dried over MgSO₄ and concentrated in vacuo. Purification by flash chromatography on silica gel (CH₂Cl₂:hexanes 2:1) afforded 650 mg (2.9 mmol, 85% yield) of a white solid. ¹H NMR: δ = 5.96 (s, 1H), 7.30 (d, J = 8.8 Hz, 1H), 7.46 (d, J = 8.8 Hz, 1H), 7.49-7.52 (m, 2H), 7.77 (m, 1H), 8.23 (m, 1H). ¹³C NMR δ = 104.0, 121.3, 122.3, 124.4, 126.1, 126.8, 127.6, 128.3, 133.7, 148.2.

2-Bromo-1-methoxynaphthalene, 5

A solution of 4 (650 mg, 2.9 mmol), KOH (325 mg, 5.8 mmol), and MeI (1.08 g, 17.4 mmol) in 10 mL of ACN was stirred at room temperature for 12 hours. The mixture was washed with water, extracted with dichloromethane, dried over MgSO₄ and concentrated in vacuo.
Purification by flash chromatography on silica gel ($\text{CH}_2\text{Cl}_2$:hexanes 1:5) afforded 550 mg (2.3 mmol, 80%) of a white solid. $^1$H NMR: $\delta =$ 4.01 (s, 3H), 7.48-7.58 (m, 4H), 7.81 (d, $J =$ 7.5 Hz, 1H), 8.12 (d, $J =$ 8.3 Hz, 1H). $^{13}$C NMR $\delta =$ 61.4, 112.6, 122.1, 125.2, 126.5, 126.8, 128.0, 129.0, 130.1, 134.0, 153.1.

**1-Methoxy-2-naphthylboronic acid, 6**

A solution of 5 (550 mg, 2.3 mmol) in 10 mL of diethyl ether was cooled to -78 °C. n-BuLi (1.6 M in hexanes, 2.2 mL, 3.5 mmol) was added dropwise and the mixture was stirred at -78 °C for 30 minutes. Trimethoxyborate (0.5 mL, 4.6 mmol) was added in one portion and the mixture was allowed to come to room temperature. After 12 hours, 10 mL of 1M HCl was added. The mixture was stirred vigorously for 30 minutes and extracted with dichloromethane. The combined organic layers were extracted with 2M NaOH and the combined aqueous layers were washed with dichloromethane. The aqueous layer was acidified to pH < 3 with 1M HCl and extracted with dichloromethane. The combined organic layers were dried over MgSO$_4$ and concentrated in vacuo to give 370 mg (1.8 mmol, 80%) of a yellow solid. $^1$H NMR: $\delta =$ 4.05 (s, 3H), 6.18 (s, 2H), 7.53-7.56 (m, 2H), 7.65 (d, $J =$ 8.3 Hz, 1H), 7.84 (d, $J =$ 8.4 Hz, 1H), 7.88 (m, 1H), 8.11 (m, 1H). $^{13}$C NMR $\delta =$ 63.7, 110.0, 122.3, 124.3, 126.1, 126.8, 127.4, 128.3, 131.0, 137.2, 163.5.

**1,1’-Dimethoxy-2-2’-binaphthalene, 7**

A solution of 5 (300 mg, 1.3 mmol), 6 (385 mg, 1.9 mmol), Pd(PPh$_3$)$_4$ (113 mg, 0.09 mmol), and K$_3$PO$_4$ (690 mg, 3.3 mmol) in 12 mL of toluene:EtOH:water (3:2:1 v/v) was stirred at 100 °C for 12 hours. The reaction mixture was allowed to cool to room temperature, quenched with water, and extracted with dichloromethane. The combined organic layers were dried over MgSO$_4$ and concentrated in vacuo. Purification by flash chromatography on silica gel ($\text{CH}_2\text{Cl}_2$:hexanes 1:1)
afforded 370 mg (1.2 mmol, 90%) of a white solid. \(^1\)H NMR: \(\delta = 3.61\) (s, 6H), 7.52-7.58 (m, 4H), 7.60 (d, \(J = 8.5\) Hz, 2H), 7.69 (d, \(J = 8.5\) Hz, 2H), 7.89 (dd, \(J = 6.2\) Hz, 2.1 Hz, 2H), 8.26 (dd, \(J = 7.1\) Hz, 1.9 Hz, 2H). \(^{13}\)C NMR \(\delta = 61.2, 122.6, 123.4, 126.0, 126.3, 126.8, 127.8, 128.4, 129.3, 134.5, 153.5.\)

**1,1’-Dihydroxy-2,2’-binaphthalene, 2\(^{15}\)**

To a solution of 7 (350 mg, 1.1 mmol) in 10 mL dichloromethane was slowly added BBr\(_3\) (1M in CH\(_2\)Cl\(_2\), 6.60 mL, 6.60 mmol), and stirring was continued at room temperature for 2 hours. The mixture was cooled to 0 °C, quenched with isopropyl alcohol, washed with water, and extracted with dichloromethane. The combined organic layers were dried over MgSO\(_4\) and concentrated in vacuo. Purification by flash chromatography on silica gel (CH\(_2\)Cl\(_2\)) afforded 302 mg (1.06 mmol, 95%) of a white solid. \(^1\)H NMR: \(\delta = 5.65\) (s, 2H), 7.39 (d, \(J = 8.4\) Hz, 2H), 7.56-7.60 (m, 6H), 7.88 (m, 2H), 8.37 (m, 2H). \(^{13}\)C NMR \(\delta = 115.5, 121.3, 122.5, 124.5, 126.0, 127.1, 127.6, 127.9, 134.7, 149.0.\)

**5.4.2. Enantioselective Sensing Experiments**

Amines and Amino Alcohols

A stock solution of 2 (0.01 M) in anhydrous THF was prepared and 350 µL portions were placed into 4 mL vials. To each vial, 50 µL of a Et\(_2\)Zn solution (0.07 M in hexanes) was added. Solutions of substrates 8 (0.035 M in anhydrous CHCl\(_3\)) and 9-20 (0.07 M in anhydrous CHCl\(_3\)) were prepared. To each vial containing 2 and Et\(_2\)Zn was added 100 µL of the substrate solution. The mixtures were stirred for 5 minutes and CD analyses were conducted using sample concentrations of 3.0 x 10\(^{-4}\) M in anhydrous diethyl ether. The CD spectra were collected with a standard sensitivity of 100 mdeg, a data pitch of 0.5 nm, a bandwidth of 1 nm, a scanning speed of 500 nm s\(^{-1}\) and a response of 0.5 s using a quartz cuvette (1 cm path length). The data were
baseline corrected and smoothed using a binomial equation. Control experiments with 8-20 (3.0 x 10^{-4} M) did not show any CD signal at the wavelengths of interest.

Figure 5.7. CD spectra of various substrates with 2.

CD spectra obtained using 2, Et₂Zn and (1R,2R)-8 (blue) and (1S,2S)-8 (red)

CD spectra obtained using 2, Et₂Zn and (R)-9 (blue) and (S)-9 (red)
CD spectra obtained using 2, Et₂Zn and (R)-10 (blue) and (S)-10 (red)

CD spectra obtained using 2, Et₂Zn and (R)-11 (blue) and (S)-11 (red)

CD spectra obtained using 2, Et₂Zn and (R)-12 (blue) and (S)-12 (red)
CD spectra obtained using $2$, Et$_2$Zn and $(R)$-$13$ (blue) and $(S)$-$13$ (red)

CD spectra obtained using $2$, Et$_2$Zn and $(1R,2S)$-$14$ (blue) and $(1S,2R)$-$14$ (red)

CD spectra obtained using $2$, Et$_2$Zn and $(R)$-$15$ (blue) and $(S)$-$15$ (red)
CD spectra obtained using 2, Et₂Zn and (R)-16 (blue) and (S)-16 (red)

![Graph](image1)

CD spectra obtained using 2, Et₂Zn and (R)-17 (blue) and (S)-17 (red)

![Graph](image2)

CD spectra obtained using 2, Et₂Zn and (1R,2S)-18 (blue) and (1S,2R)-18 (red)

![Graph](image3)
CD spectra obtained using 2, Et₂Zn and (1R,2S)-19 (blue) and (1S,2R)-19 (red)

CD spectra obtained using 2, Et₂Zn and (1R,2S)-20 (blue) and (1S,2R)-20 (red)

α-Hydroxy Carboxylic Acids

A stock solution of 2 (2.86 mg, 0.01 mmol) in anhydrous CHCl₃ was prepared and 350 µL portions were placed into 4 mL vials containing molecular sieves. Solutions of substrates 21-24 were prepared (0.07 M in anhydrous ACN) and 50 µL portions were added to each vial containing 2. Next, B(OMe)₃ (50 µL, 0.07 M in THF) was added to each vial and the mixture was stirred for 5 minutes, followed by addition of Et₃N (50 µL, 0.07 M in CHCl₃). CD analyses were conducted using sample concentrations of 3.0 x 10⁻⁴ M in anhydrous diethyl ether. All spectra were obtained utilizing the same instrumental settings as described for the analysis of substrates 8-20.
CD spectra obtained using B(OMe)$_3$, 2 and (R)-21 (blue) and (S)-21 (red)

CD spectra obtained using B(OMe)$_3$, 2 and (R)-22 (blue) and (S)-22 (red)

CD spectra obtained using B(OMe)$_3$, 2 and (R)-23 (blue) and (S)-23 (red)
CD spectra obtained using B(OMe)$_3$, 2 and (R)-24 (blue) and (S)-24 (red)

Amino Acids
To 4 mL vials containing substrates 25-30 (0.01 mmol) was added a stock solution of 2 (2.86 mg, 0.01 M) in anhydrous ACN and B(OMe)$_3$ (1.1 µL, 0.01 mmol). The CD analyses were conducted within 5 minutes using sample concentrations of 3.0 x 10$^{-4}$ in anhydrous CHCl$_3$. All spectra were obtained utilizing the same instrumental settings as described for substrates 8-20.

CD spectra obtained using B(OMe)$_3$, 2 and (R)-25 (blue) and (S)-25 (red)
CD spectra obtained using B(OMe)₃, 2 and (R)-26 (blue) and (S)-26 (red)

CD spectra obtained using B(OMe)₃, 2 and (R)-27 (blue) and (S)-27 (red)

CD spectra obtained using B(OMe)₃, 2 and (R)-28 (blue) and (S)-28 (red)
CD spectra obtained using B(OMe)$_3$, 2 and (R)-29 (blue) and (S)-29 (red)

CD spectra obtained using B(OMe)$_3$, 2 and (R)-30 (blue) and (S)-30 (red)
5.4.3. UV Experiments

**Figure 5.8.** UV spectra were collected of the complexes formed from Et₂Zn and 2 (blue) and upon addition of one equivalent of 8 (red) in anhydrous diethyl ether (1.0 x 10⁻⁴ M).

![UV spectra for Et₂Zn and 2 with 8 added](image1)

**Figure 5.9.** UV spectra were collected of the complexes formed from B(OMe)₃ and 2 (blue) and upon addition of one equivalent of 21 (red) in anhydrous CHCl₃ (1.0 x 10⁻⁴ M)

![UV spectra for B(OMe)₃ and 2 with 21 added](image2)
5.4.4. MS Analysis of the Complex Formation

A solution of 2 (2.86 mg, 0.01 mmol) and 8 (2.12 mg, 0.01 mmol) in 1 mL of a dry THF:EtOH mixture (1:1 v/v) was prepared. Then, Et₂Zn (10 µl, 0.01 mmol, 1M in hexanes) was added and the mixture was stirred for 20 minutes. Electrospray mass spectrometry (positive ion mode) showed the presence of a bimetallic complex containing 2 equivalents of 2, 8, Zn and ethanol.

Figure 5.10. ESI-MS: m/z = 1123.1 (M⁺)

A solution of 2 (2.86 mg, 0.01 mmol) and 9 (4.24 mg, 0.02 mmol) in 1 mL of a dry THF:EtOH mixture (1:1 v/v) was prepared. Then, Et₂Zn (10 µl, 0.01 mmol, 1M in hexanes) was added and the mixture was stirred for 20 minutes. Electrospray mass spectrometry (positive ion mode) showed the presence of a bimetallic complex containing 2 equivalents of 2 and Zn, 4 equivalents of 9, and 1 equivalent of ethanol.
Figure 5.11. ESI-MS: m/z = 1348.8 (M⁺)

A mixture of 2 (2.86 mg, 0.01 mmol) and B(OMe)₃ (1.04 mg, 0.01 mmol) was stirred in dry CHCl₃ for 10 minutes. To this solution was added 21 (1.58 mg, 0.01 mmol). After stirring an additional 5 minutes, Et₃N (1.02 mg, 0.01 mmol) was added, and the solution was subjected to ESI-MS analysis (negative ion mode). A complex containing equimolar amounts of 2, boron, and 21 was detected.

Figure 5.12. ESI-MS: m/z = 451 (M⁺)
5.4.5. Sensing of Primary Amines with 2-Formyl-4-methoxyphenylboronic acid (31) and Ligand 2

A stock solution of 2 (0.00375 M in anhydrous CHCl₃) was prepared and 350 µL portions were placed into 4 mL vials. To each vial was added 20 µL of the boronic acid (0.0657 M in anhydrous DMSO) and substrates 32-33 (see below) or 11 (0.0675 M in anhydrous CHCl₃). The mixtures were stirred for 5 minutes and CD analyses were conducted using sample concentrations of 3.75 x 10⁻⁵ M in anhydrous CHCl₃. All spectra were obtained utilizing the same instrumental settings as described for substrates 8-20.

5.4.6. Quantitative Ee Analysis

A calibration curve was constructed using samples of the Zn complex prepared with 2 and 8 at varying ee. Stock solutions of 2 (0.005 M) and 8 (0.005 mmol) with varying enantiomeric composition (+100, +80, +60, +40, +20, 0, -20, -40, -60, -80, -100 ee) were prepared. To these solutions was added Et₂Zn (5 µL, 1 M in hexanes, 0.005 mmol). After 5 minutes, CD analysis was carried out as described above at 3.0 x 10⁻⁴ M in anhydrous diethyl ether. The Cotton effect amplitudes at 360 nm were plotted against the enantiomeric excess of 8. Five scalemic samples of 8 were prepared and subjected to CD analysis with 2 and Et₂Zn as described above. Using the regression equation obtained from the calibration curve and the CD amplitudes measured at 360 nm, the enantiomeric excess of these samples was determined.

Table 5.3. Comparison of the actual and the experimentally determined ee’s of five scalemic samples of 8 using the CD readout of 2 at 360 nm

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<td>15.4</td>
</tr>
<tr>
<td>-26.0</td>
<td>-23.5</td>
</tr>
<tr>
<td>-68.0</td>
<td>-65.4</td>
</tr>
<tr>
<td>-89.0</td>
<td>-87.0</td>
</tr>
</tbody>
</table>
A second calibration curve was constructed using samples of the Zn complex prepared with 2 and 18 at varying ee. Stock solutions of 2 (0.005 M) and 18 (0.01 M) with varying enantiomeric composition (+100, +80, +60, +40, +20, 0, -20, -40, -60, -80, -100 ee) were prepared. To these solutions was added Et₂Zn (5 µL, 1 M in hexanes, 0.005 mmol). After 5 minutes, CD analysis was carried out as described above at 3.0 x 10⁻⁴ M in anhydrous diethyl ether. The Cotton effect amplitudes at 340 nm were plotted against the enantiomeric excess of 18. Five scalemic samples of 18 were prepared and subjected to CD analysis with 2 and Et₂Zn as described above. Using the regression equation obtained from the calibration curve and the CD amplitudes measured at 360 nm, the enantiomeric excess of these samples was determined.

**Table 5.4.** Comparison of the actual and the experimentally determined ee’s of five scalemic samples of 18 using the CD readout of 2 at 340 nm

<table>
<thead>
<tr>
<th>Actual % ee</th>
<th>Calculated % ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>87.0</td>
<td>84.4</td>
</tr>
<tr>
<td>76.0</td>
<td>76.7</td>
</tr>
<tr>
<td>12.0</td>
<td>14.9</td>
</tr>
<tr>
<td>-26.0</td>
<td>-27.2</td>
</tr>
<tr>
<td>-89.0</td>
<td>-87.2</td>
</tr>
</tbody>
</table>

**5.4.7. Investigation of the Rotational Energy Barrier of Biphenols**

HPLC experiments with 1 and 2 on a variety of chiral columns, including (S,S)-Whelk-O 1, Chiralcel® OD and Chiralpak® IA, did not show a sign of enantioseparation even at very low temperatures (-60 °C). Therefore diester 3 was prepared and the isopropyl groups were used as an NMR probe to determine the barrier to rotation about the aryl-aryl bond.
**1,1’-Biphenyl-2,2’-diol diisobutyrate, 3**

2,2’-Biphenol 1 (50 mg, 0.269 mmol) and pyridine (65 µL, 0.81 mmol) were dissolved in 5 mL of dichloromethane and cooled to 0 °C. Isobutyryl chloride (84 µL, 0.81 mmol) was added and the mixture was slowly warmed to room temperature and stirred for 4 hours. The reaction was quenched with 1M HCl and extracted with dichloromethane. The combined organic layers were washed with 0.5M NaOH, dried over MgSO₄ and concentrated in vacuo. Purification by flash chromatography on silica gel (CH₂Cl₂:hexanes 1:1) afforded 44 mg (0.14 mmol, 50%) of a colorless oil. ¹H NMR (CD₃OD): δ = 0.92 (d, J = 7.0 Hz, 6H), 2.44 (sept, J = 7.0 Hz, 2H), 7.09 (dd, J = 8.1 Hz, 0.7 Hz, 2H), 7.21 (dd, J = 7.6 Hz, 1.5 Hz, 2H), 7.25 (ddd, J = 8.1 Hz, 7.6 Hz, 0.7 Hz, 2H), 7.36 (ddd, J = 7.6 Hz, 7.6 Hz, 1.5 Hz, 2H). ¹³C NMR (CD₃OD): δ = 17.5, 33.6, 122.1, 125.4, 128.7, 130.7, 130.9, 148.4, 175.3.

Diester 3 was dissolved in CD₃OD (0.05 M) and ¹H NMR spectra were obtained at various temperatures. The temperature readings were corrected according to a standard procedure with methanol. The coalescence temperature, Tₜ, was determined as -12.3 °C (260.8 K) and Δν was 70.97 Hz at -85.14 °C. The energy barrier to rotation about the aryl-aryl bond was calculated as 52.6 kJ/mol using equation 1.

\[
\Delta G^\ddagger = [4.575 \times 10^{-3}T_c][9.972 + \log\left(\frac{T_c}{\Delta\nu}\right)]
\]  
(Equation 1)
5.4.8. Crystallography

A single crystal of the complex formed from 2, (1S,2S)-8 and Et₂Zn was obtained by slow diffusion of diethyl ether into a concentrated chloroform solution. Single crystal X-ray analysis was performed at 100 K using a Siemens platform diffractometer with graphite monochromated Mo-Kα radiation (λ = 0.71073 Å). Data were integrated and corrected using the Apex 2 program. The structures were solved by direct methods and refined with full-matrix least-square analysis using SHELX-97-2 software. Non-hydrogen atoms were refined with anisotropic displacement parameters. The asymmetric unit contains two unique complexes having (1S,2S,P,M) configuration (depicted below as complexes A and B) and one diethyl ether molecule. Formula: C₆₈H₅₂N₄O₄Zn₂, M = 580.48, crystal dimensions 0.4 x 0.2 x 0.1 mm, primitive, space group P1, a = 12.5034(16) Å, b = 14.2812(18) Å, c = 16.244(2) Å, α = 85.326(2)°, β = 78.118(2)°, γ = 78.408(2)°, V = 2778.1 Å³, Z = 4, ρcalcd = 1.388 g cm⁻³. The same complex stoichiometry of 2:2:2 (2, Zn, 8) was obtained by crystallographic analysis of a single crystal prepared by precipitation from an anhydrous ethanol solution.

A single crystal of 2 was obtained by slow evaporation of a chloroform solution (0.017 M). The asymmetric unit contains one unique molecule of 2. Formula C₁₂H₁₄O₂, M = 286.31, crystal dimensions 0.6 x 0.5 x 0.2 mm, monoclinic space group P2₁/c, a = 13.5726(13) Å, b = 12.8067 Å, c = 8.1004(8) Å, α = 90.00 β = 90.0010(10) γ = 90.00 V = 1390.7(2) Å³, Z = 4, ρcalcd = 1.3674 g cm⁻³. The aryl-aryl torsion angle was calculated as 29.24°.

![Crystal structure of 2](image-url)

**Figure 5.13.** Crystal structure of 2.
5.5. References


3 Bentley, K. W.; Nam, Y. G.; Murphy, J. M.; Wolf, C. J. Am. Chem. Soc. 2013, 135, 18052.


7 Wolf, C., Ed. Dynamic Stereochemistry of Chiral Compounds; RSC Publishing: Cambridge, 2008; p 86.


Chapter VI. Simultaneous Determination of the Enantiomeric Excess and Concentration of Chiral Compounds From a Crude Reaction Mixture with a Chiroptical Sensor

6.1 Introduction

The recent advances in chirality sensing allow fast and accurate determination of the absolute configuration and ee of many types of chiral substrates. Typically, sensors are tested with commercially available, pure chiral compounds. However, this does not address real-world HTS settings, since by-products, additives, and other reaction components are eliminated. There are several reports discussing the use of optical sensors for the analysis of asymmetric reactions. The Pu group reported the use of fluorosensors for the analysis of an asymmetric titanium tartrate-catalyzed TMSCN addition to immobilized aldehydes. Nagano also utilized fluorescence for determination of the enantiomeric outcome of nitroaldol products, while Wolf applied a fluorescence sensing assay to monitor the kinetic resolution of trans-1,2-diaminocyclohexane. Anslyn, by use of a UV indicator displacement assay, analyzed the ee of a diastereoselective Strecker reaction. Additionally, a CD sensor from Joyce and coworkers was introduced to the analysis of an enzymatic transamination. Although these examples highlight the potential of chemosensing, the reactions were carefully selected and substrates were often isolated prior to analysis.

Despite these important applications, the utility of optical chemosensors for asymmetric reaction analysis was not fully explored at the beginning of this study. A new sensing system based on the tropos binaphthol ketone was considered for determination of the absolute configuration, enantiomeric excess, and concentration of the product of the Sharpless dihydroxylation of trans-stilbene. Following the approach discussed in Chapter IV, the goal was
to develop a sensing assay that does not require purification of the crude reaction mixture prior to analysis.

Tropos ligand 1 was envisioned to form a variety of stable metal complexes. The stereodynamic nature of 1 allows for fast racemization even when bound to a metal, and this ligand was expected to populate a CD-active chiral conformation upon metal coordination of a chiral substrate (Scheme 6.1). This asymmetric transformation of the first kind would generate a chiroptical sensor response that could be used for ee and absolute configuration analysis. The concentration of the substrate could then be determined by a change in the fluorescence output of the complex.


6.2 Results and Discussion

The synthesis of 1 was accomplished in three high-yielding steps (Scheme 6.2). First, Grignard addition of 2-methoxynaphthylmagnesium bromide to 1-formyl-2-methoxynaphthalene afforded 2. The resulting secondary alcohol was oxidized with K$_2$Cr$_2$O$_7$ to give ketone 3, which was subsequently demethylated with BBr$_3$ to yield ligand 1. Single crystals of 1 were grown by diffusion of hexane into a concentrated chloroform solution. The crystal structure of 1 shows intramolecular hydrogen bonding between the ketone oxygen and naphthol protons, with the two naphthol units twisted at a 55° angle.
Scheme 6.2. Synthesis of 1.

The use of 1 as a ligand for chirality sensing was first tested using a stoichiometric amount of Et₂Zn and enantiopure trans-1,2-diphenylethylenediamine, 4 as substrate. Both the reaction between 1 and Et₂Zn and the coordination of the diamine were quantitative and complete within 5 minutes according to MS analysis. A CD signal was induced at high wavelength and at a low concentration, with the greatest signal generated in diethyl ether (Figure 6.1). Similar CD responses for the Zn complex of 1 were collected for a wide variety of substrates, including other aliphatic and aromatic amines (Figure 6.2). The substrate scope was expanded to include amino alcohols and amino acids. Interestingly, MS analysis showed a dimeric complex of 1, Zn, and an amino alcohol substrate (see Experimental Section). The absolute configuration of each substrate can be determined from the sign of the CD amplitude at 425 nm. Amines and amino acids show a negative CD amplitude for the R enantiomer, while amino alcohols and diamines showed the opposite effect.
Figure 6.1. Top: General CD sensing scheme. Bottom left: a) CD spectra of the Zn complex derived from 1 and (1R,2R)-4 (blue) and (1S,2S)-4 (red). b) CD spectra of the Zn complex derived from 1 and (R)-6 (blue) and (S)-6 (red). c) CD spectra of the Zn complex derived from 1 and (R)-9 (blue) and (S)-9 (red). All CD spectra were collected at 1 mM in diethyl ether.

Figure 6.2. Substrate scope of the stereodynamic zinc complexes of 1.

In order to determine the usefulness of 1 for fast ee analysis, the CD spectra obtained with the zinc complex of 1 and amino alcohol 14 at various ee values were collected (Figure 6.3). Plotting the CD amplitude against the ee of the substrate at three different wavelengths showed a nonlinear relationship, which may be attributed to the existence of both homo- and heterochiral species. Nonlinear regression equations allowed for accurate determination of the ee
of several unknown samples of 14 (Table 6.1). The average ee values calculated from three
different wavelengths were accurate and remained within 2.2% of the actual value. Addition of
14 to the Zn complex of 1 resulted in a fluorescence enhancement until an equimolar amount was
added, and the presence of excess of 14 did not further alter the fluorescence output of the
sensor. The use of a regression equation derived from this plot allowed accurate determination of
the concentration of unknown samples of 14.

Figure 6.3. a) CD spectra of the Zn complex derived from 1 and non-racemic samples of 14 at 1
mM in Et2O. b) Plots of the CD amplitudes at 338 nm (blue), 385 nm (red), and 445 nm (green)
vs ee. c) Plot of the fluorescence intensity of the Zn complex derived from 1 and varying
equivalents of 14.

Table 6.1. Chemosensing of amino alcohol 14.

<table>
<thead>
<tr>
<th>Sample Composition</th>
<th>Chemosensing Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ee (%)</strong></td>
<td><strong>Conc. (mM)</strong></td>
</tr>
<tr>
<td>Entry</td>
<td>338 nm</td>
</tr>
<tr>
<td>1</td>
<td>87.0</td>
</tr>
<tr>
<td>2</td>
<td>76.0</td>
</tr>
<tr>
<td>3</td>
<td>26.0</td>
</tr>
<tr>
<td>4</td>
<td>68.0</td>
</tr>
<tr>
<td>5</td>
<td>89.0</td>
</tr>
</tbody>
</table>
Ligand 1 displayed strong induced CD signals with various other metals as well. Treatment of 1 with Me₃Al in the presence of a carboxylic acid or α-hydroxy acid generated strong CD signals (Figure 6.4). The absolute configuration of the substrates can be determined from the sign of the Cotton effects at specific wavelengths. α-Hydroxy acids yield a positive CD amplitude at 450 nm for the (R) enantiomer while a negative response is observed for the (S) enantiomer. Carboxylic acids followed the opposite trend. For α-hydroxy acids, Et₃N was added, generating a negatively charged aluminate species.

![Figure 6.4](image)

**Figure 6.4.** a) CD spectra of the Al complex derived from 1 and (R)-22 (blue) and (S)-22 (red). b) CD spectra of the Al complex derived from 1 and (R)-23 (blue) and (S)-23 (red). c) CD spectra of the Ti complex derived from 1 and (1R,2R)-25 (blue) and (1S,2S)-25 (red). All CD spectra were collected at 1 mM in diethyl ether. Bottom: Substrate scope for 1 with Al (19-24) and Ti (25-29).
Zn and Al complexes of ligand 1 showed strong CD signals in the presence of amines, amino alcohols, amino acids, α-hydroxy acids and carboxylic acids. It was then proposed that diols could also generate CD responses with 1 when Ti(OiPr)₄ was used. Indeed, a variety of diols, including 1,2-, 1,3-, and 1,4-diols, showed strong CD signals in the presence of Ti and 1 (Figure 6.4). Subsequent ee and concentration analysis was conducted with 1, Ti(OiPr)₄, and hydrobenzoin 25 (Figure 6.5). Analogous to the chemosensing study with the zinc binaphtholate complex, CD and fluorescence responses allowed accurate determination of the ee and the concentration of several samples of 25 (Table 6.2). Fluorescence enhancement occurred when the molar ratio of 25 increased from 0 to 1 equivalent, and no further change was observed in the presence of excess of the substrate. The CD response showed a linear response at two distinct wavelengths when the ee of 25 was varied.

![Figure 6.5. a) Fluorescence intensity of the Ti complex derived from 1 and varying molar equivalents of 25. b) Plot of the fluorescence intensity at 600 nm of the Ti complex derived from 1 and varying molar equivalents of 25. c) Plots of the CD amplitudes at 375 nm (red) and 470 nm (blue) for the Ti complex derived from 1 and non-racemic samples of 25. All spectra were collected at 1 mM in diethyl ether.](image)
Table 6.2. Chemosensing results of 1 and diol 25 with Ti(O/Pr)$_4$.

<table>
<thead>
<tr>
<th>Sample Composition</th>
<th>Chemosensing Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entry</td>
<td>Ee (%)</td>
</tr>
<tr>
<td>1</td>
<td>76.0</td>
</tr>
<tr>
<td>2</td>
<td>68.0</td>
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<td>3</td>
<td>12.0</td>
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<tr>
<td>4</td>
<td>26.0</td>
</tr>
<tr>
<td>5</td>
<td>89.0</td>
</tr>
</tbody>
</table>

The usefulness of the titanium complexes derived from 1 for direct sensing of the yield and ee of the Sharpless asymmetric dihydroxylation (AD) of \textit{trans}-stilbene 30 to hydrobenzoin, 25 was then tested. This reaction was conducted utilizing several different reaction conditions. After a simple workup, the crude reaction mixture was treated with the Ti-binaphtholate complex, and CD and fluorescence spectra were obtained. (Table 6.3). The absolute configuration, ee, and concentration of the product 25 were determined from the previous CD and fluorescence analysis of pure hydrobenzoin. The results obtained via the sensing analysis with 1 were compared with the traditional methods of gravimetry and chiral HPLC. It was found that the results obtained via the two optical measurements were in very good agreement with the actual values. The main goal of HTS is to find reaction conditions that give high yield and asymmetric induction. If necessary, selected samples can then be more accurately analyzed by traditional methods such as HPLC. Therefore, the small difference between the actual and calculated values for the ee and concentration analysis of 25 is acceptable during HTS. Importantly, chiroptical sensing severely reduces the amount of waste typically generated by chromatography and can allow efficient screening of hundreds of reactions.
Table 6.3. Comparison of the yield, absolute configuration, and ee of hydrobenzoin obtained by asymmetric dihydroxylation.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>T (°C)</th>
<th>Yield (%)</th>
<th>ee (%) and abs. config.</th>
<th>Yield (%)</th>
<th>ee (%) and abs. config.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AD-mix-β (DHQD)$_2$-PHAL</td>
<td>0.0</td>
<td>99.1</td>
<td>99.1 (R,R)</td>
<td>95.4</td>
<td>98.9 (R,R)</td>
</tr>
<tr>
<td>2</td>
<td>AD-mix-β (DHQD)$_2$-PHAL</td>
<td>25.0</td>
<td>71.0</td>
<td>86.3 (R,R)</td>
<td>65.3</td>
<td>87.7 (R,R)</td>
</tr>
<tr>
<td>3</td>
<td>AD-mix-β (DHQD)$_2$-PHAL</td>
<td>50.0</td>
<td>17.7</td>
<td>75.4 (R,R)</td>
<td>12.2</td>
<td>75.8 (R,R)</td>
</tr>
<tr>
<td>4</td>
<td>Cinchonine</td>
<td>25.0</td>
<td>54.2</td>
<td>0.0</td>
<td>51.1</td>
<td>1.3</td>
</tr>
</tbody>
</table>

6.3. Conclusions

In conclusion, a stereodynamic bis-(naphthol) ketone 1 was developed. This ligand forms Zn, Al, and Ti complexes that can be sued for fast chirality sensing of a large variety of chiral compounds encompassing many substrate classes. Addition of chiral amines, diamines, amino alcohols, amino acids, carboxylic acids, α-hydroxy acids, and diols to the metal complexes of 1 generates strong CD and fluorescence signals that correlate to the absolute configuration, ee and concentration of the substrate. The practicality and accuracy of the stereodynamic titanium complex of 1 for the determination of the yield and enantioselectivity of the asymmetric catalytic dihydroxylation of trans-stilbene by two fast optical measurements of crude reaction mixtures were demonstrated.
6.4. Experimental Section

6.4.1. Synthesis of 1

**1,1-Bis(2-methoxy-1-naphthyl)methanol, 2**

A solution of 2-methoxy-1-bromonaphthalene (500 mg, 2.1 mmol), Mg turnings (102 mg, 4.2 mmol) and I₂ (32 mg, 0.13 mmol) in 6 mL of THF was stirred at reflux for 2 hours. The reaction mixture was cooled to 0 °C and 2-methoxy-1-naphthaldehyde (432 mg, 2.3 mmol, 0.8 M in THF) was added dropwise. The reaction mixture was then stirred at room temperature for 2 hours, quenched with NH₄Cl and extracted with CH₂Cl₂. The combined organic layers were dried over MgSO₄ and concentrated in vacuo. Purification by flash chromatography on silica gel (hexanes:EtOAc 4:1) afforded 625 mg (1.8 mmol, 86%) of a white solid. ¹H NMR δ = 3.65 (s, 6H), 6.01 (d, J = 8.7 Hz, 1H), 7.28-7.42 (m, 6H), 7.75 (dd, J = 8.8 Hz, 7.6 Hz, 4H), 8.10 (d, 8.4 Hz, 2H). ¹³C NMR δ = 57.1, 68.5, 115.0, 123.5, 123.6, 125.5, 126.8, 128.6, 129.6, 129.7, 132.4, 155.3. Anal. Calcd. C_{23}H_{20}O₃: C, 80.21; H, 5.85. Found: C, 80.51; H, 6.14.

**Bis(2-methoxy-1-naphthyl)ketone, 3**

A solution of 2 (370 mg, 1.1 mmol) and K₂Cr₂O₇ (348 mg, 1.2 mmol) in 8 mL of DMF was stirred at 100 °C for 12 hours. The mixture was allowed to cool to room temperature, quenched with water, and extracted with CH₂Cl₂. The combined organic layers were dried over MgSO₄ and concentrated in vacuo. The residue was washed with hexanes to give 326 mg (1.0 mmol, 90%) of a light brown solid. ¹H NMR δ = 3.37 (s, 6H), 7.15 (d, J = 9.0 Hz, 2H), 7.40 (dd, J = 7.2 Hz, 7.2 Hz, 2H), 7.51 (dd, J = 7.3 Hz, 7.3 Hz, 2H), 7.81 (d, J = 8.2 Hz, 2H), 7.88 (d, J = 9.0 Hz, 2H), 8.18 (d, J = 8.7 Hz, 2H). ¹³C NMR δ = 56.7, 113.9, 124.0, 125.1, 127.2, 127.4, 127.9, 129.2, 131.7, 131.9, 155.6, 199.8. Anal. Calcd. C_{23}H_{18}O₃: C, 80.68; H, 5.30. Found: C, 80.67; H, 5.59.
**Bis(2-hydroxy-1-naphthyl)ketone, 1**

A solution of 3 (320 mg, 0.9 mmol) and BBr$_3$ (1 M in CH$_2$Cl$_2$, 5.6 mL, 5.6 mmol) in 5 mL of CH$_2$Cl$_2$ was stirred at 0 °C for 30 minutes. The reaction mixture was quenched with H$_2$O and extracted with CH$_2$Cl$_2$. The combined organic layers were dried over MgSO$_4$ and concentrated in vacuo. Purification by flash chromatography (hexanes:EtOAc 3:1) afforded 275 mg (0.88 mmol, 95%) of a yellow solid. $^1$H NMR $\delta$ = 6.83 (dd, $J = 8.4$ Hz, 7.1 Hz, 2H), 7.04 (d, $J = 8.6$ Hz, 2H), 7.09 (dd, $J = 8.6$ Hz, 7.1 Hz, 2H), 7.28 (d, $J = 9.0$ Hz, 2H), 7.64 (d, $J = 9.0$ Hz, 2H), 7.94 (d, $J = 8.4$ Hz, 2H), 10.84 (s, 2H). $^{13}$C NMR $\delta$ = 117.4, 119.3, 123.9, 124.1, 127.3, 128.3, 128.4, 131.3, 136.7, 160.1, 200.4. Anal. Calcd. C$_{21}$H$_{14}$O$_3$: C, 80.24; H, 4.49. Found: C, 80.16; H, 4.66.

### 6.4.2. Enantioselective Sensing Experiments

Amines and Amino Alcohols:

A stock solution of 1 (0.01 M) in anhydrous THF was prepared and 500 µL portions were placed into 4 mL vials containing one equivalent of diamines 4 and 5, amino alcohols 9-14 (0.005 mmol) or two equivalents of amines 6-8. To each vial was then added Et$_2$Zn (5 µL, 0.005 mmol, 1 M in hexanes), causing an immediate color change from yellow to orange. The mixtures were stirred for 5 minutes and CD spectra were collected with a standard sensitivity of 100 mdeg, a data pitch of 0.5 nm, a bandwidth of 1 nm, a scanning speed of 500 nm s$^{-1}$ and a response of 0.5 s using a quartz cuvette (1 cm path length). The data were baseline corrected and smoothed using a binomial equation.
Figure 6.6. CD Spectra of various substrates with 1.

CD Spectra obtained using Et₂Zn, 1 and (1R,2R)-4 (blue) and (1S,2S)-4 (red)

CD Spectra obtained using Et₂Zn, 1 and (1R,2S)-5 (blue) and (1S,2R)-5 (red)

CD Spectra obtained using Et₂Zn, 1 and (R)-6 (blue) and (S)-6 (red)
CD Spectra obtained using Et$_2$Zn, 1 and (1R,2R,3R,5S)-7 (blue) and (1S,2S,3S,5R)-7 (red)

CD Spectra obtained using Et$_2$Zn, 1 and (R)-8 (blue) and (S)-8 (red)

CD Spectra obtained using Et$_2$Zn, 1 and (R)-9 (blue) and (S)-9 (red)
CD Spectra obtained using Et₂Zn, 1 and (1S,2R)-10 (blue) and (1R,2S)-10 (red)

CD Spectra obtained using Et₂Zn, 1 and (R)-11 (blue) and (S)-11 (red)
CD Spectra obtained using Et₂Zn, 1 and (R)-12 (blue) and (S)-12 (red)

CD Spectra obtained using Et₂Zn, 1 and (1S,2R)-13 (blue) and (1R,2S)-13 (red)

CD Spectra obtained using Et₂Zn, 1 and (1S,2R)-14 (blue) and (1R,2S)-14 (red)
Amino Acids:

A stock solution of 1 (0.01 M) in anhydrous DMSO was prepared and 500 µL portions were placed into 4 mL vials containing one equivalent of amino acids 15-18. To each vial was then added Et₂Zn (5 µL, 0.005 mmol, 1M in hexanes), causing an immediate color change from yellow to orange. The mixtures were stirred for 5 minutes and CD analyses were conducted as described above.

CD Spectra obtained using Et₂Zn, 1 and (R)-15 (blue) and (S)-15 (red)

CD Spectra obtained using Et₂Zn, 1 and (R)-16 (blue) and (S)-16 (red)
Carboxylic Acids:

A stock solution of \( \text{I (0.01 M)} \) in anhydrous THF was prepared and 500 µL portions were placed into 4 mL vials containing one equivalent of carboxylic acids 19-24. To each vial was then added Me\(_3\)Al (2.5 µL, 0.005 mmol, 2M in hexanes), causing an immediate color change from yellow to red. Et\(_3\)N (0.7 µL, 0.005 mmol) was also added to solutions with substrates 19-22. The mixtures were stirred for 5 minutes and CD analyses were conducted as described above.
CD Spectra obtained using Me₃Al, 1 and (R)-19 (blue) and (S)-19 (red)

CD Spectra obtained using Me₃Al, 1 and (R)-20 (blue) and (S)-20 (red)

CD Spectra obtained using Me₃Al, 1 and (R)-21 (blue) and (S)-21 (red)
CD Spectra obtained using Me₃Al, 1 and (R)-22 (blue) and (S)-22 (red)

CD Spectra obtained using Me₃Al, 1 and (R)-23 (blue) and (S)-23 (red)
CD Spectra obtained using Me₃Al, 1 and (R)-24 (blue) and (S)-24 (red)

Diols:
A stock solution of 1 (0.01 M) in anhydrous THF was prepared and 500 µL portions were placed into 4 mL vials containing a diol 25-29 (0.005 mmol). To each vial was then added Ti(OiPr)₄ (1.48 µL, 0.005 mmol), and an immediate color change from yellow to red was observed. The mixtures were stirred for 10 minutes and CD analyses were conducted using sample concentrations of 1.13 x 10⁻⁴ M in anhydrous diethyl ether.

CD Spectra obtained using Ti(OiPr)₄, 1 and (1R,2R)-25 (blue) and (1S,2S)-25 (red)
CD Spectra obtained using Ti(OiPr)$_4$, I and (1R,2R)-26 (blue) and (1S,2S)-26 (red)

CD Spectra obtained using Ti(OiPr)$_4$, I and (1R,2R)-27 (blue) and (1S,2S)-27 (red)

CD Spectra obtained using Ti(OiPr)$_4$, I and (1R,2R)-28 (blue) and (1S,2S)-28 (red)
CD Spectra obtained using Ti(OiPr)$_4$, 1 and (1R,2R,3S,5R)-29 (blue) and (1S,2S,3R,5S)-29 (red)

6.4.3. Calibration Curve and Ee Analysis of 14

A calibration curve was constructed using samples of the Zn complex prepared with 1 and 14 at varying ee. Stock solutions of 1 (0.00375 M in THF) and 14 (0.07 M in THF) with varying enantiomeric composition (+100, +80, +60, +40, +20, 0, -20, -40, -60, -80, -100 ee) were prepared. To these solutions was added Et$_2$Zn (1.3 µL, 0.0013 mmol, 1M in hexanes). After 5 minutes, CD analysis was carried out as described above at 1.13 x 10$^{-4}$ M in anhydrous diethyl ether. The Cotton effect amplitudes at 338, 385, and 445 nm were plotted against the enantiomeric excess of 14.

6.4.4. Concentration Determination of 14

The change in the fluorescence of the complex formed from 1 and Et$_2$Zn upon addition of 14 was analyzed. A calibration curve was constructed using samples containing various amounts of 14. First, 350 µL solutions of 1 (0.00375 M in THF) were placed in 16 vials. To each vial was then transferred a solution of 14 (0.07 M in THF) in varying amounts (0, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 120, 140, 160, 180 and 200 mol%). Et$_2$Zn (1.3 µL, 0.0013 mmol, 1M in hexanes) was added to each vial and the mixtures were allowed to react for 5 minutes. Fluorescence
spectra were collected using an excitation wavelength of 490 nm with slit widths of 3 nm and 6 nm and a quartz cuvette (1 cm path length). The fluorescence intensity at 600 nm increased as the concentration of 14 increased from 0 to 100 mol%. When the concentration of 14 was in excess of 100 mol%, the intensity remained constant. Plotting and curve fitting of the fluorescence intensity (I) at 600 nm against the concentration (c) of 14 ranging from 0 to 100 mol% gave a polynomial equation (I = -47072(c)^2 + 154201(c) + 204014) with R^2 = 0.99603.

**Figure 6.7.** Fluorescence spectra of the complexes formed from 1, Et₂Zn and varying concentrations of 14 from 0-100 mol% (blue) and 120-200 mol% (red).

### 6.4.5. Calibration Curve and Ee Analysis with 25

A calibration curve was constructed using samples of the Ti complex prepared with Ti(OiPr)_4, 1 and 25 at varying ee. Stock solutions of 1 (0.00375 M in THF) and 25 (0.07 M in THF) with varying enantiomeric composition (+100, +80, +60, +40, +20, 0, -20, -40, -60, -80, -100 ee) were prepared. To these solutions was added Ti(OiPr)_4 (2.6 µL, 0.0013 mmol, 0.5 M in THF). After 15 minutes, CD analysis was carried out as described above at 1.13 x 10^-4 M in anhydrous diethyl
ether. The Cotton effect amplitudes at 375 and 470 nm were plotted against the enantiomeric excess of 25.

**Figure 6.8.** CD Spectra of 1 and varying ee of 25.

![CD Spectra](image)

### 6.4.6. Concentration Determination of 25

The change in the fluorescence of the complex between 1 and Ti(OiPr)₄ upon addition of 25 was analyzed. A calibration curve was constructed using samples containing various amounts of 25. First, 350 µL solutions of 1 (0.00375 M in THF) were placed in 13 vials. To each vial was then transferred a solution of 25 (0.07 M in THF) in varying amounts (0, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 120, 140, and 160 mol%). Ti(OiPr)₄ (2.6 µL, 0.0013 mmol, 0.5 M in THF) was added to each vial and the mixtures were allowed to react for 15 minutes. Fluorescence spectra were collected as described above. The fluorescence intensity at 585 nm increased as the concentration of 25 increased from 0 to 100 mol%. When the concentration of 25 was in excess of 100 mol%, the intensity remained constant. Plotting and curve fitting of the fluorescence intensity (I) at 585 nm against the concentration (c) of 25 ranging from 0 to 100 mol% gave a polynomial equation (I = -584891(c)³ + 777014(c)² + 548022(c) + 254088) with $R^2 = 0.99401$. 

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6.4.7. Ee and Concentration Analysis of Hydrobenzoin 25 Obtained by Asymmetric Sharpless Dihydroxylation

A solution of AD-mix-β (179.0 mg), methanesulfonamide (13.2 mg, 0.14 mmol) and trans-stilbene (25 mg, 0.14 mmol) was stirred in 8 mL of a 1:1 water:tBuOH mixture. After stirring vigorously overnight, excess Na$_2$SO$_3$ was added and stirring continued for an additional 1 hour. The reaction mixture was quenched with CH$_2$Cl$_2$, washed with 2M NaOH and dried over MgSO$_4$. The reaction was also carried out as described above with stilbene (25 mg, 0.14 mmol), K$_3$Fe(CN)$_6$ (137.0 mg, 0.42 mmol), K$_2$CO$_3$ (57.6 mg, 0.42 mmol), OsO$_4$ (14.1 µL, 0.0013 mmol), cinchonine (1.0 mg, 0.0031 mmol) and methanesulfonamide (13.2 mg, 0.14 mmol) at room temperature.

The efficacy of 1 for the determination of both concentration and ee was tested using the asymmetric Sharpless dihydroxylation as an example. Solutions of 1 (1.57 mg, 0.005 mmol) and the crude product obtained as described above (1.07 mg) in 0.5 mL THF were prepared and treated with Ti(OiPr)$_4$ (1.48 µL, 0.005 mmol). A fluorescence spectrum was obtained via the method described in section 4.4 at a concentration of 1.14 x 10$^{-4}$ M, and the concentration was calculated using the regression equation obtained in section 4.4. Then, a CD spectrum was obtained at 1.14 x 10$^{-4}$ M. The Cotton effect intensity (mdeg) was normalized for the concentration calculated by the fluorescence analysis using the relative mol% (χ) of hydrobenzoin as shown in equations 1 (470 nm) and 2 (375 nm). This value was then applied in the linear regression equations to determine the enantiomeric excess based on the average values at 470 and 375 nm (equations 1 and 2, respectively).
\[ ee = \frac{m_{\text{deg}} + 1.0671}{0.1936} \quad \text{Equation 1} \]
\[ ee = \frac{m_{\text{deg}} - 0.6221}{-0.2839} \quad \text{Equation 2} \]

For comparison, the reaction mixtures were purified by flash chromatography on silica gel (CH\(_2\)Cl\(_2\):EtOAc 3:1) to isolate pure hydrobenzoin and to determine yield and ee. The ee was determined by HPLC on a Chiralcel OJ column using hexanes:iPrOH (92:8 v/v) as mobile phase at 1 mL/min, \( t_{1, (S,S)} = 19.4 \) min, \( t_{2, (R,R)} = 23.4 \) min.

Overall, the use of ligand 1 with Ti(OiPr)\(_4\) as a chemosensor for the determination of ee and concentration of hydrobenzoin requires far less time and solvent than column chromatography and HPLC analysis. Because both spectroscopic measurements were obtained at the same concentration, one sample is sufficient to obtain reaction yield and ee using a total of 2.5 mL of solvent. Comparatively, purification of the crude reaction mixture requires \( \sim 90 \) mL solvent, and HPLC analysis requires 25-30 mL. The spectroscopic measurements are also time efficient, with each measurement requiring \( \sim 15 \) seconds, while HPLC requires 25-30 minutes to completely separate the two enantiomers.
Figure 6.9. HPLC readouts for hydrobenzoin 25.

HPLC Spectrum for the reaction using AD-mix-β at 0 °C

HPLC Spectrum for the reaction using AD-mix-β at 25 °C

HPLC Spectrum for the reaction using AD-mix-β at 50 °C
HPLC Spectrum for the reaction using cinchonine at 25 °C

6.4.8. MS Analysis of the Complex Formation

A solution of [1] (1.57 mg, 0.005 mmol) and [14] (0.90 mg, 0.005 mmol) in 1 mL of a dry THF:MeOH mixture (1:1 v/v) was prepared. Then, Et₂Zn (5 µl, 0.005 mmol, 1M in hexanes) was added and the mixture was stirred for 10 minutes. Electrospray mass spectrometry (positive ion mode) showed the presence of a bimetallic complex containing 2 equivalents of [1, 14, Zn and 1 equivalent of methanol.

![Figure 6.10. ESI-MS: m/z = 1179.0 (M⁺)](image)
A mixture of 1 (1.57 mg, 0.005 mmol) and Me₃Al (2.5 µl, 0.005 mmol, 2M in hexanes) was stirred in a THF:MeOH mixture (1:1 v/v) for 10 minutes. To this solution was added 19 (0.76 mg, 0.005 mmol). After stirring an additional 5 minutes, Et₃N (0.7 µl, 0.005 mmol) was added, the mixture was subjected to ESI-MS analysis (negative ion mode). A complex containing 2 equivalents of 1, Al, and 19 was observed.

Figure 6.11. ESI-MS: m/z = 979.9 (M⁻); 489.9 (M₂⁻)

A solution of 1 (1.57 mg, 0.005 mmol) and 25 (1.07 mg, 0.005 mmol) in 1 mL of a dry CHCl₃:THF mixture (3:1 v/v) was prepared. Then, Ti(OiPr)₄ (1.5 µl, 0.005 mmol) was added and the mixture was stirred for 10 minutes. Electrospray mass spectrometry (positive ion mode) showed the presence of a bimetallic complex containing 2 equivalents of 1, 25, Ti and 1 equivalent of isopropyl alcohol.
6.4.9. NMR Stoichiometry Study

In order to determine the stoichiometry for the complex derived from 1, 25, and titanium, the displacement of the isopropyl units from Ti was monitored by $^1$H NMR. The septet representing the tertiary proton of the isopropyl alkoxide bound to Ti is centered at 4.47 ppm in CDCl$_3$. When one equivalent of 1 is added, a new septet appears at 4.01 ppm and is present in a 1:1 ratio with the original septet, indicating that two isopropyl alcohol units were displaced by the ligand as expected. When one equivalent of 25 is added to the complex of 1 and Ti, the remaining isopropoxides are displaced as evidenced by the disappearance of the septet at 4.47 ppm with the septet at 4.01 ppm remaining.
Figure 6.13. Excerpt of the NMR spectrum showing the methine proton septet in [Ti(OiPr)$_4$] (red), after addition of one equivalent of 1 (green), and upon addition of one equivalent of 25 (blue).

A similar change was observed for the methyl doublet, which is centered at 1.23 ppm when bound to Ti. As above, when one equivalent of 1 is added, a new doublet appears centered at 1.19 ppm and has a ratio of 1:1 with the original doublet. Upon addition of 25, the original methyl doublet nearly disappeared, while the new doublet remained.
Figure 6.14. Excerpt of the NMR spectrum showing the methyl doublet of [Ti(OiPr)$_4$] (red), after addition of one equivalent 1 (green), and upon addition of one equivalent of 25 (blue).

6.4.10. Crystallography

A single crystal of compound 3 was obtained by slow evaporation of a concentrated chloroform solution. Crystallographic analysis was performed at 100 K using a Siemens platform diffractometer with graphite monochromated Mo-Kα radiation ($\lambda = 0.71073$ Å). Data were integrated and corrected using the Apex 2 program. The structure was solved by direct methods and refined with full-matrix least-square analysis using SHELX-97-2 software. Non-hydrogen atoms were refined with anisotropic displacement parameters. The asymmetric unit contains one molecule of 3. Crystal structure data: Formula C$_{23}$H$_{18}$O$_3$, M = 342.37, crystal dimensions 0.4 x
0.2 x 0.1 mm, monoclinic, space group C2/c, $a = 26.52 \text{ Å}$, $b = 8.52 \text{ Å}$, $c = 18.28 \text{ Å}$, $\alpha = 90.0^\circ$, $\beta = 125.72^\circ$, $\gamma = 90.0^\circ$, $V = 3359.47 \text{ Å}^3$, $Z = 8$, $\rho_{\text{calcd}} = 1.354 \text{ g cm}^{-3}$.

Figure 6.15. Crystal structure of 3.

A single crystal of compound 1 was obtained by slow evaporation of a concentrated chloroform solution. Crystallographic analysis was performed with identical parameters as listed above. The asymmetric unit contains one molecule of 1. Crystal structure data: Formula C$_{21}$H$_{14}$O$_3$, $M = 314.32$, crystal dimensions 0.5 x 0.2 x 0.1 mm, orthorhombic, space group P2$_1$2$_1$2$_1$, $a = 7.4826(5) \text{ Å}$, $b = 13.4485(8) \text{ Å}$, $c = 14.9052(9) \text{ Å}$, $\alpha = 90.0^\circ$, $\beta = 90.0^\circ$, $\gamma = 90.0^\circ$, $V = 1499.91(16) \text{ Å}^3$, $Z = 4$, $\rho_{\text{calcd}} = 1.392 \text{ g cm}^{-3}$.

Figure 6.16. Crystal structure of 1.
6.5. References


