FUNCTIONALIZED 1,8-DIARYLNAPHTHALENES:
APPLICATIONS IN ENANTIOSELECTIVE SENSING AND
STEREOSELECTIVE CYCLOADDITIONS

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FUNCTIONALIZED 1,8-DIARYLNAPHTHALENES: APPLICATIONS IN
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CYCLOADITIONS

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ABSTRACT

The unique structure of 1,8-diarylnaphthalenes provides an excellent opportunity to
design sensors with a chromophoric binding pocket and the ability to transform a binding
event with a chiral substrate into a strong and quantifiable signal. Since both arene rings
readily rotate about the two chiral axes, 1,8-bis(3’-formyl-4’-hydroxyphenyl)naphthalene
exists as a mixture of enantiomeric anti-conformers that rapidly interconvert via a meso
syn-isomer. Diimine formation between this stereodynamic probe and chiral substrates
disturbs this equilibrium and strongly favors the population of a single diastereomer
through intramolecular hydrogen bonding. The cofacial arrangement of the two
salicylaldehyde rings favors intramolecular π–π interactions and subsequent generation
of intense Cotton effects at high wavelengths. This sensor provides information about the
absolute configuration and enantiomeric composition of a wide range of amino alcohols
and amino acids based on well-defined and understood central-to-axial chiral
amplification processes.

The incorporation of moderate bulk in the form of methyl groups into the ortho-
positions of 1,8-bis(3’-formyl-4’-hydroxyphenyl)naphthalene resulted in the formation of
conformational isomers that are stable to interconversion and separable at room
temperature. The axially chiral stereoisomers of 1,8-bis(2’-methyl-4’-hydroxy-5’-
formylphenyl)naphthalene were isolated via formation of diastereomers with chiral amino alcohols, chromatographic separation and hydrolysis. The Gibbs activation energy for atropisomerization was calculated as 103.7 (102.4) kJ/mol for the conversion of the anti-(syn-) to the syn-(anti-) isomer. The diimine derivatives were also investigated and it was found that they undergo an asymmetric transformation of the first kind, which significantly facilitates the preparation of enantiopure atropisomers on the gram scale.

The energy barrier for the conversion of the (M,M,S,S)-isomer to the syn-isomer, \( \Delta G^\phi_{(M,M,S,S) \rightarrow (M,P,S,S)} \), was determined as 115.7 kJ/mol and proved to be significantly higher than the rotational barriers of the (P,P,S,S) and (P,M,S,S)-diastereomers.

An analogous 1,8-diarylnaphthalene skeleton was developed to examine stereoselective cycloadditions. 1,8-Dipyridynaphthalene had previously been shown to preorganize fumaric acid for quantitative photoaddition in the solid state. Extensive screening of conditions suitable for cocrystallization of 1,8-dipyridynaphthalene and trans-cinnamic, mesaconic or trans,trans-muconic acids showed that the desired packing motif and the stoichiometry in the solid state based on non-covalent interactions cannot always be controlled. A series of templates for the covalent attachment and preorganization of olefinic substrates was then synthesized in an attempt to overcome these limitations. It was found that immobilization of trans-cinnamic acid to 1,8-bis(4’-anilino)naphthalene provided an alternative means for stereoselective photodimerization. The use of this recoverable template effectively biases the [2+2]dimerization of trans-cinnamic and trans-3-(3,4-dimethylphenyl)acrylic acids towards cis,trans,cis-cyclobutanetetracarboxylic acids, and proceeded with high yield and excellent stereoselectivity.
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“…How would you like to live in Looking-glass House, Kitty? I wonder if they'd give you milk in there? Perhaps Looking-glass milk isn't good to drink…”


I. Introduction

I.1. General Introduction

Chirality is a fascinating property that is ubiquitous on the microscopic and macroscopic levels in nature; it can be found in proteins and DNA or sea shells, snails and circumnutating plants. On the molecular level, most natural compounds such as nucleic acids, sugars, amino acids, proteins, hormones, antibiotics, flavors, fragrances or synthetic chemicals like pharmaceutical drugs are chiral, and their activity and toxicity are typically related to their absolute configuration and enantiopurity. Whether it is Euclidian or topological chirality, enantiomers often exhibit stunningly different physiochemical properties. The economics of molecular chirality are equally astounding. For instance, single enantiomer drugs constitute more than 50% of the pharmaceutical market, with one drug like Lipitor earning 7.5 billion dollars in 2009 alone (Figure I.1).\(^1\) Tragic examples like that of thalidomide, of which the \((R)\)-enantiomer treats morning sickness in pregnant women while its antipode is teratogenic, has urged regulatory agencies such as the Food and Drug Administration to strictly control the enantiomeric composition of pharmaceuticals.\(^2\) Similarly, the \((S,S)\)-enantiomer of ethambutol combats tuberculosis while the other causes blindness. The \((S)\)-form of naproxen is widely used to treat arthritis pains, while the \((R)\)-enantiomer is avoided since it leads to liver poisoning.\(^3\) Development of fast, accurate and automated methods for the unequivocal determination
of the absolute configuration and %ee of chiral substances remains central especially for the high-throughput screening of asymmetric reactions.

![Chemical structures](image)

Figure I.1. Structures of pharmaceutical drugs sold as single enantiomers. From left to right. Lipitor (Pfizer), Zocor (Merck), Valsartan (Novartis) and Paxil (GSK).

A compound can be chiral due to the presence of an asymmetric center, or other chiral elements such as a chiral plane or axis, as long as it has no symmetry plane, rotation-reflection axis or inversion center. Atropisomers (atropos: from Greek α meaning not, tropos meaning turn) are a class of stereoisomers that arise from restricted rotation about a single bond. Although atropisomers have been known since the early 1920s, this interesting class of compounds received little attention until enantiomerically pure biaryls such as BINOL, 1, were discovered to be exceptional ligands in asymmetric catalysis. Atropisomers can be classified into nonbridged (1, 2) or bridged compounds (3, 4), indicating the structural variety of axially chiral compounds (Figure I.2). The enantiomeric purity of biaryls in nature can be as high as 100% for compounds such as vancomycin, while others like gossypol, 2, occur as scalemic mixtures with varying %ee as a function of the plant species. The importance of 2 stems from the fact that is has antispermaticogentic, antitumor and antimalarial activities depending on its axial
chirality. On the other hand, \((P,M,M)\)-diazonamide, 4, has been shown to possess potent nanomolar activity against several human cancer cell lines.\(^{11}\)

![Figure 1.2. Structures of (M)-BINOL, (M)-gossypol, (M)-steganone and (P,M,M)-diazonamide.](image)

The atropisomeric chirality of biaryls is primarily a result of steric interactions that force the two aryls rings out of the plane.\(^{12}\) The torsion angle between the aryl planes is neither zero nor ninety, but rather varies between 42 and 90°.\(^{13}\) In fact, steric interactions force the rings out of a common plane, while \(\pi\)-electron overlap favors a smaller interplanar angle. In contrast to the racemization pathways of compounds containing a stereogenic carbon atom, atropisomeric enantiomers generally interconvert without the breaking of a covalent bond (Figure I.3). The number, size and nature of substituents on biaryl systems determine whether the individual enantiomers can be isolated. While most terta-ortho substituted biphenyls can be resolved and are stable to racemization, tri- and di-ortho substituted biphenyls are resolvable only if the groups are sufficiently large.\(^{14}\) Mono-ortho substituted species undergo fast rotation about the aryl-aryl bond and are not resolvable. Substituents in the meta position enhance the racemization barrier by preventing the ortho group of bending outward during the coplanar transition state.
Electron-rich substituents in the *para* position typically decrease the racemization barrier, while electron-withdrawing groups have the opposite effect.

![Figure I.3. Biphenyl racemization.](image)

In few cases, racemization of biaryls is explained by a reversible ring-opening reaction (Scheme I.1).\(^{15}\)

![Scheme I.1. Racemization of 4,6-dimethyl-1-o-tolylpyrimidin-2-one.](image)

Numerous synthetic methods achieving high chemical and optical yields of biaryls have been reported.\(^{16}\) For instance, an intramolecular diastereoselective biaryl coupling using a \(C_2\)-symmetric diol as a chiral auxiliary has led to excellent enantiopurities of a series of biphenols (Scheme I.2).\(^{17}\)
Scheme I.2. Atropodiastereoselective biaryl coupling using a chiral auxiliary.

Other methods such as dynamic kinetic resolution of stereodynamic biphenyl lactones with an enantiopure mentholate as the $O$-nucleophile, have been shown to give the $(P)$-biaryl diol with enantiomeric ratios greater than 99:1 (Scheme I.3).¹⁸

Scheme I.3. Dynamic kinetic resolution of flexible biphenyls.

Atropos and tropos ligands have been used for a variety of applications, most significantly in catalytic asymmetric carbon-carbon bond formation (Ene, Aldol, Diels-Alder reactions)¹⁹ and hydrogenations (Scheme I.4).²⁰

Scheme I.4. Asymmetric hydrogenation of 1-acetonaphtone by XylylBIPHEP-RuCl₂ with (S,S)-diphenylethylenediamine.
These ligands have found further application in the field of asymmetric activation/poisoning of racemic ligands. As shown in Scheme I.5, 10 mol% of racemic BINOLato-Ti(OiPr)$_2$ and 10 mol% of enantiopure 2,2'-biphenol have been used to catalyze an asymmetric carbonyl-ene reaction with selectivities up to 97 %ee.$^{21}$ Coordination of (R)-5 onto the titanium generates two diastereomeric complexes. It was found that the (R,R)-diastereomer was significantly more catalytically active than the (S,R)-complex, and thus controlled the stereochemical outcome. One advantage of this strategy is that the activated catalyst can lead to products with higher %ee’s than the enantiomerically pure BINOLate-Ti complex.

Scheme I.5. Asymmetric activation of racemic BINOLato titanium complex using (R)-5.
I.2. References


II. Objectives

Recognizing the importance and shortcomings of stereochemical analysis of amino alcohols and unprotected amino acids, we aimed to develop sensing methods for the determination of the absolute configuration and %ee of these compounds. The unique structure of 1,8-bisphenolnaphthalenes was expected to provide an excellent opportunity to design a sensor that would transform a binding event with a chiral substrate into a strong UV, fluorescence or CD signal. For example, diimine formation between 1,8-bis(3′-formyl-4′-hydroxyphenyl)naphthalene which was expected to rapidly racemize at 25 °C, and chiral analytes was envisioned to strongly favor the population of a single enantiomer with distinct Cotton effects through intramolecular hydrogen bonding. The operational simplicity of a UV or CD based assay could then lead towards automation and high throughput screening using only minute amounts of sample, sensor and solvent. In contrast to most previously reported enantioselective sensing assays, this approach would not require the use of an enantiopure ligand or metal complex and should be suitable for challenging substrates such as alanine or acyclic amino alcohols. Alternatively, the development of 1,8-bisphenolnaphthalenes that are conformationally stable was expected to provide new means for quantifiable chiral recognition events and thus enantioselective sensing.

A similar scaffold was envisioned to enable stereoselective photodimerizations of unsaturated carboxylic acids. 1,8-Dipyridylnaphthalene had previously been used to preorganize fumaric acid in the solid state and thus provided quantitative amounts of cis,trans,cis-cyclobutane-tetracarboxylic acid via [2+2]photoaddition. First, it was decided to evaluate cocrystal formation with 1,8-dipyridylnaphthalene and trans-cinnamic,
mesaconic or \textit{trans,trans}-muconic acids and to explore the possibility of dimerization via this non-covalent solid-state synthesis approach. Second, a series of templates for the covalent attachment and preorganization of olefinic substrates was to be synthesized to overcome possible limitations that might be experienced with 1,8-dipyridynaphthalene. Immobilization of \textit{trans}-cinnamic acid molecules to 1,8-bis(3’-methyl-4’-anilino)naphthalene and 1,8-bis(4’-anilino)naphthalene was expected to provide an alternative means for stereoselective photodimerization. The template structure affords two cofacial aniline rings that should favor a proximate, parallel arrangement of covalently attached cinnamoyl units and thus set the stage for the synthesis of \textit{cis,trans,cis}-cyclobutanedicarboxylic acids.
III. Chiral Amplification with a Stereodynamic Triaryl Probe: Assignment of the Absolute Configuration and Enantiomeric Excess of Amino Alcohols

III.1. Introduction

Amino alcohols constitute an important family of compounds due to their significant biological activity and role in synthetic chemistry. Amino alcohol units are found in many anticancer drugs, antibiotics and other bioactive natural products. Among these are daunorubicin and doxorubicin, some of the most useful and potent agents in cancer chemotherapy, and WP631 and naloxone, two powerful antibiotics (Figure 1).  

![Figure III.1. Structures of daunorubicin (left) and naloxone (right).](image)

Moreover, amino alcohols are very useful substances in the total synthesis of natural products and asymmetric catalysis, and have been used as building blocks for the construction of heterocyclic molecules (Scheme III.1). It is therefore essential to devise assays for determining the absolute configuration and enantiopurity of amino alcohols.

![Scheme III.1. Ephedrine-catalyzed asymmetric hydrogenation of β-ketoesters.](image)

For this purpose, Pu and co-workers have examined a variety of BINOL derivatives, including the dendrimers shown in Figure III.2. In order to increase the fluorescence intensity of the BINOL core, light-harvesting branches were attached to make 1, 2 and 3. As the dendrimer generation increases, the fluorescence intensity and the association constants with $\alpha$-amino alcohols improve. Dendrimer 3 was used for the chiral sensing of several amino alcohols, including 2-amino-4-methyl-1-pentanol, 17. The (S)-enantiomer of this substrate quenched the fluorescence of (S)-3 more efficiently than (R)-17, while the latter was more efficient when (R)-3 was used as sensor. This confirms that the measured fluorescence change is a consequence of chiral recognition and not caused by the presence of a quenching impurity. The highest selectivity was reported using sensor (S)-2 and 17, with $K_{SV}(S)/K_{SV}(R) = 1.26$. Replacement of the acetylene units in 1, 2 and 3 by single C-C bonds gave a new set of BINOL sensors that maintained the same sense of enantiodiscrimination. Studies with sensor (S)-4 and 17 revealed fairly low enantioselectivities ($K_{SV}(S)/K_{SV}(R) = 1.18$).

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**ii** Stern Volmer equation $I_0/I = 1 + K_{SV}[Q]$, where $I_0$ is the fluorescence intensity of the sensor in the absence of a substrate, $I$ is the fluorescence intensity in presence of a substrate, $[Q]$ is the substrate concentration, and $K_{SV}$ is the Stern Volmer constant which describes the efficiency of quenching.
Wolf et al. developed several enantioselective sensors, and successfully utilized them for determining the concentration and %ee of carboxylic acids, amino acids, amines and amino alcohols. The coordination of two molecules of enantiopure 5 to a scandium(III)
center generates a stable complex with a strong charge-transfer band at 360-480 nm (Figure III.3).  

![Graphical representation of complexes](image)

Figure III.3. Axially chiral 1,8-diacridynaphthalene N,N'-dioxides 5 and 6.

Subsequent displacement of the N,N'-dioxide ligand with several classes of substrates including amino alcohols allows accurate %ee determination by UV spectroscopy (Scheme III.2). Alternatively, a Sc(III) complex carrying two ligands of 6 proved to be strongly fluorescent and can be used in essentially the same assay. Addition of chiral amino alcohols results in stepwise displacement of 6 from the metal center. Since the ligand exchange involves diastereomeric intermediates, the UV or fluorescence change is different for enantiomeric substrates. The determination of substrate concentration and %ee was conducted using racemic and enantiopure ligand 6, respectively, with excellent accuracy.  

\[
\text{Sc}[(+)-5]_2 + (R)-14 \xrightleftharpoons{K_{1R}}^{K_{2R}} \text{Sc}[(+)-5 (R)-14] + (+)-5 \\
\text{Sc}[(+)-5 (R)-14] + (R)-14 \xrightleftharpoons{K_{1R}}^{K_{2R}} \text{Sc}[(R)-14]_2 + (+)-5
\]

Scheme III.2. Stepwise displacement of ligand 5 from scandium by (R)-14.

Enantioselective recognition of amino alcohols is also possible with 2,15-dihydroxyhexahelicene. The fluorescence intensity of 7 is almost five times higher than
that of BINOL, which increases sensitivity and allows analysis at lower concentrations. Using 2-amino-1-propanol, 14, and 2-amino-3-methyl-1-butanol, 18, Stern-Volmer ratios (K_{SV}(R)/K_{SV}(S)) of 2.10 and 1.40 were obtained. Interestingly, no chiral discrimination was observed with the diethyl ether of 7. Also, a helical polybinaphthyl sensor showed remarkable fluorescence quenching in the presence of N-methyl ephedrine, but an enantiomeric fluorescence difference ratio (ef)\textsuperscript{iii} of only 1.12.\textsuperscript{10}

![Figure III.4. Helically chiral 2,15-dihydroxyhexahelicene, or helixol 7.](image)

Supramolecular assemblies have also been introduced to enantioselective sensing. For example, a chiral metallacycle exhibiting rhenium corners was constructed through metal-directed self-assembly of enantiopure BINOL derivatives 8 (Figure III.5).\textsuperscript{11} The fluorescence of enantiopure (R)-9 can be quenched by both enantiomers of 14 to different extents, with a Stern-Volmer ratio (K_{SV}(R)/K_{SV}(S)) of 1.22. The opposite trend in enantioselectivity was observed upon employing (S)-9.

\textsuperscript{iii} The enantiomeric fluorescence difference ratio (ef) is defined as \([(I_R - I_0)/(I_S - I_0)]\) where I_0 is the fluorescence emission of the sensor alone and I_R and I_S are the fluorescence intensities after the addition of the (R)- and (S)-enantiomers, respectively.
Liquid crystals composed of rapidly interconverting biphenols have been reported to amplify the central chirality of amino alcohols through hydrogen bonding (Figure III.6). This central to axial chirality transfer is ultimately amplified to the supramolecular level and expressed by the liquid crystal’s cholesteric pitch.\textsuperscript{12}

A visual detection method for the chiral recognition of amino alcohols based on enantioselective gel collapsing has been reported. The gel of an (\textit{R})-BINOL-terpyridine-Cu(II) complex remains stable upon the addition of (\textit{R})-phenylglycinol but collapses upon the addition of the same amount of (\textit{S})-phenylglycinol.\textsuperscript{13} Several examples of chiral
sensing of amino alcohols with helical polymers have been presented.\textsuperscript{14} In a study conducted by Onouchi \textit{et al.}, a poly(phenylacetylene) polymer bearing phosphonic ester groups was found to form a helical conformation upon addition of \((R)-\)amino alcohols, which produced an ICD signal in the UV-vis region (Figure III.7). The imprinted macromolecular helicity was maintained even after the chiral amino alcohols were removed and replaced by achiral substrates.\textsuperscript{15}

![Figure III.7. Poly(phenylacetylene) polymer bearing a phosphonic monoethyl ester residue.](image)

Chiroptical spectroscopy has been applied extensively in the stereochemical analysis of chiral compounds. In particular, the efficacy of methods based on circular dichroism has received increasing attention in recent years.\textsuperscript{16} Circular dichroism is a widely used technique for the assignment of the absolute configuration and for conformational analysis of chiral compounds.\textsuperscript{17} Smith \textit{et al.} derivatized numerous classes of substrates such as amines and amino alcohols with salicylaldehyde and examined the resulting Cotton effects (CE) of the condensation products (Scheme III.3). The CE was attributed to the coupled oscillator mechanism and its sign was correlated to the absolute configuration of the chiral analyte.\textsuperscript{18}
Scheme III.3. Salicylaldehyde derivatization of chiral analytes containing a primary amine.

Chirality rules such as the benzoate sector rule correlate the sign of CEs with absolute configurations in cases where only a single chromophore is present.\textsuperscript{19} However, spatial interactions between two chromophores also give rise to CEs, with the sign dependent on the relative orientation of the two electric dipole transition moments. In most cases, a right-handed screw has been correlated to a positive CE. Knowledge of the transition moment vectors enables one to devise a chirality rule for the determination of absolute configuration, provided that the dominant mechanism is dipolar coupling.\textsuperscript{20} The covalent linkage of a chiral compound to a porphyrin, phthalocyanine or other chromophoric moieties has been reported to generate strong CEs,\textsuperscript{21} which provides a means to determine the chirality of UV-silent substrates.\textsuperscript{22} The achiral zinc porphyrin tweezer 10 forms a host-guest complex with chiral amino alcohols (Figure III.8). This adduct affords a bisignate CD curve in n-hexanes which has been correlated to the absolute configuration of the substrate. However, in solvents such as methylene chloride, chloroform, benzene, toluene and acetonitrile, the same exciton-coupling CD rule does not allow for correct absolute configuration assignment.\textsuperscript{23}
In particular, the covalent attachment of a conformationally flexible biphenyl unit to chiral amino acids, carboxylic acids and alcohols followed by isolation and CD analysis has been shown to allow a reliable assignment of the absolute configuration. For example, a flexible bridged biphenyl scaffold was attached to a series of chiral α-substituted carboxylic acids (Figure III.9). The corresponding biphenyl amides display a CE around 250 nm, and the sign has been successfully related to the absolute configuration of the substrate. In aliphatic acids, the preferred twist is determined exclusively by steric interactions, while in aromatic carboxylic acids, aryl-aryl edge-to-face interactions have to be considered.

Exciton-coupling CD has also been used to determine the absolute configuration of natural products. Fumonisins are chiral mycotoxins produced by *Fusarium moniliforme*.
and other fungi. Through the covalent attachment of \( p \)-dimethylaminobenzoate and subsequent examination of the CD signal, the structure of FB\(_1\) was confirmed to be (2\(S\),3\(S\),5\(R\)).\(^{26}\) Chiral agents that undergo chiral recognition via hydrogen bonding\(^{27}\) and metal complexation\(^{28}\) can provide an entry to in situ analysis without elaborate work-up procedures. Both NMR and CD spectroscopy with lanthanide complexes have been used to analyze the absolute configuration of chiral substrates. Among the lanthanide cations, Eu\(^{3+}\) and Yb\(^{3+}\) form complexes with various chiral substrates and exhibit characteristic CD signals. For instance, Tsukube et al. have demonstrated that achiral lanthanide tris(\(\beta\)-diketonates) can act as ICD probes for chiral amino alcohols, with the magnitude of the CE increasing with bulkier substituents at the chiral carbon, and its sign dictated by the absolute configuration of the substrate.\(^{29}\) The ICD analysis of lanthanide complexes has also been exploited for the quantification of the enantiomeric purity of amino alcohols.\(^{30}\) The diastereomeric lanthanide complexes have different stability constants and different geometries that can be detected spectroscopically. As opposed to the CEs obtained with (\(R\))-amino alcohols and europium tris(\(\beta\)-diketonates), a reversed S-shaped CD signal is observed with the (\(S\))-enantiomers. This has been attributed to a bidentate coordination of the amino alcohols leading to the less sterically hindered conformation (Figure III.10).\(^{31}\)

Other metals have also been employed in the ICD analysis of amino alcohols. For example, the CD spectra of complexes prepared from dirhodium(II) tetraacetate and 1,2-amino alcohols provide information about the absolute configuration of the latter; however, the small magnitudes of the Cotton effects observed do not allow accurate %\(\text{ee}\) determination.\(^{32}\)
Figure III.10. Possible bidendate coordination of (R)- and (S)-amino alcohols to the lanthanide complex, leading to S- or reverse S-shaped CEs. (Shaded sphere represents Eu complex).

Compared to ICD analysis of amines, amino acids, carboxylic acids and alcohols, only few methods for the determination of both the absolute configuration and enantiomeric composition of amino alcohols have been developed. Remaining drawbacks of some of these protocols are elaborate derivatization and purification steps prior to CD analysis, generation of modest Cotton effects at low wavelengths, and narrow application scope.

III.2. Results and Discussion

In continuation of previous studies with stereodynamic chiral biaryls and triaryls, and 1,8-diheteroarylnaphthalene-derived sensors, we decided to prepare 1,8-bis(3’-formyl-4’-hydroxyphenyl)naphthalene, 13. The unique structure of 1,8-diarylnaphthalenes provides an excellent opportunity to design a sensor that carries a
chromophoric binding pocket with the ability to transform a binding event with a chiral substrate into a strong CD signal. The stereodynamic, fluxional and CD-silent probe 13 exhibits two salicylaldehyde units attached to the peri-positions of naphthalene.$^{37}$ It can easily be prepared in 48% overall yield through a Suzuki coupling of boronic acid 11 and 1,8-diiodonaphthalene, followed by deprotection of 12, without the need for stereoselective synthesis or resolution (Scheme III.4).


Slow evaporation of a solution of 13 in chloroform gave single crystals suitable for X-ray analysis. Although the anti-conformation is generally expected to be thermodynamically favored in solution, 13 crystallizes in its syn-conformation (Figure III.11). The splaying angle between the two cofacial salicylaldehyde rings was determined as 13.5° which results in a centroidal arene-arene distance of 3.33 Å. The projection along the naphthalene unit shows that the two salicylaldehyde rings are almost perfectly aligned, having a torsion angle of only 4.3°.
Figure III.11. Single crystal structure of syn-13. The side and top views show the π-stacking of the two salicylaldehyde rings (left and middle). The view along the naphthalene ring reveals that both salicylaldehyde rings are almost perfectly aligned (right).

1,8-Diphenyl- and 1,8-dipyridynaphthalenes are known to undergo fast rotation about the two aryl-aryl bonds at room temperature. In general, the enantiomeric anti-isomers of these triaryls rapidly interconvert via the thermodynamically less stable meso syn-intermediate with a rotational energy barrier of 60-75 kJ/mol. In analogy to similar 1,8-diaryl naphthalenes, triaryl 13 can be expected to undergo facile rotation about the two aryl-aryl bonds at room temperature (Scheme III.5). Since both arene rings readily rotate about the two chiral axes, the sensor exists as a mixture of enantiomeric anti-conformers that rapidly interconvert via a meso syn-isomer.

Diimine formation with chiral amino alcohols was envisioned to disturb this equilibrium and strongly favor the population of a single diastereomer through intramolecular hydrogen bonding (Scheme III.5). Indeed, titration of 13 with either enantiomer of amino alcohol 14 showed a new characteristic UV maximum above 400 nm, and MS and NMR analysis proved quantitative diimine formation in chloroform within 5 minutes (Figure III.13). Analysis of the condensation reaction by NMR and MS did not show any sign of the monoimine intermediate, indicating that the second condensation step is faster than the first.

Figure III.12. Structures of the amino alcohols used in this study.

Figure III.13. UV plot of 13 titrated with (R)-14 in CHCl₃, reaction concentration was 0.02 M, UV concentration was 10.0x10⁻³ M. Pure 13 (red), 1 equiv of 14 after 5 min (green), 2 equiv after 5 and 10 min (both light blue) and 18 equiv after 5 min (dark blue).
The corresponding CD spectra show that reaction with this simple acyclic amino alcohol results in a remarkably strong Cotton effect and similar results were obtained with several other substrates (Figure III.14 and Chapter III.4.3.). Since it is known that salicylaldehyde can be used for CD analysis of the absolute configuration of amines and amino acids, we employed both 13 and free salicylaldehyde in CD sensing experiments of 14. CD and NMR analysis showed that the reaction with salicylaldehyde requires more time and is still not complete after 90 minutes. Nonetheless, the corresponding salicylidenimine remains CD silent above 300 nm in chloroform and ethanol even at tenfold concentration. Apparently, the strong Cotton effect at high wavelengths and the short condensation reaction time are due to the unique structure of sensor 13.

![CD plot](image)

Figure III.14. CD plot of the diimine obtained from (R)-14 CHCl₃ (green) and (S)-14 (red) both (5.0 x 10⁻⁴ M), and the (R)-14 derived salicylidenimine (blue, 5.0 x 10⁻³ M).

We were able to grow single crystals of the diimines 23 and 24, produced from 13 and amino alcohols 14 and 15, respectively. Crystallographic analysis of the orange
crystals of 23 and 24 proved that the central chirality of the substrates induces a rigid, axially chiral triaryl scaffold. Condensation of 13 and the (S)-enantiomer of 14 and 15 resulted in well-defined amplification of chirality and the sensor was found to adopt a (P,P)-conformation that is stabilized by intramolecular hydrogen bonding (Figure III.15 and Chapter III.4.4). Importantly, we obtained (M,M,R,R)-23 when (R)-14 was employed in the same experiment. As expected, the two phenyl rings in these crowded structures are not perfectly coplanar but slightly splayed. The splaying angle (the angle between the two phenyl planes) in (M,M,R,R)-23 and (P,P,S,S)-23 is 15.9°. The salicyldenimine rings are also not perfectly orthogonal to the naphthalene ring but afford a torsion angle of -52.6° and +52.1°, respectively. Finally, (M,M,R,R)-23 and (P,P,S,S)-23 show opposite twisting which is expressed by the angle between the two phenyl-naphthalene bonds viewed along the naphthalene plane. The twisting angles are -14.6° and +14.7°. The separation of the centroids of the two phenyl rings was determined as 3.392 and 3.391 Å, which enforces strong π−π-interactions between the two salicyldenimine units. The C=N···HOCphenyl hydrogen bonding lengths are 1.692 Å and 1.649 Å and the CaliphOH···OCphenyl hydrogen bonds are 1.899 Å and 2.011 Å, respectively. The sense of asymmetric induction and the three-dimensional arrangement including bond angles and hydrogen bond lengths in (P,P,S,S)-24, which was obtained from (S)-15, closely match those discussed for (P,P,S,S)-23 (see Chapter III.4.4). This parallel behavior underscores the generality of the chiral amplification process shown in Scheme 5. Crystallographic analysis of the diimines obtained from opposite enantiomers of a chiral amino alcohol proved that the central chirality of the substrate controls the arrangement of the two
pivotal aryl-aryl bonds in the probe (Figure III.15). The corresponding axially chiral structure is locked by intramolecular hydrogen bonding and favors strong Cotton effects.

![Figure III.15. X-ray structures of (M,M,R,R)- and (P,P,S,S)-23. View into the cleft (top). View along the naphthalene plane (bottom). Selected measurements: (M,M,R,R)-23: N1···H1 1.692 Å, H2···O1’ 1.899 Å, twisting angle between salicyldenimine-]

This arrangement allows the two imino alcohol moieties in 23 and 24 to participate in four hydrogen bonds while the alkyl groups occupy the sterically least hindered positions and the hydrogens attached to the chiral center are directed towards the more sterically crowded areas close to the salicylidenimine planes. The high degree of central-to-axial chirality induction and the corresponding strong CD signals are thus a result of concurrent optimization of hydrogen bonding and minimization of steric interactions. The stereodynamic sensor is effectively locked into a single conformation which is known to favor intense Cotton effects. The diimines obtained with amino diols 20 and 21 show weaker CEs in the wavelength range scanned, probably because of competitive hydrogen bonding of the two available hydroxyl groups. The sense of axial chirality and the sign of the observed ICD signal which can be attributed to exciton coupling of the proximate cofacial salicylidenimine chromophores are ultimately controlled by the central chirality of the substrate. Salicylidenimines can form a CD active quinoid-like tautomer. The ICD observed with 13 is more likely a result of ECCD. NMR and X-ray analysis do not show the quinoid structure. The phenolic C-O bond lengths in 23 and 24 are 1.357 Å and 1.361 Å, which is close to the value in phenol (1.349 Å); the C-O bond length in quinone is 1.294 Å. The sign of the CD spectrum can be used to determine the absolute configuration of the amino alcohols used in this study (except amino diols 20 and 21).

Using crystallographic and spectral data, we can devise a chirality rule that correlates the sign of the ICD to the central chirality of the chiral amino alcohol. An \((R)\)-amino alcohol reacts with 13 to generate an \((M,M,R,R)\)-diimine, with a negative sense of twist (-14.6°)
and thus a negative CE between 380 and 440 nm. The opposite is true with the (S)-enantiomer that generates a (P,P,S,S)-diimine (+14.7°) and hence a positive CE.

To evaluate the practical use of sensor 13, a calibration curve was determined using 13 and amino alcohol 14 in varying %ee (Figure III.16). To 13 (4.0 mg, 0.01 mmol) and molecular sieves (4 Å, 8-12 mesh) in 450 µL of anhydrous CHCl₃, 2 equivalents of a solution of substrate 14 in 200 µL CHCl₃ (%ee range: +100.0, +70.4, +39.3, +0.5, -39.8, -72.4 and -100.0) were added and the mixture was allowed to stir for 5.0 minutes at room temperature. All reactions were conducted at 0.02 M and then diluted to 5.0x10⁻⁴ M to collect the CD spectra in triplicate. The resulting curves were corrected using binomial smoothing, while no baseline correction was needed. The CD amplitudes (mdeg) at 362 nm were plotted vs. %ee. This calibration curve shows a linear relationship (%ee = 2.6799 x CD signal₃₆₂nm – 0.9182). Six scalemic samples of 14 with varying %ee were prepared and treated with the sensor as described above. Based on the measured CD amplitude at 362 nm and the calibration curve, the enantiomeric excess of these unknown samples was determined (Table III.1). This simple assay correctly provides the absolute configuration of the major enantiomer and gives accurate ee’s that are within 3.6% of the actual values.
Figure III.16. Top: CD spectra of the diimines obtained with scalemic mixtures of 14. Bottom: Calibration curve showing the CD amplitude at 362 nm of the diimine obtained with sensor 13 as a function of the %ee of 14.

Table III.1. Experimental vs. actual %ee values of six scalemic samples of 14.

<table>
<thead>
<tr>
<th>Actual %ee (R)-14</th>
<th>Experimental %ee (R)-14</th>
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<tbody>
<tr>
<td>74.9</td>
<td>77.0</td>
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<tr>
<td>-67.8</td>
<td>-64.2</td>
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<td>36.4</td>
<td>36.9</td>
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<td>-22.5</td>
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<td>92.9</td>
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<tr>
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</table>
Probe 13 was further used for quantitative %ee determination of substrates 15 and 16 (Tables III.2 and III.3). An enantiomeric excess calibration curve was obtained for each substrate as described above, followed by the analysis of several unknowns (Chapter III.4.5). Calculated results correlate well with actual values, indicating that 13 is suitable for the accurate quantification of the enantiopurity of several amino alcohol analytes.

Table III.2. Experimental vs. actual %ee values of four scalemic samples of 15.

<table>
<thead>
<tr>
<th>Actual %ee (R)-15</th>
<th>Experimental %ee (R)-15</th>
</tr>
</thead>
<tbody>
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<td>+91.4</td>
</tr>
<tr>
<td>+73.0</td>
<td>+66.9</td>
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<td>-51.6</td>
</tr>
<tr>
<td>+27.2</td>
<td>+24.0</td>
</tr>
</tbody>
</table>

Table III.3. Experimental vs. actual %ee values of three scalemic samples of 16.

<table>
<thead>
<tr>
<th>Actual %ee (R)-16</th>
<th>Experimental %ee (R)-16</th>
</tr>
</thead>
<tbody>
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<td>+90.1</td>
<td>+96.0</td>
</tr>
<tr>
<td>-42.2</td>
<td>-43.2</td>
</tr>
<tr>
<td>-63.1</td>
<td>-59.5</td>
</tr>
</tbody>
</table>

III.3. Conclusions

A stereodynamic chromophoric sensor that undergoes rapid racemization via rotation about two chiral axes has been developed and used for the quantitative analysis of the %ee and absolute configuration of several amino alcohols. 1,8-Bis(3’-formyl-4’-hydroxyphenyl)naphthalene, 13, can be easily prepared in two steps, and combines several attractive features: (1) the generation of intense Cotton effects at high wavelength reduces interference with chiral impurities and is a general requisite for accurate %ee
quantification; (2) fast diimine formation followed by in situ CD measurements allows
time-efficient analysis and eliminates the need for elaborate purification steps; (3) the
operational simplicity of the CD assay provides an entry towards automation and high
throughput screening; (4) only minute sample, sensor and solvent amounts are needed;
(5) the sensor provides information about the absolute configuration and enantiomeric
composition of cyclic and acyclic substrates based on well-defined chiral amplification.
To evaluate the practical use of the recyclable probe, scalemic samples of 2-
aminopropanol, 2-aminobutanol and 2-hydroxy propylamine, 14-16, covering a wide %ee
range were analyzed. The results obtained by our in situ CD sensing method were in
excellent agreement with actual %ee’s.

III.4. Experimental Section

III.4.1. Synthetic Procedures

All reagents and solvents were used without further purification. Reactions were
carried out under nitrogen atmosphere and under anhydrous conditions. 1,8-
Diiodonaphthalene was prepared from 1,8-diaminonaphthalene as described in the
literature.41 Products were purified by flash chromatography on SiO₂ (particle size 0.032-
0.063 mm). NMR spectra were obtained at 400 MHz (¹H NMR) and 100 MHz (¹³C
NMR) using CDCl₃ as the solvent. Chemical shifts are reported in ppm relative to TMS.

1,8-Bis(3’-formyl-4’-methoxyphenyl)naphthalene (12)42

A solution of 1,8-diiodonaphthalene, (1.7 g, 4.5 mmol), 3-formyl-4-
methoxyphenylboronic acid (11), (3.2 g, 18.0 mmol), Pd(PPh₃)₄ (1.3 g, 1.1 mmol) and
Na$_2$CO$_3$, (2.4 g, 22.4 mmol) in 60 mL of toluene:EtOH:water (3:2:1, v/v) was stirred at 100 °C for 14 hours. The resulting mixture was allowed to come 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$_2$:MeOH 99.7:0.3) afforded 12 in 69% yield as a yellow solid.

$^1$H NMR: δ = 3.82 (s, 6H), 6.58 (d, $J = 8.4$ Hz, 2H), 7.15 (dd, $J = 2.1$, 8.4 Hz, 2H), 7.32 (d, $J = 2.1$, 2H), 7.37 (d, $J = 7.1$ Hz, 2H), 7.54 (dd, $J = 7.1$ Hz, 8.0 Hz, 2H), 7.95 (d, $J = 8.0$ Hz, 2H), 10.30 (s, 2H).

$^{13}$C NMR: δ = 55.8, 110.8, 123.3, 125.2, 129.0, 129.5, 130.64, 135.3, 136.4, 135.7, 137.4, 138.2, 159.9, 189.4.

1,8-Bis(3'-formyl-4'-hydroxyphenyl)naphthalene (13)

To a solution of 1,8-bis(3'-formyl-4'-methoxyphenyl)naphthalene, 12, (0.38 g, 1.0 mmol) in 15 mL of anhydrous dichloromethane at 0 °C, BBr$_3$ (5.8 mL, 5.8 mmol) was added dropwise and the mixture was stirred for one hour. It was then quenched with isopropyl alcohol and then with water, and extracted with dichloromethane. The combined organic layers were dried over MgSO$_4$ and concentrated in vacuum. Purification by flash chromatography on silica gel (dichloromethane:hexanes 20:1) afforded 13 in 70% yield as a white solid.

$^1$H NMR: δ = 6.64 (m, 2H), 7.00-7.25 (m, 4H), 7.42 (d, $J = 7.0$ Hz, 2H), 7.58 (dd, $J = 7.0$ Hz, 8.0 Hz, 2H), 8.00 (d, $J = 8.0$ Hz, 2H), 9.62 (s, 2H), 10.75 (s, 2H).

$^{13}$C NMR: δ = 116.6, 116.9, 119.2, 125.4, 129.3, 131.0, 134.8, 135.2, 135.5, 137.6, 137.8, 159.9, 195.9.

Anal. Calcd. for C$_{24}$H$_{16}$O$_4$: C, 78.25; H, 4.38; O, 17.37. Found: C, 78.40; H, 4.31; O, 17.27.
**Diimine Formation**

UV and NMR monitoring of the reaction between 13 and 2 equivalents of amino alcohol (R)-14 showed quantitative conversion after 5 minutes. Electrospray mass spectra (1mg/mL in ACN) also proved formation of the desired condensation product.

$^1$H NMR Spectrum of the diimine obtained from 13-and (R)-14.
Mass spectrum of the diimine obtained from 13-and (R)-14.

ESI-MS: m/z = 483.3 (M+1)^+

### III.4.2. Sensing Experiments

The following conditions have been optimized in terms of reaction time, solvent, concentration and equivalents. To a mixture of 13 (4.0 mg, 0.01 mmol) and molecular sieves (4 Å, beads, 8-12 mesh) in 600 µL of anhydrous CHCl₃, 2 equivalents of the amino alcohol were added and the mixture was allowed to stir for 5.0 minutes. Prior to each use, the CD instrument was purged with nitrogen for 20 minutes and the chiller was set to equilibrate at 25.0 °C. Spectra were collected between 345 and 540 nm with a standard sensitivity of 100 mdeg, a data pitch of 0.5 nm, a band width 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 adjusted through baseline correction and binomial smoothing. The concentration of all samples was 5.0x10⁻⁴ M in chloroform. Control experiments with salicylaldehyde were conducted to compare the CD signal of salicylideneimine with that of sensor-derived diimine. At a concentration of 0.4 M, 2 equivalents of enantiopure
amino alcohol 14 were added under the same conditions as described above for sensor 13. Upon completion of the reaction, the CD spectrum was collected at 5.0×10⁻³ M. The CD was silent in the region of interest for both enantiomers in chloroform and ethanol even at 10 times the concentration of the diimine obtained with 13. The reaction between salicylaldehyde and amino alcohol 14 was monitored by MS, ¹H NMR and UV spectroscopy which showed 50% conversion after 5 minutes, 92% after 60 minutes and 98% after 90 minutes.
III.4.3. CD and MS Data

CD Spectra of the 13-derived diimines obtained from (R)-15 (black) and (S)-15 (red) at 5.0x10^{-4} M in chloroform.

Mass spectrum of the diimine obtained from 13 and (R)-15.

ESI-MS: m/z = 511.3 (M+1)^+, 533.4 (M+Na)^+
CD Spectra of the 13-derived diimines obtained from (R)-16 (black) and (S)-16 (red) at 5.0x10^{-4} M in chloroform.

Mass spectrum of the diimine obtained from 13 and (R)-16.

ESI-MS: m/z = 483.3 (M+1)^+
CD Spectra of the 13-derived diimines obtained from (R)-17 (black) and (S)-17 (red) at 5.0x10^{-4} M in chloroform.

Mass spectrum of the diimine obtained from 13 and (R)-17.

ESI-MS: m/z = 566.4 (M+1)^+, 533.4 (M+Na)^+
CD Spectra of the 13-derived diimines obtained from (R)-18 (black) and (S)-18 (red) at 5.0x10^{-4} M in chloroform.

Mass spectrum of the diimine obtained from 13 and (R)-18.

ESI-MS: m/z = 539.3 (M+1)^+, 561.2 (M+Na)^+, 583.4 (M+2Na)^+
CD Spectra of the 13-derived diimines obtained from \((R)-19\) (black) and \((S)-19\) (red) at 5.0x10\(^{-4}\) M in chloroform.

Mass spectrum of the diimine obtained from 13 and \((R)-19\).

ESI-MS: \(m/z = 635.3\ (M+1)^+, \ 657.3\ (M+Na)^+\)
CD Spectra of the 13-derived diimines obtained from \((R)-20\) (black) and \((S)-20\) (red) at 5.0x10^{-4} \text{ M} in chloroform.

![CD Spectra](image)

Note that CIP rules result in change of \(R\) and \(S\) descriptors due to the presence of the hydroxymethyl group while the actual spatial orientation at the chiral carbon atom of the amino alcohol unit stays the same (compare to first example).

Mass spectrum of the diimine obtained from 13 and \((R)-20\).

![Mass Spectrum](image)

ESI-MS: \(m/z = 515.4 (M+1)^{+}\), 537.1 (M+Na)^{+}, 559.3 (M+2Na)^{+}
CD Spectra of the 13-derived diimines obtained from (R)-21 (black) and (S)-21 (red) at 5.0x10^{-4} M in chloroform.

Mass spectrum of the diimine obtained from 13 and (R)-21.

ESI-MS: m/z = 543.4 (M+1)^+, 565.4 (M+Na)^+, 587.2 (M+2Na)^+
CD Spectra of the 13-derived diimines obtained from (R)-22 (black) and (S)-22 (red) at 5.0x10^{-4} M in chloroform.

Mass spectrum of the diimine obtained from 13 and (R)-22.

ESI-MS: m/z = 631.4 (M+1)^+, 653.4 (M+Na)^+, 687.3 (M+2Na)^+
III.4.4. Crystallization and X-Ray Diffraction

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.

A crystal of 13 was obtained by slow evaporation of a solution of 5.0 mg of 13 in 3 mL CHCl₃. Crystal structure data for 13: Formula C₂₄H₁₆O₄, M = 368.38, crystal dimensions 0.6 x 0.4 x 0.3 mm, monoclinic, space group C2/c, a = 20.4576(27) Å, b = 6.8831(9) Å, c = 25.3924(34) Å, α,γ = 90°, β = 98.623(2)°, V = 3535.13 Å³, Z = 7, \( \rho_{\text{calc}} \) = 1.3841 g cm⁻³.

![Crystal structure of 13.](image)

<table>
<thead>
<tr>
<th>Important crystallographic measurements</th>
<th>13</th>
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</thead>
<tbody>
<tr>
<td>O1-H1 [Å]</td>
<td>1.952</td>
</tr>
<tr>
<td>Phenyl-phenyl [Å]</td>
<td>3.334</td>
</tr>
<tr>
<td>(centroid to centroid)</td>
<td></td>
</tr>
<tr>
<td>Splaying angle [°]</td>
<td>13.45</td>
</tr>
<tr>
<td>Torsion angle [°]</td>
<td>4.34</td>
</tr>
</tbody>
</table>

Figure III.17. Crystal structure of 13.
A crystal of \((M,M,R,R)-23\) was obtained by slow evaporation of a solution of 5.0 mg of \((M,M,R,R)-23\) in 5 mL CHCl\(_3\). Crystal structure data for \((M,M,R,R)-23\): Formula C\(_{30}\)H\(_{30}\)N\(_2\)O\(_4\), \(M = 482.57\), crystal dimensions 0.6 x 0.5 x 0.4 mm, tetragonal, space group P\(_4_3\)2\(_1\)2, \(a = 12.0825\) (8) Å, \(b = 12.0825\) (8) Å, \(c = 17.3970\) (11) Å, \(\alpha, \beta, \gamma = 90^\circ\), \(V = 2539.7(3)\) Å\(^3\), \(Z = 8\), \(\rho_{\text{calc}} = 1.257\) g cm\(^{-3}\).

![Crystal structure of \((M,M,R,R)-23\).](image)

A crystal of \((P,P,S,S)-23\) was obtained by slow evaporation of a solution of 5.0 mg of \((P,P,S,S)-23\) in 5 mL CHCl\(_3\). Crystal structure data for \((P,P,S,S)-23\): Formula C\(_{30}\)H\(_{30}\)N\(_2\)O\(_4\), \(M = 482.57\), crystal dimensions 0.6 x 0.5 x 0.4 mm, tetragonal, space group P\(_4_1\)2\(_1\)2, \(a = 12.0796\) (7) Å, \(b = 12.0796\) (7) Å, \(c = 17.3913\) (10) Å, \(\alpha, \beta, \gamma = 90^\circ\), \(V = 2537.7(3)\) Å\(^3\), \(Z = 8\), \(\rho_{\text{calc}} = 1.263\) g cm\(^{-3}\).
A crystal of \((P,P,S,S)-24\) was obtained by slow evaporation of a solution of 5.0 mg of \((P,P,S,S)-24\) in 5 mL CHCl₃. Crystal structure data for \((P,P,S,S)-24\): Formula C₃₂H₆₄N₂O₄, \(M = 510.62\), crystal dimensions 0.4 x 0.3 x 0.2 mm, tetragonal, space group P4₁2₁2, \(a = 12.3733(13) \, \text{Å}, \quad b = 12.3733 \, (13) \, \text{Å}, \quad c = 17.4603(19) \, \text{Å}, \quad \alpha, \beta, \gamma = 90^\circ, \quad V = 2673.1(5) \, \text{Å}^3, \quad Z = 4, \quad \rho_{\text{calc}} = 1.189 \, \text{g cm}^{-3}.\)
## Important crystallographic measurements

<table>
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<tr>
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<tbody>
<tr>
<td>(C1-O1) [Å]</td>
<td>1.357</td>
<td>1.358</td>
<td>1.362</td>
</tr>
<tr>
<td>(N1-H1) [Å]</td>
<td>1.692</td>
<td>1.648</td>
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<td>(O1-H2') [Å]</td>
<td>1.899</td>
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<td>Salicylidenimine-salicylidenimine [Å] (centroid to centroid)</td>
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<td>3.391</td>
<td>3.397</td>
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<td>Twisting angle between salicylidenimine-naphthalene bonds [°]</td>
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<td>+14.7</td>
<td>+13.7</td>
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<tr>
<td>Splaying angle between salicylidenimines [°]</td>
<td>15.9</td>
<td>15.9</td>
<td>14.7</td>
</tr>
<tr>
<td>Angle between the salicylidenimine ring and naphthalene plane [°]</td>
<td>-52.6</td>
<td>+52.1</td>
<td>+52.8</td>
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III.4.5. Ee Calibration Curves using 15 and 16

To 13 (4.0 mg, 0.01 mmol) and molecular sieves (4 Å, 8-12 mesh) in 400 µL of anhydrous CHCl₃, 2 equivalents (150 µL) of a previously stirred solution of 15 (+100.0, +68.4, +37.1, 0.0, -70.0, and -100.0 %ee) were added and the mixture was allowed to stir for 5.0 minutes at room temperature. All reactions were conducted at 0.02 M and then diluted to 5.0 x 10⁻⁴ M to collect the CD in triplicates. The resulting curves were corrected using binomial smoothing, while no baseline correction was needed. The CD amplitudes (mdeg) at 358 nm were plotted vs. %ee (%ee = 1.904 x CD signal₃₅₈nm + 2.7054).

\[ y = 1.904x + 2.7054 \]
\[ R^2 = 0.9748 \]

Figure III.21. Calibration curve showing the CD amplitude at 358 nm of the diimine obtained with sensor 13 as a function of the enantiomeric excess of amino alcohol 15.

To 13 (4.0 mg, 0.01 mmol) and molecular sieves (4Å, 8-12 mesh) in 400 µL of anhydrous CHCl₃, 2 equivalents (150 µL) of a previously stirred solution of 16 (+100.0, +64.9, +43.0, -0.9, -40.1, and -100.0 %ee (R)) were added and the mixture was allowed to stir for 5.0 minutes at room temperature. All reactions were conducted at 0.02 M and
then diluted to $5.0 \times 10^{-4}$ M to collect the CD in triplicates. The resulting curves were corrected using binomial smoothing, while no baseline correction was needed. The CD amplitudes (mdeg) at 360 nm were plotted vs. %ee ($\%ee = 4.4921 \times \text{CD}_{360\text{nm}} - 5.3514$).

$$y = 4.4921x - 5.3514 \quad R^2 = 0.995$$

Figure III.22. Calibration curve showing the CD amplitude at 360 nm of the diimine obtained with sensor 13 as a function of the enantiomeric excess of amino alcohol 16.
III.5. References


IV. Enantioselective CD Analysis of Amino Acids Based on Chiral Amplification with a Stereodynamic Probe

IV.1. Introduction

The development of molecular sensors with the potential use in high-throughput stereoselective analysis of chiral compounds has received increasing attention in recent years. Due to their biological relevance and prevalence, amino acids are inarguably among the most important sensing targets. Representing an important fraction of nature’s chiral pool, amino acids are fundamental to the chemical industry and precursors to many important organic compounds. In biological systems, amino acids are not only used to build peptides and proteins, but also as precursors for heme, serotonin and other complex compounds, or simply as a source of energy. Industrial applications include the production of pharmaceuticals such as L-DOPA, eflornithine and 5-hydroxytryptophan (Figure IV.1).

Figure IV.1. Structures of L-DOPA (left, treatment of Parkinsonism), eflornithine (middle, treatment of sleeping sickness) and 5-hydroxytryptophan (right, drug candidate for the treatment of depression).

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Furthermore, amino acids have extensively been used as chiral catalysts and reagents in asymmetric synthesis. For instance, proline and its derivatives effectively catalyze the stereoselective reduction of prochiral methyl ketones\textsuperscript{6} and imines,\textsuperscript{7} addition of enolates to carbonyl compounds\textsuperscript{8} or cross-aldol reactions of cyclohexanone and various aldehydes,\textsuperscript{9} just to name a few (Schemes IV.1 and IV.2). Other amino acids have been successfully employed in enantioselective Diels-Alder reactions,\textsuperscript{10} addition of diethyl zinc to aldehydes\textsuperscript{11} or hydrogenation of enamides.\textsuperscript{12}

\[ \text{Scheme IV.1. (S)-Proline-catalyzed reduction of methyl ketones.} \]

\[ \text{Scheme IV.2. Cross-aldol condensation between cyclohexanone and aromatic aldehydes using (S)-proline as catalyst.} \]

Monosodium (S)-glutamate is widely used for the flavor enhancement of canned, frozen or dried food (Figure IV.2).\textsuperscript{13} Of further interest to the food and flavor industry is aspartame, a methyl ester of the dipeptide of (S)-aspartic acid and (S)-phenylalanine, which is used as an artificial sweetener.\textsuperscript{14} Monitoring the stereochemical integrity of amino acids is essential since their activity is strictly related to their stereochemistry, and because certain techniques of food processing can cause racemization.\textsuperscript{15} Since (S)-amino acids are bitter and (R)-amino acids are sweet, the use of chemosensors as “artificial
%"tongues" for the detection of organic molecules in solution has been reported, albeit with limited success.\textsuperscript{16}

![Figure IV.2. Structures of monosodium (S)-glutamate (left) and aspartame (right).](image)

While a nonspecific sensor that can be used to analyze a wide range of amino acids is desirable, many of the sensing systems found in the literature have a limited application scope. To date, several examples of amino acid probes have been reported but few have been exploited for time-efficient determination of the absolute configuration and quantification of the enantiomeric excess. Free amino acids are challenging substrates partly because of their low solubility in common organic solvents. For this reason, most sensing assays are conducted with N-protected substrates. BINOL-based fluorescent sensors typically necessitate large excesses of N-Boc-protected amino acids.\textsuperscript{17} Pu and coworkers have introduced several enantioselective fluorosensors for N-protected amino acids (Figure IV.3). While the bisbinaphthyl-based macrocycles 1 and 2 showed greater enantioselectivities than their acyclic analogues 3 and 4, the introduction of conjugated substituents in the 6,6'-positions significantly increases the fluorescence response and allows for a 100-fold reduction in the sensor concentration.\textsuperscript{18} 1,2-Diphenylethylene diamine derivatives 1 were found to enantioselectively recognize N-protected phenylglycine. Upon addition of four thousand equivalents of the (R)-enantiomer, the fluorescence emission is four times higher than in the presence of the same excess of the (S)-enantiomer.\textsuperscript{19} Utilizing cyclohexane-1,2-diamine-derived sensor 2, Pu et al. examined
were obtained for substrates such as mandelic and hexahydromandelic acids.\textsuperscript{20} Other BINOL systems bearing imidazolium\textsuperscript{21} or benzoyl units\textsuperscript{22} have also been reported with maximum $I_R/I_S$ ratios of 4.5 and 7.2, respectively.\textsuperscript{23}

\begin{center}
\includegraphics[width=\textwidth]{figure_iv_3}
\end{center}

**Figure IV.3.** Structures of bisbinaphthyl-based fluorescent probes ($R = H$, $p$-ethoxyphenyl) with 1,2-diphenylethylene (1 and 3) or cyclohexane-1,2-diamine (2 and 4) ligands.

Mei has demonstrated that 1,8-diheteroarylnaphthalenes and their $N,N'$-dioxide derivatives embed amino acids into a highly stereoselective cleft via hydrogen bonding.

\textsuperscript{ii} The enantiomeric fluorescence difference ratio (ef) is defined as $[(I_R-I_0)/(I_S-I_0)]$ where $I_0$ is the fluorescence emission of the sensor alone and $I_R$ and $I_S$ are the fluorescence intensities after the addition of the (R)- and (S)-enantiomers, respectively.
interactions (Figure IV.4).\textsuperscript{24} For instance, the use of axially chiral 1,8-
diacridynaphthalene 5 allows quantitative enantiodifferentiation of nine protected amino
acids.\textsuperscript{25} The replacement of the tert-butyl groups in 5 by 3,5-dimethylphenyl substituents
gave 6 which was used for the enantioselective sensing of several protected amino acids
using both fluorescence lifetime and intensity.\textsuperscript{26} The oxidation of 6 to its corresponding
$N,N'$-dioxide 7 expanded the application scope to include both the determination of the
%ee and concentration of several protected and unprotected amino acids, as well as
amines, amino alcohols and carboxylic acids.\textsuperscript{27} Competitive binding between a scandium
complex of 7 and amino acids generates a quantifiable UV change. For example,
concentration and %ee values of valine samples were determined with excellent accuracy
($1.58 \times 10^{-5}$ M and 97% ee compared to actual values of $1.60 \times 10^{-5}$ M and 95% ee).

![Figure IV.4. Axially chiral 1,8-diacridynaphthalenes 5 and 6 and $N,N'$-dioxide 7.](image)

Noteworthy, a wide range of macrocyclic enantioselective fluorosensors,\textsuperscript{28} including
a chiral terpyridine crown ether specific for $\alpha$-phenylglycine methyl ester
hydrochloride,\textsuperscript{29} a tryptophan-derived calix[4]arene for $N$-Boc protected alanine,\textsuperscript{30} and a
(+)-tubocurarine receptor suitable for the analysis of phenylalanine, have been reported.\textsuperscript{31}
Somewhat less attractive fluorescence sensing approaches rely on covalent attachment of
a dansyl or a pyrene fluorophore to the amino acid substrate, followed by enantioselective
recognition using either a chiral copper(II) complex \(^{32}\) or excess of \(\alpha\)-acid glycoprotein and bovine serum albumine. \(^{33}\) On the other hand, fluorescent cyclodextrin-based sensors are quite common, but present several shortcomings. Copper(II) complexes of phenylalanine-tethered \(\beta\)-cyclodextrins generally have a limited substrate scope. \(^{34}\) Bohne realized that a pyrene-cyclodextrin inclusion complex can be used to differentiate between the enantiomers of tryptophan in the presence of alcohols or alkyl sulfates. \(^{35}\) Corradini \textit{et al.} have shown that incorporation of a carefully designed copper binding site and a dansyl fluorophore into \(\beta\)-cyclodextrins allows for enantioselective ligand exchange with a "switch on" detection of amino acids. \(^{36}\)

Compared to the diversity of fluorescent sensors, few NMR, \(^{37}\) UV \(^{38}\) and circular dichroism (CD) \(^{39}\) probes for amino acids have appeared in the literature. Dowden’s group developed a homochiral macrocyclic receptor which, upon addition of an amino acid, forms diastereomeric complexes that give distinct \(^1\)H NMR amide signals (Figure IV.5). \(^{40}\)

![Figure IV.5. Macrocyclic sensor for the NMR analysis of Cbz-protected alanine and phenylalanine.](image)

Anslyn’s group developed a practical UV-vis indicator displacement assay utilizing a chiral copper complex for the quantitative analysis of the enantiomeric composition of 12 free amino acids in aqueous media buffered at 7.5. \(^{41}\) The screening of several diamine scaffolds led to a chiral copper complex exhibiting a cyclohexane-1,2-diamine ligand and
a chrome azurol S indicator ligand (CAS). Upon addition of a chiral substrate, the CAS ligand is displaced to a different extent by opposite enantiomers, causing a quantifiable change in the UV signal (Scheme IV.3). Differences in absorbances ($A_{\text{max}}$ at 602 nm $\approx 1.8$ AU) range from 0.025 with the enantiomers of alanine to 0.392 with those of isoleucine.

Scheme IV.3. Anslyn’s stereoselective competitive binding assay.

The screening of an asymmetric reaction producing scalemic mixtures of valine gave %ee’s with average errors of 4.7 and 12% compared to values obtained by HPLC and NMR, respectively (Scheme IV.4).\textsuperscript{42}

Scheme IV.4. Valine-forming asymmetric reaction to test Anslyn’s UV-based sensor.

Smith et al. have worked extensively to establish rules for the correlation of the absolute configuration of different classes of molecules including amines and amino...
acids to the sign of the Cotton effects in the CD spectra of their $N$-salicylidene derivatives. The sign of the Cotton effect reflects the directionality of the interaction between the dominant molecular dipoles (right-handed twist for a positive CD), which are deduced by conformational analysis. $N$-Salicylidene derivatives formed with $\alpha$-amino acids undergo intramolecular hydrogen bonding in hexanes and show CD maxima near 315, 255 and 215 nm. In polar solvents, a broad band around 400 nm is attributed to a quinoid tautomer, with a positive Cotton effect indicating the presence of an (S)-enantiomer. An induced circular dichroism (ICD) assay for amino esters was reported using chiral zinc porphyrins; (S)-amino esters consistently induced a bisignate CD signal in the Soret band with a negative Cotton effect at longer wavelengths around 430 nm. Canary et al. have demonstrated that a one-step derivatization procedure with 2-bromomethylquinoline and subsequent coordination to copper(II) generates ICD signals around 240 nm that allow the assignment of the absolute configuration of several amino acids. The central chirality of the tetradentate amino acid derivative controls the direction of the twist between the two quinoline moieties and thus the induced ellipticity resulting from exciton-coupled circular dichroism (Scheme IV.5). The same group demonstrated that isolation and purification of these complexes can be used for the determination of the enantiopurity of the original amino acid mixture.

Scheme IV.5. Derivatization of free amino acids with 2-bromomethylquinoline followed by the formation of a Cu(II) complex.
Coordination of amino acids to a Cu(II) complex tethered to a β-cyclodextrin or to chiral porphyrins has also been reported to result in induced circular dichroism.\textsuperscript{48} Lanthanide complexes have successfully been used to distinguish between antipodes of amino acids by both NMR and CD spectroscopy.\textsuperscript{49} Enantioselective amino acid sensing by differential pulse voltammetry has also been realized.\textsuperscript{50} For instance, a chiral polyaniline film was deposited on a platinum electrode via electropolymerization of aniline in aqueous (1\textit{R})- or (1\textit{S})-10-camphorsulfonic acid, and was used to differentiate between the enantiomers of phenylalanine.\textsuperscript{51} Moreover, nanotubes fitted with a tailored peptide have been found to selectively respond to the adsorption of enantiomers of alanine and phenylalanine, resulting in different resonance frequencies.\textsuperscript{52} Immobilization of antibodies on a microcantilever surface generates a probe that undergoes an electromechanical response as a function of the concentration and %ee of solid-phase bound amino acids.\textsuperscript{53} Enzymatic assays with liver alcohol dehydrogenase have been shown to distinguish between the enantiomers of methionine through stereoselective fluorescence quenching of the former, albeit with a limited selectivity ratio \textit{I}_{\text{S}}/I_{\text{R}} of 1.1.\textsuperscript{54}

\textbf{IV.2. Results and Discussion}

Recognizing the importance and shortcomings of stereochemical analysis of unprotected amino acids, we decided to develop a metal-free sensing method for the determination of the absolute configuration and %ee. Generally, amino acid sensing assays are based on the competitive formation of diastereomeric adducts with different thermodynamic stabilities, or distinct UV, fluorescence or CD signals. However, the induction of axial and helical chirality in stereodynamic biphenyls and 2,2’-
dihydroxybenzophenone, respectively, upon covalent attachment of amino acids, provides alternative entries to stereoselective analysis (Scheme IV.6.).

\[ \text{Scheme IV.6. Induction of helical chirality in 2,2'}^\text{'}\text{-dihydroxybenzophenone using tetramethylammonium salts of amino acid enantiomers.} \]

Based on these reports and our finding that 1,8-bis(3'-formyl-4'-hydroxyphenyl)naphthalene 8 shows remarkable chiral amplification upon condensation with amino alcohols (see Chapter III), we envisioned that diimine formation between this stereodynamic sensor and two equivalents of an amino acid would generate a rigid, axially chiral scaffold exhibiting a strong CD signal.

\[ \text{Figure IV.6. Structure of the stereodynamic probe 8.} \]

Through extensive screening of various reaction conditions, it was found that free amino acids treated with tetrabutylammonium hydroxide (TBAOH) quantitatively react
with 8 in DMSO towards the corresponding diimines. This condensation can be monitored by mass spectrometry (Chapter IV.4.3.) and by the disappearance of the formyl peaks of 8 in the NMR spectra. Unprotected amino acids 4-11 were selected for this study to cover a wide range of steric bulk and to determine the effects of additional functionalities such as alcohol groups (Figure IV.7).

![Figure IV.7. Structures of the amino acids used in this study.](image)

As expected, enantiomeric substrates yielded products with opposite Cotton effects (Figure IV.9 and Chapter IV.4.2). Based on the rapid enantioconversion of the sensor at room temperature and in analogy to our observations with chiral amino alcohol substrates, it is assumed that the conformational isomerism of the diimines derived from CD-silent 8 is controlled by the central chirality of the amino acid. Accordingly, diimine formation perturbs the equilibrium of the stereoisomers of 8 and favors the population of a single rotamer, stabilized by intramolecular hydrogen bonding. Upon diimine formation, each carboxylate group is expected to participate in hydrogen bonding with the neighboring salicylidenimine unit to lock the resulting diimine into a conformation that minimizes steric repulsion between the two substrate moieties (Figure IV.8). The strong Cotton effects observed with the diimines obtained with 8 are therefore attributed to the cofacial arrangement of the two salicylidenimine units, indicating the formation of
a more rigid structure whose axial chirality is dictated by the central chirality of the antipode used. This in turn controls the sign of the torsion angle between the aromatic rings on the peri-positions of the naphthalene, which is believed to determine the sign of the induced Cotton effect (right-handed twist for a positive ICD peak). Importantly, employing free salicylaldehyde under the same experimental conditions gave imines that proved CD-silent in the 335-540 nm region. Similarly, diimines obtained from 8 and amino esters displayed a silent CD spectrum. Acidification of the solutions containing the diimines derived from 9-13 gave blue shifted CD signals with significantly higher amplitudes (Figure IV.9). Protonation of the imine and the carboxylate groups should facilitate hydrogen bonding between the phenol and the carboxylic acid groups in the opposite salicylideniminium ring, resulting in a rigid structure with increased π-stacking (Figure IV.8). Based on the basicity of salicylidenimines, we expect that the imine groups are more easily protonated than free carboxylic acid groups.56

Figure IV.8. Proposed hydrogen bonding motif in 8-derived diimines obtained in the presence of TBAOH (left) and under acidic conditions (right).
Figure IV.9. UV (top) and CD (bottom) spectra of diimine products obtained with (R)-valine in the presence of TBAOH and upon acidification with HCl in ether (solid and dashed blue lines, respectively) and with (S)-valine (solid and dashed red lines). All spectra were recorded using samples having a concentration of $2.50 \times 10^{-4}$ M in CHCl$_3$. 
The blue-shift in the UV and CD spectra of the valine-derived diimine and the enhanced amplitudes may thus be attributed to a redirection of the hydrogen bonding motif between the proximate functionalities and an increase in the polarization of the salicylidenimininium moieties. Acidification of a solution containing a diimine derived from 8 and two equivalents of 2-amino-1-propanol was found to cause a similar blue shift but gave a decreased CD amplitude. The presence of both the carboxylate and the free carboxylic acid functions generated under acidic conditions plays a crucial role in determining the stereochemical arrangement and the chiroptical properties of the amino acid derived diimine scaffold. The significance of hydrogen bonding for the generation of a rigid structure and intense Cotton effects is in agreement with solvent effects. The CD amplitudes of the diimines formed from 8 were strongly diminished when chloroform was replaced with ethanol as solvent. All attempts to obtain a crystal structure of the amino acid derived diimines investigated have been unsuccessful.

In analogy to valine, the 8-derived diimines obtained from alanine, leucine, methionine and phenylalanine display strong CD signals at high wavelengths (Figure IV.10). In all cases, the diimines produced from enantiomeric amino acids gave opposite CD signals with 8, with maxima located at similar wavelengths.
Figure IV.10. CD Spectra of the diimines obtained from 8 and (R)-alanine (9), (R)-leucine (10), (R)-valine (11), (R)-methionine (12), and (R)-phenylalanine (13) at $2.5 \times 10^{-4}$ M in CHCl$_3$.

The diimines derived from amino acids 9-13 show a consistent relationship between the absolute configuration of the substrate and the sign of the Cotton effect; all (R,R)-diimines give positive Cotton effects around 462 nm (Figure IV.10). The induced axial chirality of the diimine product and the corresponding CD signal can thus be correlated to the central chirality of the amino acid used. In terms of side chain sensitivity, an increase in the ellipticity around 462 nm with an increase in bulk of the side chain is noted (analytes 4, 5 and 6). In contrast, a negative Cotton effect was obtained with the (R)-enantiomers of tyrosine and serine (Figures IV.11 and IV.12). These remarkably distinct CD spectra could be attributed to different dipole moments and conformations of the respective diimines in solution.
Figure IV.11. CD Spectra of the diimines obtained from 8 and (R)-alanine (9), (R)-serine (15) (both 2.5x10^{-4} M) and (R)-2-amino-1-propanol (17) (5.0 x 10^{-4} M) in CHCl₃.

Figure IV.12. CD Spectra of the diimines obtained from 8 and (R)-phenylalanine (13) and (R)-tyrosine (16) collected at 2.5x10^{-4} M in CHCl₃.
Importantly, enantioselective sensing of proline and alanine often suffers from low selectivity and poor accuracy. Leung et al. reported that the analysis of the %ee of several scalemic alanine samples with a UV-based indicator displacement assay has a 22.6% average error.\(^{57}\) Yin et al. found that optically active polyaniline films used in enantioselective potentiometric sensing did not distinguish between the enantiomers of alanine. This was attributed to the size and configuration of the film cavity with respect to the substrate.\(^ {58}\) We were pleased to find that acidified diimines obtained from 8 and alanine displayed remarkable Cotton effects with this challenging analyte, with the potential for devising a quantitative assay for %ee determination (Figure IV.13). On the other hand, CD spectra for proline-derived diimines of 8 were silent under neutral conditions, but a relatively small signal emerges upon acidification and might be suitable for analysis of its absolute configuration (Figure IV.13).

![Figure IV.13. CD Spectra of the diimines obtained from 8 and (R)- and (S)-alanine (green and orange, respectively) and (R)- and (S)-proline (blue and red, respectively) after acidification, collected at 2.5x10^-4 M in chloroform.](image-url)
The appearance of strong Cotton effects at high wavelengths is quite promising for both qualitative and quantitative CD analysis of unprotected amino acids. While the sign of the ICD band allows the fast determination of the absolute configuration of a guest species, the amplitude should allow for the determination of the %ee. To evaluate the practical use of sensor 8, a calibration curve was obtained with leucine in varying %ee (+100.0, +69.1, +37.9, +0.4, -80.65, and -100.0), by plotting the CD amplitudes at 460 nm (mdeg) vs. the corresponding %ee (Figure IV.14).

Figure IV.14. CD Spectra obtained from 8 and leucine in varying %ee (top). Calibration curve between CD at 460 nm (mdeg) and the %ee of leucine mixtures (bottom).
Four scalemic samples exhibiting 79.1, 53.7, -67.2 and -88.7% ee were then examined. Formation of the sensor-derived diimines and subsequent CD analysis gave 78.0, 50.1, -63.0 and -92.0% ee, respectively. These results are in good agreement with the actual values and thus show that sensor 8 can be used for the assignment of the absolute configuration of unprotected amino acids and for the accurate determination of the enantiopurity of small sample amounts.

IV.3. Conclusions

A metal-free chiroptical sensing method using readily available and recyclable 8 for the determination of the absolute configuration and enantiomeric composition of several unprotected aliphatic and aromatic amino acids has been introduced. The ICD analysis is based on the condensation of a stereodynamic probe exhibiting two salicylaldehyde rings with free amino acids, to afford a diimine scaffold that undergoes substrate-controlled amplification of chirality. The cofacial arrangement of the two salicylaldehyde rings in the sensor favors intramolecular π-π interactions and subsequent exciton coupling. The intense Cotton effects of these amino acid-derived diimines occur at relatively high wavelengths, eliminating possible interference with CD active analytes and impurities. In contrast to most previously reported enantioselective sensing assays for amino acids, this approach does not require the use of an enantiopure ligand or metal complex and is suitable for challenging substrates such as alanine. This facile and reproducible ICD assay avoids the need for protection and purification, and has been successfully applied in quantifying the %ee of leucine samples.
IV.4. Experimental Section

IV.4.1. Diimine Formation and CD Analysis

All reagents and solvents were used without further purification. Reactions were carried out under nitrogen atmosphere and under anhydrous conditions. Sensor 8 was prepared as described in Chapter II.4. The following conditions have been optimized in terms of reaction time, solvent, concentration and number of equivalents. To a solution of the selected amino acid in 400 µL of anhydrous DMSO, a stoichiometric amount of tetrabutylammonium hydroxide (1.0 M in MeOH) was added and allowed to stir for 1 minute. To a mixture of 8 (4.0 mg, 0.01 mmol) in DMSO, 2 equivalents of the prepared amino acid solution were added and the mixture was allowed to stir for 2 hours at 70 °C. All reactions were conducted at 0.02 M and then diluted with chloroform to $2.50 \times 10^{-4}$ M to collect the CD spectra in triplicate.

Prior to each use, the CD instrument was purged with nitrogen for 20 minutes and the temperature was set to 25.0 °C. Spectra were collected between 335 and 545 nm with a standard sensitivity of 100 mdeg, a data pitch of 0.5 nm, a band width 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 adjusted by baseline correction and binomial smoothing. To collect CDs under acidic conditions, a stoichiometric amount of HCl (2M in ether, accounting for the two equivalents of TBAOH and the two carboxylate groups in the diimine formed) was added and allowed to stir for 2 minutes. Samples were then diluted to $2.50 \times 10^{-4}$ M with chloroform. Control experiments with salicylaldehyde were conducted to compare the CD signal of salicyldienmine with that of the sensor-derived diimine. At a concentration of 0.4 M, 2 equivalents of enantiopure valine were added.
under the same conditions as described above for sensor 8. The reaction was complete after 2 hours, and the CD spectrum was collected at 5.0 x 10⁻⁴ M. No CD signal was detected in the region of interest for both salicylidenimine enantiomers in chloroform or ethanol, even at 10 times the concentration of the diimines obtained with 8. Electrospray mass spectrometry (1mg/mL in methanol, negative detection mode) of several dimines proved the formation of the desired condensation product (Chapter IV.4.3).
IV.4.2. CD data

CD Spectra of the 8-derived diimines obtained from (R)-9 (blue) and (S)-9 (red), under neutral (solid lines) and acidic (dashed lines) conditions, at \(2.50 \times 10^{-4}\) M in chloroform.

CD Spectra of the 8-derived diimines obtained from (R)-10 (blue) and (S)-10 (red), under neutral (solid lines) and acidic (dashed lines) conditions, at \(2.50 \times 10^{-4}\) M in chloroform.
CD Spectra of the 8-derived diimines obtained from (R)-11 (blue) and (S)-11 (red), under neutral (solid lines) and acidic (dashed lines) conditions, at 2.50 x 10^{-4} M in chloroform.

CD Spectra of the 8-derived diimines obtained from (R)-12 (blue) and (S)-12 (red), under neutral (solid lines) and acidic (dashed lines) conditions, at 2.50 x 10^{-4} M in chloroform.
CD Spectra of the 8-derived diimines obtained from (R)-13 (blue) and (S)-13 (red), under neutral (solid lines) and acidic (dashed lines) conditions, at 2.50 x 10^{-4} M in chloroform.

CD Spectra of the 8-derived diimines obtained from (R)-14 (blue) and (S)-14 (red), under neutral (solid lines) and acidic (dashed lines) conditions, at 2.50 x 10^{-4} M in chloroform.
CD Spectra of the 8-derived diimines obtained from (R)-15 (blue) and (S)-15 (red), under neutral (solid lines) and acidic (dashed lines) conditions, at 2.50 x 10^{-4} M in chloroform

CD Spectra of the 8-derived diimines obtained from (R)-16 (blue) and (S)-16 (red), under neutral (solid lines) and acidic (dashed lines) conditions, at 2.50 x 10^{-4} M in chloroform
IV.4.3. MS Analysis of the Diimines

Mass spectrum of the diimine obtained from 8 and valine.

![Mass spectrum of diimine with valine](image)

ESI-MS: m/z = 565.3 (M+1)

Mass spectrum of the diimine obtained from 8 and phenylalanine.

![Mass spectrum of diimine with phenylalanine](image)

ESI-MS: m/z = 661.3 (M+1)
Mass spectrum of the diimine obtained from 8 and leucine.

ESI-MS: m/z = 593.3 (M+1)^+

Mass spectrum of the diimine obtained from 8 and methionine.

ESI-MS: m/z = 629.3 (M+1)^+
IV.5. References


V. The Dynamic Stereochemistry of Atropisomeric 1,8-Bisphenolnaphthalenes

V.1. Introduction

The intriguing structure and dynamic stereochemistry of axially chiral compounds has fueled their use in asymmetric synthesis, chiral recognition, the design of microscopic devices such as molecular motors and switches, drug discovery and other areas.\(^1\) Undoubtedly, the exceptional diversity and unique stereochemical, electronic, and photochemical properties of both conformationally stable and rapidly racemizing axially chiral biaryls and polyaryls have led to a wide variety of applications.\(^2\) It is therefore not surprising that structural analysis along with the study of enantiomerization and diastereomerization processes of mono- and disubstituted naphthalenes have received significant attention.\(^3\) Alkyl,\(^4\) aryl\(^5\) and heteroaryl\(^6\) groups have been introduced into the naphthalene framework to study the energy barrier to rotation about the naphthyl-alkyl or naphthyl-aryl bond and intramolecular interactions between proximate alkyl and aryl groups.

In continuation of previously conducted studies with stereodynamic chiral biaryls and triaryls,\(^7\) and 1,8-diheteroarylnaphthalene-derived sensors,\(^8\) 1,8-bis(3’-formyl-4’-hydroxyphenyl)naphthalene 1, was synthesized as described in Chapter II (Scheme V.1).

\[
\text{Scheme V.1. Synthesis of 1,8-bis(3’-formyl-4’-hydroxyphenyl)naphthalene 1.}
\]
Triaryl 1 undergoes fast rotation about the two aryl-aryl bonds at room temperature, resulting in the interconversion of the enantiomeric anti-isomers via the thermodynamically less stable meso syn-intermediate. We realized that imine formation with amino alcohols disturbs this equilibrium and strongly favors population of a single diastereomer that is stabilized by intramolecular hydrogen bonding (Scheme V.2). The diimine formed displays strong Cotton effects at high wavelengths and NMR and crystallographic analysis showed that the central chirality of the amino alcohol substrate induces a rigid, axially chiral triaryl scaffold with literally perfect stereocontrol: Condensation of 1 and (R)-amino alcohols results in well-defined amplification of chirality and the triaryl was found to adopt an (M,M)-conformation. The opposite sense of chiral induction was observed with (S)-amino alcohols. We were able to demonstrate that the fast diimine formation, followed by in situ CD measurements allows time-efficient determination of the absolute configuration and the enantiomeric purity of amino alcohols (Chapter III). Further experiments conducted with amino acids allowed for the expansion of the sensing scope of 1 (Chapter IV).9

Scheme V.2. Central-to-axial chirality induction upon diimine formation with stereodynamic triaryl 1.
A less fluxional analogue of 1 was envisioned to provide further insights into (a) the chiral amplification process, (b) the effect of the intramolecular hydrogen bonding on the conformational stability of the diimine derivatives and (c) the potential use of these compounds in enantioselective recognition and catalysis. Since Clough and Roberts estimated the energy barrier to syn/anti-diastereomerization of 1,8-bis(2-methylphenyl)naphthalene, 4, as approximately 100 kJ/mol,\textsuperscript{10} we expected that incorporation of methyl groups into the ortho-positions of 1 would produce conformational isomers that are stable to interconversion and separable at room temperature (Scheme V.3). We therefore decided to prepare 1,8-bis(2′-methyl-4′-hydroxy-5′-formylphenyl)naphthalene, 5, exhibiting moderate bulk adjacent to the chiral axes which should suffice to isolate and characterize the stereoisomers of this atropisomer and its diimine derivatives, while racemization and diastereomerization reactions could be studied at elevated temperatures.

Scheme V.3. Structures of 4 exhibiting anti-parallel (anti-isomer) and parallel (syn-isomer) 2-methylphenyl moieties and of 5.
V.2. Results and Discussion

V.2.1. Preparation of Racemic and Enantiopure 5

The synthesis of 5 began with the Suzuki coupling of 1,8-diiodonaphthalene and commercially available 4-methoxy-2-methylphenylboronic acid, 6 (Scheme V.4). Initially, we screened the effect of various catalysts, solvents, base and temperature to identify suitable reaction conditions for the construction of the sterically congested scaffold of 5. We were pleased to find that 1,8-bis(2’-methyl-4’-methoxyphenyl)naphthalene, 7, can be obtained in literally quantitative amounts using Pd(PPh$_3$)$_4$ as catalyst and K$_3$PO$_4$ as base in toluene. NMR analysis revealed that 7 was a 1:3 mixture of the syn- and anti-isomers. The Vilsmeier reaction of 7 with excess of phosphorous oxychloride and dimethyl formamide furnished 1,8-bis(2’-methyl-4’-methoxy-5’-formylphenyl)naphthalene, 8, with 99% yield in approximately the same diastereomeric ratio as 7. The diastereomers of 8 could be isolated using flash chromatography (V.4.1). Attempts to brominate the benzylic positions of 8 proved unsuccessful, even after protecting the aldehyde groups. Finally, deprotection of the syn/anti-mixture of 8 with boron tribromide gave 5, with a syn/anti-isomer ratio of 1:4 in 77% yield (Figure V.1).

Scheme V.4. Synthesis of 1,8-bis(2’-methyl-4’-hydroxy-5’-formylphenyl)naphthalene 5.
Figure V.1. $^1$H NMR spectrum of the syn/anti-mixture of racemic 5 in CDCl$_3$. $s =$ syn-5, $a$ = anti-5.

Racemic 5 was converted to ($P,P,R,R$)-9 and ($M,M,R,R$)-9 by condensation with 2 equivalents of ($R$)-2-amino-1-propanol. The diimine formation proceeds with quantitative yields and is completed at room temperature within one hour. Chromatographic purification on silica gel allows for the isolation of the two diastereomeric products (Scheme V.5 and V.4.1). Heating of the diastereomeric mixture of 9 to establish thermodynamic equilibrium reveals that the first eluted diimine corresponds to the more stable diastereomer (V.2.2). Based on the sense of chiral amplification observed with the diimines of 1 and CD and crystallographic analysis of 5 and 9, it can be assumed that ($P,P,R,R$)-9 is the thermodynamically favored atropisomer. Pure ($P,P,R,R$)-9 (43.2 mg, 0.08 mmol) was dissolved in 5 mL of 1 M NaOH, and 1 mL of aqueous HCl (12.1 M) was added dropwise at 0 °C. The mixture was allowed to stir for 10 minutes. The
resulting suspension was extracted with CH$_2$Cl$_2$ and 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 enantiopure (P,P)-5 (28.5 mg, 0.07 mmol) in 85% yield, with no sign of the syn-diastereomer based on NMR analysis. The enantiopurity of 5 was confirmed by derivatization to the corresponding diimine using (R)-2-amino-1-propanol. The NMR spectrum of the condensation product showed the presence of a single diastereomer.

Scheme V.5. Isolation of enantiopure 5.

Slow evaporation of a solution of enantiopure (P,P)-5 in chloroform gave single crystals suitable for X-ray studies (Figure V.2). As expected, crystallographic analysis shows that the two salicylaldehyde rings reside in almost perfectly perpendicular orientation relative to the naphthalene backbone, exhibiting a C$_2$-symmetric structure with a torsion angle of 5.32°. The splaying between the two phenyl rings was determined as 20.51° which results in a centroidal phenyl-to-phenyl separation of 3.47 Å. Based on the enforced π-stacking of the proximate salicylaldehyde rings, the positive Cotton effect and the large CD amplitudes of (P,P)-5 can be attributed to strong exciton coupling of the cofacial chromophores (Figure V.4).
V.2.2. Deracemization of 5 via Diastereomerization of 9

Based on our experience with stereolabile 1, which spontaneously adopts a single conformation upon diimine formation with enantiopure amino alcohols and the kinetic analysis of 4 by Clough and Roberts, we investigated the possibility of converting the atropisomeric mixture of 9 into a single stereoisomer upon heating. Such an asymmetric transformation of the first kind would generate the thermodynamically favored diimine isomer and thus facilitate the formation of enantiopure 5 with a theoretical yield of 100%, without the need for elaborate chromatographic separation of the equimolar of \((M,M,R,R)\)- and \((P,P,R,R)\)-9 mixture. Several cases in which an asymmetric transformation of the first kind was used to manipulate the diastereomeric ratio of axially chiral compounds have been reported. For example, Meyers et al. found that the stereochemical outcome of the diastereoselective oxazoline-mediated asymmetric Ullmann coupling of aryl bromides is significantly improved upon heating of the product mixture.\(^{11}\) This transformation favors the formation of the desired \((P)\)-atropisomer, a key intermediate for the total synthesis of permethylated tellimagrandin.\(^{12}\) The same principle
has been used for the deracemization of ortho-dihydroxylated biaryl ligands VANOL and VAPOL, and for the preparation of the aglycon of vancomycin.

We realized that (M,M,R,R)- and (P,P,R,R)-9, formed from racemic 5 and (R)-2-amino-1-propanol at 25°C, showed distinct NMR spectra, for example two doublets at 1.26 and 1.40 ppm corresponding to the imino alcohol methyl groups (Figure V.3). We therefore used NMR analysis to monitor the atropisomerization process. Upon heating to 60.0 °C, the signals of the thermodynamically less favored diastereomer decreased in intensity and diastereomerically enriched (P,P,R,R)-9 was obtained after 14 hours (>98 % de).

Figure V.3. 1H NMR Spectra of diimine diastereomers obtained from racemic 5 and (R)-2-amino-1-propanol and quantitative conversion towards (P,P,R,R)-9. (A) 60 °C, 0 h, (B) 60 °C, 14 h. * corresponds to (M,M,R,R)-9, ‡ corresponds to (P,P,R,R)-9.
Racemic 5 (10.14 mg, 0.026 mmol) was dissolved in 1.0 mL of CDCl$_3$. Molecular sieves (4 Å, beads, 8-12 mesh) were added and the mixture was stirred with 2 equivalents of (R)-2-amino-1-propanol (3.84 mg, 0.051 mmol) for one hour at 25°C. After the diimine formation was complete, $^1$H NMR analysis indicated the presence of two diastereomers - evidenced for example by the two doublets at 1.26 and 1.40 ppm. (Figure V.3). Upon heating to 58.0 °C, the signals of the thermodynamically less favored diastereomer decreased in intensity. In agreement with the chiral amplification observed upon diimine formation of 1,8-bis(3'-formyl-4'-hydroxyphenyl)naphthalene with (R)-2-amino-1-propanol, it is assumed that the central chirality of amino alcohol controls the stereoselective outcome of this atropisomerization process. The mixture is almost entirely converted to the more stable diastereomer after 19 h and then hydrolyzed to (P,P)-5 as described above. We previously reported that condensation of stereolabile 1 and (R)-2-amino-1-propanol exclusively generates the (M,M,R,R)-stereoisomer which is the thermodynamically favored conformer due to stabilization by intramolecular hydrogen bonding and concomitant minimization of steric repulsion. Accordingly, diimine formation with (S)-2-amino-1-propanol gave the (P,P,S,S)-enantiomer, Scheme V.2. These results are in perfect agreement with the asymmetric transformation of a mixture of (M,M,R,R)- and (P,P,R,R)-9 towards the latter diastereomer. In analogy to the chiral amplification process observed with 1, the central chirality of the imino alcohol moiety in 9 controls the sense of achiral amplification and induces the same sense of axial chirality. Since the atropisomerization occurs with more than 99% de, it provides quantitative access to stereochemically pure 9 on the gram scale, which can then be hydrolyzed.

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1 The (M,M)-scaffold in 1 corresponds to the (P,P)-conformation in 5 and 9 because the presence of the ortho-methyl groups in the latter results in a change in the CIP priorities.
without concomitant isomerization to enantiopure 5. Having developed a convenient procedure producing \((P,P)\)-5, we were able to prepare \((P,P,R,R)\)-9 and \((P,P,S,S)\)-9, the thermodynamically less stable diastereomer, via condensation with either enantiomer of 2-amino-1-propanol. Analyzing the CD spectra of the enantiomeric \((M,M,R,R)\)-and \((P,P,S,S)\)-diimines of 1, we previously speculated that the Cotton effects are predominantly controlled by the sense of axial chirality while the chiral centers in the imino alcohol units were expected to have little or no effect on the chiroptical properties. Comparison of the CD spectra of \((P,P)\)-5, \((P,P,R,R)\)-9 and \((P,P,S,S)\)-9, all exhibiting the same sense of axial chirality, now clearly shows that this assumption was correct (Figure 4). The three atropisomers exhibit a pronounced positive Cotton effect, and the incorporation of the diimino alcohol units results in a significant red shift. Importantly, the diastereomeric \((P,P)\)-diimines of 9 show almost perfectly superimposable CD spectra, which underscores the overwhelming or possibly exclusive contribution of the relative orientation of the two cofacial salicylidenimine rings to the observed CD activity. It is noteworthy that the CD amplitudes of the less stable \((P,P,S,S)\)-9 diastereomer are slightly diminished compared to \((P,P,R,R)\)-9. This is probably due to noticeable atropisomerization of \((P,P,S,S)\)-9 to its \((M,M,S,S)\)-diastereomer, \textit{i.e.} it is likely that the CD spectra obtained with \((P,P,S,S)\)-9 and \((P,P,R,R)\)-9 only differ because the former was not perfectly diastereomerically pure.
Figure V.4. CD Spectra of \((P,P)-5\) (blue), \((P,P,R,R)-9\) (red) and \((P,P,S,S)-9\) (green) at 5.0 x 10^{-5} M in CHCl₃.

V.2.3. CD Analysis and Isomerization Kinetics of 5

Interconversion of the stereoisomers of 5 requires one salicylaldehyde ring to rotate about the chiral naphthyl-phenyl axis (Scheme V.6). Accordingly, the edge of the rotating ring points towards the adjacent phenyl moiety in the transition state. In general, this process can proceed via two T-shaped transition states having the methyl group of the rotating phenyl ring either directed towards or away from the other phenyl ring. The latter orientation is expected to afford significantly less steric hindrance and is therefore the favored interconversion pathway.

Scheme V.6. Interconversion of the stereoisomers of 5.
A solution of \((P,P)-5\) (1.11 mg, 2.78 \(\mu\)mol) in 4.0 mL of anhydrous chloroform was stirred at 45.0 °C and small aliquots were taken at one hour intervals and diluted to 5.0 \(\times\) \(10^{-5}\) M for CD analysis. After 10 hours, the CD signals disappeared indicating complete racemization (Figure V.5). The \(\text{syn/anti}\)-ratio of 5 at 45.0 °C in chloroform at equilibrium was determined by \(^1\text{H}-\text{NMR}\) spectroscopy as 23.4:76.6. The observed ratio corresponds to a difference in Gibbs free energy of the \(\text{anti}\) and \(\text{syn}\)-isomers, \(\Delta G\), of 1.3 kJ/mol according to the Boltzmann equation (1).\(^\text{ii}\)

\[
2 \frac{N_{\text{syn}}}{N_{\text{anti}}} = \exp(-\Delta G^0/RT) \quad (1)
\]

---

\(^\text{ii}\) The factor 2 in equation (1) accounts for the two enantiomeric \(\text{anti}\)-isomers of 5.

Figure V.5. Decrease of the CD signal of \((P,P)-5\) as a result of racemization in chloroform (\(6.95 \times 10^{-4}\) M) at 45.0 °C. The CD spectra were collected at 25 °C at a concentration of 5.0 \(\times\) \(10^{-5}\) M in chloroform.
Figure V.6. Plot of the mole fraction of \((P,P)\)-5 versus time at 278.5 nm. For conditions, see Figure V.5.

Figure V.6 shows the decrease of the mole fraction of \((P,P)\)-5 as a function of time at 278.5 nm. The mathematical solution for the kinetics of consecutive, first-order, reversible reactions involving 3 species such as the \(syn/anti\)-interconversion of 5 has been reported by Vriens.\(^\text{15}\) Curve fit analysis using equation 2 allowed determination of the rate constant for the \(anti\) to \(syn\)-isomerization, \(k_1\).

\[
x = C_1e^{D_1kt} + C_2e^{D_2kt} + \frac{\alpha}{K_1K_2E_2}
\]

\(k_1\) = rate constant of the \(anti\) to \(syn\)-interconversion, \(K_1\) = equilibrium constant for the formation of the \(syn\)-isomer, \(K_2\) = equilibrium constant for the formation of either \(anti\)-isomer, \(\alpha\) = ratio of forward rate constants (\(k_2/k_1\)) for the consecutive, reversible, first-order reactions, \(k_2\) = rate constant for \(syn\) to \(anti\)-interconversion, \(C_1, C_2, D_1, D_2, E_2\) are constants. Curve fitting to \(y = A1*exp(-x/t1) + A2*exp(-x/t2) + y0\) was performed using
OriginPro 8.1, with $A_1 = 0.299$, $A_2 = 0.351$, $t_1 = 61.60$, $t_2 = 264.22$, $y_0 = 0.350$, $R^2=0.9993$.

The syn/anti-ratio of 5 (CDCl$_3$, 45.0 °C, 5.0 mg/mL) at equilibrium was determined as 0.27 by $^1$H-NMR. The mixture consists of 76.6% of racemic anti-5 and 23.4% of syn-5.

$K_1 = 0.610$ and $K_2 = 1/K_1 = \alpha = 1.64$.

$$E_1 = 1 + \frac{1}{K_1} + \alpha + \frac{\alpha}{K_2}$$

$$D_1 = \frac{-E_1 + \sqrt{E_1^2 - 4E_2}}{2}$$

$$C_1 = \frac{-1 - D_2 + \frac{\alpha}{K_1 K_2 D_1}}{D_1 - D_2}$$

$$E_2 = a \left(1 + \frac{1}{K_1 K_2} + \frac{1}{K_2}\right) = D_1 D_2$$

$$D_2 = \frac{-E_1 - \sqrt{E_1^2 - 4E_2}}{2}$$

$$C_2 = \frac{1 + D_1 - \frac{\alpha}{K_1 K_2 D_2}}{D_1 - D_2}$$

Using the above equations, the rate constants for the reversible interconversion steps, $k_1$ and $k_2$, can now be calculated.

$E_1 = 5.27$, $E_2 = 4.27$

$D_1 = -1.00$, $D_2 = -4.27$

$C_1 = 0.50$, $C_2 = 0.12$

Since $D_2 k_1 = -1/t_1 = -0.01623$, $k_1 = 6.33 \times 10^{-5}$ s$^{-1}$

Using the Eyring equation, the Gibbs activation energy, $\Delta G^\ddagger$, for the atropisomerization of 5 was calculated as 103.7 (102.4) kJ/mol for the conversion of the anti-(syn-) to the syn-(anti-) isomer.

$K^\ddagger_{\text{anti$\rightarrow$syn}} = k_1 h/k_b T = 9.550 \times 10^{18}$, $\Delta G^\ddagger_{\text{anti$\rightarrow$syn}} = -RT \ln K^\ddagger_{\text{anti$\rightarrow$syn}} = 103.7$ kJ.mol$^{-1}$.

Also, $D_1 k_1 = -1/t_2 = -0.003785$, $k_1 = 6.31 \times 10^{-5}$ s$^{-1}$

$K^\ddagger_{\text{anti$\rightarrow$syn}} = k_1 h/k_b T = 9.515 \times 10^{18}$, $\Delta G^\ddagger_{\text{anti$\rightarrow$syn}} = -RT \ln K^\ddagger_{\text{anti$\rightarrow$syn}} = 103.7$ kJ.mol$^{-1}$.
Since \( k_2 = k_1/K_1 \), \( k_2 = 1.04 \times 10^{-4} \text{ s}^{-1} \)

\[
K^\#_{\text{syn-anti}} = \frac{k_2 h}{b T} = 1.566 \times 10^{-17}, \quad \Delta G^\#_{\text{syn-anti}} = -RT \ln K^\#_{\text{syn-anti}} = 102.4 \text{ kJ.mol}^{-1}.
\]

V.2.4. Isomerization Kinetics of 9

V.2.4.1. Determination of the Initial Rate Constant for the Isomerization of \((P,P,S,S)-9\)

The analysis of the atropisomerization of 9 is more complicated since it involves four different rate constants (Scheme V.7). Because CD analysis does not provide quantitative information about individual diastereomer concentrations, NMR spectroscopy was employed to monitor the conversion of \((P,P,S,S)-9\) to the thermodynamically stable atropisomer \((M,M,S,S)-9\) via the intermediate \((M,P,S,S)\)-isomer.

Scheme V.7. Interconversion of the atropisomers of 9.

Enantiopure \((P,P)-5\) (10.14 mg, 0.026 mmol) was dissolved in 1.0 mL of CDCl₃. Molecular sieves (4 Å, beads, 8-12 mesh) were added and the mixture was stirred with 2 equivalents of \((S)\)-2-amino-1-propanol (3.84 mg, 0.051 mmol) for one hour at 25 °C. The mixture was then heated to 58.0 °C and \(^1\text{H}\)-NMR spectra were collected at short intervals to follow the decay of \((P,P,S,S)-9\) (same signals as \((M,M,R,R)-9\), Figure V.3) before the appearance of any \((M,M,S,S)-9\) (same signals as \((P,P,R,R)-9\), Figure V.3). By plotting the
mol fraction of \((P,P,S,S)\)-9 versus time, the initial rate of the reaction can be obtained from the slope of the fitted line (Figure V.7). Curve fitting to \(y = A1x + B\) was performed using OriginPro 8.1, with \(A1 = -0.00245\) and \(B = 0.8634\), \(A2 = 0.351\), and an \(R^2\) of 0.9929. The initial rate constant denoted \(k_1\) was determined as \(4.08 \times 10^{-5} \text{ s}^{-1}\), \(\Delta G^\varepsilon_{(P,P,S,S)\rightarrow(M,P,S,S)} = 109.2 \text{ kJ/mol}\).

![Figure V.7. Plot of the mol fraction of \((P,P,S,S)\)-9 versus time (min).](image)

**V.2.4.2. Determination of the Rate Constants for the Isomerization of 9**

A solution of \((P,P,S,S)\)-9 was heated to 58.0 °C and the isomerization was studied by integration of the benzylic \(^1\text{H}\) NMR signals of the three diastereomers ((\(P,P,S,S\))-9 (1.69 ppm), (\(M,P,S,S\))-9 (1.81 ppm) and (\(M,M,S,S\))-9 (1.66 ppm)) until equilibrium was reached.

\[
(P,P,S,S)\)-9 \quad k_1 \quad (P,M,S,S)\)-9 \quad \frac{k_3}{k_2} \quad (M,M,S,S)\)-9
\]

\[
(P,P,S,S)\)-9 \quad \frac{k_1}{k_2} \quad (P,M,S,S)\)-9 \quad \frac{k_3}{k_4} \quad (M,M,S,S)\)-9
\]
Equilibrium was reached after 2 days, and the atropisomeric ratio was determined as 94.4:3.9:1.7 \([\{(M,M,S,S):(P,P,S,S):(M,P,S,S)\}](\text{Figure 8})\). Following Vriens’ mathematical treatment for two consecutive reversible reactions and curve fitting, the individual rotational energy barriers were determined.

The constants \(K_1\) and \(K_2\) were then determined according to Vriens as \(K_1 = k_1/k_2 = \left[\frac{(P,M,S,S)-9}{(P,P,S,S)-9}\right] = 0.417\) and \(K_2 = k_3/k_4 = \left[\frac{(M,M,S,S)-9}{(P,M,S,S)-9}\right] = 57.10\).

By plotting the mol fraction of the \textit{syn-9} intermediate as a function of time, we can determine \(y_{\text{max}}\), the maximum mol fraction of \((P,M,S,S)-9\), as 0.1435 (Figure V.8).

We can then find \(\alpha\), since \(y_{\text{max}} = \alpha^{(a/1-\alpha)}\). \(\alpha = 4.546\).

We then proceed to calculate the following constants by using the equations given in IV.2.3.

\(E_1 = 8.02, E_2 = 4.82\)

\(D_1 = -0.654, D_2 = -7.37\)

\(C_1 = 0.905, C_2 = 0.0554\)
Figure V.8. Change in the mol fraction of $(P,P,S,S)^{-}\text{9}$ (red), $(P,M,S,S)^{-}\text{9}$ (black) and $(M,M,S,S)^{-}\text{9}$ (blue) at 58.0 °C in chloroform.

Curve fitting of the change in the mol fraction of $(P,P,S,S)^{-}\text{9}$ to $y = A1*\exp (-x/t1) + A2*\exp(-x/t2) + y0$ was performed using OriginPro 8.1 and afforded $A1 = 0.755$, $A2 = 0.173$, $t1 = 516.21$, $t2 = 25.88$, $y0 = 0.038$, $R^2=0.9994$. Curve fitting of the change in the mol fraction of $(M,M,S,S)^{-}\text{9}$ to $y = A1*\exp (-x/t1) + y0$ afforded $A1 = 0.906$, $t1 = 560.54$, $y0 = 0.949$, $R^2=0.9981$.

Since $D_1k_1 = -1/t1 = -0.00194$, $k_1 = 0.00296$ min$^{-1}$ (similar to initial rate, IV.2.4.1)

$$K^{\#}_{(P,P,S,S)^{-}\text{9} \rightarrow (P,M,S,S)^{-}\text{9}} = k_1h/k_bT = 7.16 \times 10^{18}$$

$$\Delta G^{\#}_{(P,P,S,S)^{-}\text{9} \rightarrow (P,M,S,S)^{-}\text{9}} = -RT\ln K^{\#}_{(P,P,S,S)^{-}\text{9} \rightarrow (P,M,S,S)^{-}\text{9}} = 108.7 \text{kJ.mol}^{-1}.$$

Since $k_2 = k_1/K_1$, $k_2 = 1.19 \times 10^{-4}$ s$^{-1}$, $K^{\#}_{(P,M,S,S)^{-}\text{9} \rightarrow (P,P,S,S)^{-}\text{9}} = k_2h/k_bT = 1.72 \times 10^{-17}$

$$\Delta G^{\#}_{(P,M,S,S)^{-}\text{9} \rightarrow (P,P,S,S)^{-}\text{9}} = -RT\ln K^{\#}_{(P,M,S,S)^{-}\text{9} \rightarrow (P,P,S,S)^{-}\text{9}} = 106.3 \text{kJ.mol}^{-1}.$$

Since $k_3 = \alpha*k_1$, then $k_3 = 2.25 \times 10^{-4}$ s$^{-1}$, $K^{\#}_{(P,M,S,S)^{-}\text{9} \rightarrow (M,M,S,S)^{-}\text{9}} = k_3h/k_bT = 3.26 \times 10^{-17}$
\[ \Delta G^\circ_{(P,M,S,S) \rightarrow (M,M,S,S),9} = -RT \ln K^\circ_{(P,M,S,S) \rightarrow (M,M,S,S),9} = 104.5 \text{ kJ.mol}^{-1}. \]

Since \( k_4 = k_3/K_2 \), then \( k_4 = 3.93 \times 10^{-6} \text{ s}^{-1} \), \( K^\circ_{(M,M,S,S),9 \rightarrow (P,M,S,S),9} = k_4 h/k_b T = 5.70 \times 10^{-19} \)

\[ \Delta G^\circ_{(M,M,S,S) \rightarrow (P,M,S,S),9} = -RT \ln K^\circ_{(M,M,S,S) \rightarrow (P,M,S,S),9} = 115.7 \text{ kJ.mol}^{-1}. \]

Based on the equilibrium of 9 discussed above, the thermodynamically favored \((M,M,S,S)\)-atropisomer is more stable than the syn-intermediate by 11.2 kJ/mol while conversion of the latter to \((P,P,S,S)\)-9 is driven by only 2.4 kJ/mol. Comparison of the relative amounts of the two \textit{anti}-isomers of 9 reveals a difference in Gibbs free energy of 8.8 kJ/mol. Crystallographic analysis of syn-9 and \((P,P,R,R)\)-10 shows that these results can be explained by selective intramolecular hydrogen bonding and concomitant optimization of steric repulsion in \((M,M,S,S)\)-9, \textit{vide infra}. The interconversion of \((P,P,S,S)\)-9 to the syn-diastereomer has a Gibbs activation energy, \( \Delta G^\circ_{(P,P,S,S) \rightarrow (M,M,S,S),9} \), of 108.7 kJ/mol. The intermediate \textit{syn}-isomer undergoes diastereomerization to the two \textit{anti}-conformers and the corresponding activation energies were calculated as 106.3 kJ/mol \( \left( \Delta G^\circ_{(M,P,S,S) \rightarrow (P,P,S,S),9} \right) \) and 104.5 kJ/mol \( \left( \Delta G^\circ_{(M,P,S,S) \rightarrow (M,M,S,S),9} \right) \). As expected from the asymmetric transformation experiments discussed above, the energy barrier for the conversion of \((M,M,S,S)\)-9 to the \textit{syn}-isomer, \( \Delta G^\circ_{(M,M,S,S) \rightarrow (M,M,S,S),9} \), is significantly higher and was determined as 115.7 kJ/mol. Comparison to the kinetic study discussed in Chapter V.2.4.1, which can be approximately treated as an irreversible first-order reaction (less than 2% completion), it shows that the rotational energy barrier, \( \Delta G^\circ_{(P,P,S,S) \rightarrow (M,P,S,S),9} \), of 109.2 kJ/mol is in very good agreement with the value determined here (108.7 kJ/mol).
V.2.4.3. Single Crystal of syn-9

Attempts to grow a single crystal of (P,P,R,R)- or (M,M,S,S)-9 for crystallographic analysis were unsuccessful. But we were able to obtain a crystal structure of the syn-isomer (Figure V.9). This atropisomer has a torsion angle of 18.33° and the splaying between the two phenyl rings is 21.09° corresponding to a centroidal phenyl-to-phenyl separation of 3.52 Å. The steric repulsion between the two salicylidenimine rings explains the low relative stability compared to the (P,P,R,R)- or the (M,M,S,S)-isomer.

![Figure V.9. Different views of the single crystal structure of syn-9.](image)

V.2.5. Asymmetric Transformation of the First Kind with 10

To better understand the overwhelming thermodynamic stability of the (P,P,R,R)- and the (M,M,S,S)-configuration, we decided to prepare the corresponding diimine using (R)-2-amino-3-methyl-1-butanol. The diimine (P,P,R,R)-10 was prepared in quantitative yields from racemic 5 and (R)-2-amino-3-methyl-1-butanol using the same asymmetric transformation protocol as described above for 9. The hydrolysis of (P,P,R,R)-10 to


$(P,P)$-5 was conducted as described above with $(P,P,R,R)$-9 and gave enantiopure $(P,P)$-5 in 80% yield. The CD spectra of $(P,P,R,R)$-10 and $(P,P)$-5 are shown in Figure V.10.

![Figure V.10. CD Spectra of $(P,P)$-5 (blue), $(P,P,R,R)$-10 (red) at 5.0 x $10^{-5}$ M in CHCl$_3$.](image)

The unidirectional atropisomerization of $(P,P,S,S)$-10 to $(M,M,S,S)$-10 was monitored by CD spectroscopy and is in perfect agreement with the results obtained with 9. Enantiopure $(P,P)$-5 (10.14 mg, 0.026 mmol) was dissolved in 1.0 mL of CDCl$_3$. Molecular sieves (4 Å, beads, 8-12 mesh) were added and the mixture was stirred with 2 equivalents of $(S)$-2-amino-3-methyl-1-butanol (5.52 mg, 0.051 mmol) for one hour at 25.0 °C. The mixture was then heated to 50.0 °C. Aliquots were taken at one hour intervals and diluted to 5.0 x $10^{-5}$ M with anhydrous CHCl$_3$ for CD analysis. After 24 hours, the CD signal indicated almost complete diasteriomerization (Figure V.11).
Figure V.11. Change in the CD signal of \((P,P,S,S)-10\) as a result of diastereomerization at 50.0 °C. The CD spectra were collected at 25.0 °C with a concentration of 5.0 x 10^{-5} M in CHCl_3.

Fortunately, a crystal of \((P,P,R,R)-10\) was obtained by crystallization from a hexane solution (Figure V.12). Crystallographic analysis revealed a torsion angle of 18.17° and splaying between the two phenyl rings was calculated as only 13.46° resulting in a centroidal phenyl-to-phenyl separation of 3.33 Å. The significantly reduced splaying compared to \(syn-9\) is quite remarkable and results from reduced steric repulsion between the imino alcohol units and additional hydrogen bonding between the alcohol groups and the phenol units in the opposite salicylidenimine ring. The arrangement of the two salicylidenimines in \((P,P,R,R)-10\) allows formation of a total of four intramolecular hydrogen bonds (the phenol groups also undergo hydrogen bonding with the adjacent imines) while the steric bulk of the imino alcohol moieties is placed outside of this ring.
structure in the least crowded positions. The C=N· · ·HOC\textsubscript{phenyl} and the C\textsubscript{aliph}OH· · ·OC\textsubscript{phenyl} hydrogen bond lengths are 1.861 and 2.178 Å, respectively. In analogy to the results obtained with 9, we observed quantitative asymmetric transformation of the first kind with 10, which can be used to either prepare pure (M,M,S,S)- or (P,P,R,R)-atropisomers of these diimines. The kinetic and thermodynamic analyses of the unidirectional atropisomerization process of 9 and 10 discussed above are in perfect agreement with the crystallographic data showing distinct stabilization of the (P,P,R,R)-isomer due to intramolecular hydrogen bonding and minimized steric repulsion between the imine moieties.

Figure V.12. Different views of the crystal structure of (P,P,R,R)-10 showing the hydrogen bonding motif.

V.2.6. Investigation of More Stable 1,8-Bisphenolnaphthalenes

We screened different boronic acids such as 4-methoxy-2-trifluoromethylphenyl (11) and 4-methoxy-2,6-dimethylphenyl boronic acid (12). Suzuki coupling using 1,8-diiodonaphthalene and 11 gave the desired 1,8-diarylnaphthalene scaffold in 88% yield,
but 13 proved unreactive towards further derivatization (Scheme V.8). We were not able to attach the di-ortho substituted boronic acid 12 to the naphthalene despite the screening of numerous reaction conditions. In a further attempt to enlarge the steric bulk and increase the rotational barrier towards atropisomerization, mono- and dibromination at the benzylic positions in 7 were realized. However, 14 and 15 did not undergo electrophilic aromatic substitutions including the Vilsmeier reaction.


V.2.7. Kinetic Resolution

We also found that (P,P)-5 can be used for the kinetic resolution of the enantiomers of 2-amino-1-propanol. Enantiopure (P,P)-5 (15.89 mg, 0.040 mmol) was dissolved in 1.0 mL of anhydrous CHCl₃. Molecular sieves (4 Å, beads, 8-12 mesh) were added and the mixture was stirred with 4 equivalents of racemic 2-amino-1-propanol (12.04 mg, 0.160 mmol) for 5 hours at 25 °C. The mixture was then extracted with water, and the aqueous layer was freeze-dried to recover the unreacted amino alcohol. The crude material (6.02 mg, 0.080 mmol) was dissolved in 1.5 mL of chloroform and treated with benzoyl chloride (117.8 mg, 0.80 mmol) in the presence of triethylamine (162.2 mg, 1.60 mmol). The mixture was allowed to stir for 16 hours, then 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:EtOAc 9:1) afforded 16 (22.0 mg, 0.074 mmol) as a colorless oil in 93%. Chiral HPLC analysis on Chiralpak AD using hexanes:ethanol (90:10) as mobile phase showed that the (S)-amino alcohol was enriched to 54% ee, by comparison to standards. As expected, formation of \((P,P,R,R)-9\) was favored with 77% of the unreacted amino alcohol having (S)-configuration. Upon moving to shorter reaction times (4 h) and lower temperatures (-20 °C), values of only 6 %ee (S) were found. These results indicate that the resolution goes through an imine formation/hydrolysis process that requires time to reach equilibrium. Other amino alcohol analytes such as racemic cis-1,2-aminooindanol and 2-amino-3-methyl-1-butanol were found to be enriched to only 10.0 %ee after 1 h at 25 °C.

\[
\begin{align*}
\text{HO} & \quad \text{HO} \\
\text{(P,P)-5} & \quad \text{NH}_2 \\
1. \text{NH}_2 & \quad 5 \text{ h, CH}_3\text{C}_2 \quad 25 \text{ °C} \\
2. \text{H}_2\text{O, DCM} & \quad \text{2. PhCOCl} \\
1. \text{Freeze-dry} & \quad \text{TEA, CH}_2\text{Cl}_2 \quad 16 \text{ h} \\
\end{align*}
\]


V.3. Conclusions

The stereodynamics of highly congested atropisomeric 1,8-bisphenolnaphthalenes have been investigated. 1,8-Bis(2’-methyl-4’-hydroxy-5’-formylphenyl)naphthalene was synthesized and resolved into its enantiomers. The Gibbs activation energy for the atropisomerization of 5 was calculated as 103.7 (102.4) kJ/mol for the conversion of the
anti-(syn-) to the syn-(anti-) isomer. The corresponding diimines 9 and 10, undergo asymmetric transformations of the first kind, which eventually allowed for the gram scale synthesis of the enantiomers of 5 after diimine hydrolysis. The atropisomerization kinetics of diimine 9 were studied in detail and involved four different rate constants for the conversion of \((P,P,S,S)\)-9 to the thermodynamically stable atropisomer \((M,M,S,S)\)-9 via the intermediate \((M,P,S,S)\)-isomer. The interconversion of \((P,P,S,S)\)-9 to the syn-diastereomer has a Gibbs activation energy, \(\Delta G_{(P,P,S,S)\rightarrow(M,M,S,S)}^{\neq} 9\), of 108.7 kJ/mol. The intermediate syn-isomer undergoes diastereomerization to the two anti-conformers and the corresponding activation energies were calculated as 106.3 kJ/mol \(\Delta G_{(M,P,S,S)\rightarrow(P,P,S,S)}^{\neq} 9\) and 104.5 kJ/mol \(\Delta G_{(M,P,S,S)\rightarrow(M,M,S,S)}^{\neq} 9\). The energy barrier for the conversion of \((M,M,S,S)\)-9 to the syn-isomer, \(\Delta G_{(M,M,S,S)\rightarrow(M,P,S,S)}^{\neq} 9\), was found to be significantly higher (115.7 kJ/mol), which is in perfect agreement with the stereochemical outcome of the asymmetric transformation of the first kind.

V.4. Experimental Section

V.4.1. Synthetic Procedures

All reagents and solvents were used without further purification. Reactions were carried out under nitrogen atmosphere and under anhydrous conditions. Products were purified by flash chromatography on SiO\(_2\) (particle size 0.032-0.063 mm). NMR spectra were obtained at 400 MHz (\(^1\)H NMR) and 100 MHz (\(^{13}\)C NMR) using CDCl\(_3\) as solvent. Chemical shifts are reported in ppm relative to TMS. For CD analysis, samples were diluted to \(5.0 \times 10^{-5}\) M with anhydrous chloroform and the instrument was purged with nitrogen for 20 minutes. Spectra were collected between 245 and 540 nm at 25.0 °C with
a standard sensitivity of 100 mdeg, a data pitch of 0.5 nm, a band width 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 adjusted by baseline correction and binomial smoothing.

1,8-Bis(2’-methyl-4’-methoxyphenyl)naphthalene (7)
A solution of 1,8-diiodonaphthalene, (1.70 g, 4.5 mmol), 2-methyl-4-
methoxyphenylboronic acid, 2, (2.20 g, 13.4 mmol), Pd(PPh$_3$)$_4$ (0.78 g, 0.67 mmol) and
K$_3$PO$_4$, (4.30 g, 20.1 mmol) in 50 mL toluene was stirred at 100 °C for 18 hours. The
resulting mixture was allowed to come 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 2:3) afforded 1.65 g (4.5 mmol, >99%) of off-white crystals containing
syn- and anti-isomers of 7.
$^1$H NMR: δ = 1.76 (s, 4.6H), 1.83 (s, 1.4H), 3.69 (s, 4.4H), 3.71 (s, 1.4H), 6.28-6.39 (m,
4H), 6.66 (d, $J$ = 8.2 Hz, 0.5H), 6.87 (d, $J$ = 8.2 Hz, 1.5H), 7.16 (d, $J$ = 6.8 Hz, 2H), 7.46
(dd, $J$ = 7.2, 7.8 Hz, 2H), 7.89 (d, $J$ = 8.0, 2H). $^{13}$C NMR: δ = 20.9, 21.0, 55.1, 55.2,
109.9, 110.3, 114.3, 114.4, 124.8, 125.0, 128.5, 129.0, 130.2, 130.4, 131.0, 131.6, 132.3,
134.8, 134.9, 135.2, 135.4, 136.5, 136.9, 139.5, 157.6, 158.1. Anal. Calcd. for C$_{26}$H$_{24}$O$_2$:
C, 84.75; H, 6.57. Found: C, 84.74; H, 6.61.

1,8-Bis(2’-methyl-4’-methoxy-5’-formylphenyl)naphthalene (8)
Phosphorous oxychloride (2.9 mL, 31.2 mmol) and dimethyl formamide (2.4 mL, 31.2
mmol) were stirred in 10 mL of chloroform at room temperature for one hour. Then, 7
(0.60 g, 1.6 mmol) was added and the mixture was refluxed at 90 °C for 48 hours. It was then cooled to 0 °C, carefully 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:EtOAc 25:1) afforded 0.69 g (1.6 mmol, 99%) of syn/anti-8 as a white powder. The diastereomers of 8 can be separated using flash chromatography with gradient elution starting with dichloromethane to collect the anti-isomer (73%), then increasing the polarity to DCM:EtOAc 15:1 to recover the syn-diastereomer (27%).

¹H NMR anti-8: δ = 1.81 (s, 6H), 3.80 (s, 6H), 6.35 (s, 2H), 7.15 (d, J = 7.0 Hz, 2H), 7.38 (s, 2H), 7.50 (dd, J = 7.0 Hz, 8.2 Hz, 2H), 7.94 (d, J = 8.2 Hz, 2H), 10.28 (s, 2H). ¹³C NMR: δ = 21.5, 55.5, 112.1, 121.6, 125.2, 127.8, 129.2, 130.1, 130.2, 134.8, 135.4, 137.4, 146.2, 160.3, 189.0. Anal. Calcd. for C₂₈H₂₄O₄: C, 79.22; H, 5.70. Found: C, 78.99; H, 5.72.

1,8-Bis(2'-methyl-4'-hydroxy-5'-formylphenyl)naphthalene (5)

To a solution of 1,8-bis(2'-methyl-4'-methoxy-5'-formylphenyl)naphthalene, 8, (0.78 g, 1.9 mmol) in 35 mL of anhydrous CH₂Cl₂ at 0 °C, BBr₃ (11.8 mL, 11.8 mmol) was added dropwise and the mixture was stirred for six hours. The reaction was carefully quenched with isopropyl alcohol followed by addition of 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 20:1) afforded 0.58 g of 5 (1.5 mmol, 77%) as a white solid. The anti/syn-ratio was determined as 4 by ¹H-NMR spectroscopy. Enantiopure anti-5 was obtained via formation of 9 or 10 as described
below and hydrolysis or by asymmetric transformation of the first kind and subsequent hydrolysis.

\[
\text{H NMR (P,P)-5: } \delta = 1.85 (s, 6H), 6.40 (s, 2H), 7.08 (s, 2H), 7.20 (d, J = 7.1 Hz, 2H), 7.54 (dd, J = 7.0 Hz, 7.1 Hz, 2H), 7.99 (d, J = 7.0 Hz, 2H), 9.66 (s, 2H), 10.73 (s, 2H).
\]

\[
\text{C NMR: } \delta = 21.7, 117.5, 118.0, 125.3, 125.4, 129.4, 129.5, 130.6, 132.9, 135.0, 136.9, 146.5, 160.5, 195.1. \text{ Anal. Calcd. for } C_{26}H_{20}O_4: \text{ C}, 78.77; \text{ H}, 5.09. \text{ Found: C}, 78.69; \text{ H}, 5.42.
\]

**Diimine (P,P,R,R)-9**

To racemic *anti-5* (67.0 mg, 0.17 mmol) dissolved in 8 mL of CHCl₃ over molecular sieves (4 Å, beads, 8-12 mesh), 2 equivalents of (R)-2-amino-1-propanol (25.4 mg, 0.34 mmol) were added and the mixture was allowed to stir for one hour at room temperature. The mixture was then extracted with water, dried over MgSO₄ and concentrated in vacuo. Chromatographic purification using EtOAc:EtOH (99.5:0.5) as mobile phase allowed the isolation of the two diastereomeric products (P,P,R,R)-9 and (M,M,R,R)-9 as yellow solids in quantitative yield.

\[
\text{H NMR (P,P,R,R)-9: } \delta = 1.26 (d, J = 6.4 Hz, 6H), 1.67 (s, 6H), 3.43 (t, J = 6.4 Hz, 2H), 3.62 (m, 2H), 3.72 (dd, J = 2.0 Hz, 12.0 Hz, 2H), 6.50 (s, 2H), 6.56 (s, 2H), 7.16 (d, J = 7.0 Hz, 2H), 7.49 (dd, J = 7.0 Hz, 8.0 Hz, 2H), 7.95 (m, 4H). \text{ Anal. Calcd. for } C_{32}H_{34}N_2O_2: \text{ C}, 75.27; \text{ H}, 6.71; \text{ N}, 5.49. \text{ Found: C}, 75.05; \text{ H}, 6.98; \text{ N}, 5.14.
\]
Hydrolysis of \((P,P,R,R)-9\) to \((P,P)-5\): Pure \((P,P,R,R)-9\) (43.2 mg, 0.08 mmol) was dissolved in 5 mL of 1 M NaOH, and 1 mL of aqueous HCl (12.1 M) was added dropwise at 0 °C. The mixture was allowed to stir for 10 minutes. The resulting suspension was extracted with CH\(_2\)Cl\(_2\) and 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 enantiopure \((P,P)-5\) (28.5 mg, 0.07 mmol) in 85% yield, with no sign of the syn-diastereomer based on NMR analysis. The enantiopurity of 5 was confirmed by derivatization to the corresponding diimine using \((R)-2\)-amino-1-propanol. The NMR spectrum of the condensation product showed the presence of a single diastereomer.

**Diimine \((P,P,R,R)-10\)**

To racemic 5 (200 mg, 0.51 mmol) dissolved in 15 mL of CHCl\(_3\) over molecular sieves (4 Å, beads, 8-12 mesh), 2 equivalents of \((R)-2\)-amino-3-methyl-1-butanol (104 mg, 1.02 mmol) were added and the mixture was allowed to stir at 70 °C for 16 h. Upon completion of the asymmetric transformation, the mixture was cooled to room temperature, extracted with water, dried over MgSO\(_4\), and concentrated in vacuo. Chromatographic purification using CH\(_2\)Cl\(_2\):EtOAc (1:1) as mobile phase gave \((P,P,R,R)-10\) (285 mg, 0.50 mmol) in 99.8% yield. The hydrolysis of \((P,P,R,R)-10\) to \((P,P)-5\) was conducted as described above with \((P,P,R,R)-9\) and gave enantiopure \((P,P)-5\) in 80% yield.

\(^1\)H NMR \((P,P,R,R)-10\): \(\delta = 0.96\ (d, J = 6.8\ \text{Hz}, 12\text{H}), 1.64\ (s, 6\text{H}), 1.91\ (m, 2\text{H}), 3.05\ (m, 2\text{H}), 3.68\ (t, J = 10.5\ \text{Hz}, 2\text{H}), 3.87\ (m, 2\text{H}), 6.50\ (s, 2\text{H}), 6.59\ (s, 2\text{H}), 7.16\ (d, J = 7.0\ \text{Hz}, 2\text{H}), 7.50\ (dd, J = 7.0\ \text{Hz}, 8.0\ \text{Hz}, 2\text{H}), 7.94\ (m, 4\text{H}). \(^{13}\)C NMR: \(\delta = 18.6, 20.0, 20.8,\)
29.9, 64.2, 114.7, 118.1, 125.2, 128.9, 129.7, 130.9, 131.1, 133.2, 134.7, 138.1, 142.3, 163.0, 165.0. Anal. Calcd. for C_{36}H_{42}N_{2}O_{4}: C, 76.29; H, 7.47; N, 4.94. Found: C, 76.18; H, 7.28; N, 4.87.

1,8-Bis(2’-trifluoromethyl-4’-methoxyphenyl)naphthalene (13)

A solution of 1,8-diiodonaphthalene, (0.23 g, 0.61 mmol), 2-trifluoromethyl-4-methoxyphenylboronic acid, 11, (0.73 g, 3.33 mmol), Pd(PPh$_3$)$_4$ (0.21 g, 0.18 mmol) and K$_3$PO$_4$, (0.58 g, 2.72 mmol) in 5 mL of toluene was stirred at 100 °C for 40 hours. The resulting mixture was allowed to come 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 2:5) afforded 0.25 g (0.53 mmol, 88%) of 13 as a white solid.

$^1$H NMR: δ = 3.75 (s, 6H), 6.55 (dd, $J$ = 2.5 Hz, 8.5 Hz, 2H), 6.82-6.89 (m, 4H), 7.20 (d, $J$ = 7.1 Hz, 2H), 7.46 (d, $J$ = 7.1 Hz, 8.2 Hz, 2H), 7.95 (d, $J$ = 1.1 Hz, 8.2 Hz, 2H).

1,8-Bis(2’-bromomethyl-5’-formylphenyl)naphthalene (14)

To a solution 7 (0.20 g, 0.54 mmol) in 6 mL of carbon tetrachloride, N-bromosuccinimide (0.19 g, 1.1 mmol) and benzoyl peroxide (0.08 g, 0.40 mmol) were added and the mixture was refluxed under UV light (365 nm, 150 W) for 18 hours. It was then cooled to room temperature, carefully quenched with 1 M NaHSO$_3$ 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 1:2) afforded 0.21 g (0.40 mmol, 73%) of 14 as a white solid.
$^1$H NMR: $\delta = 3.83$ (s, 6H), 4.56 (s, 4H), 6.38 (dd, $J = 2.8$ Hz, 8.4 Hz, 2H), 6.59 (d, $J = 8.4$ Hz, 2H), 7.29 (d, $J = 2.8$ Hz, 2H), 7.38 (dd, $J = 1.4$ Hz, 7.2 Hz, 2H), 7.58 (dd, $J = 7.2$ Hz, 8.0 Hz, 2H), 8.07 (dd, $J = 1.4$ Hz, 8.0 Hz, 2H).

$^{13}$C NMR: $\delta = 40.4, 55.5, 114.4, 115.4, 125.1, 128.9, 129.8, 130.2, 130.4, 131.0, 131.4, 135.0, 135.7, 139.0$.

**1,8-Bis(2'-dibromomethyl-5'-formylphenyl)naphthalene (15)**

To a solution of 7 (0.49 g, 1.3 mmol) in 9 mL of carbon tetrachloride, N-bromosuccinimide (1.1 g, 6.4 mmol) and benzoyl peroxide (0.19 g, 0.80 mmol) were added, and the mixture was allowed to reflux under UV light (365 nm, 150 W) for 18 hours. It was then cooled to room temperature, carefully quenched with 1 M NaHSO$_3$ 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 1:2) afforded 0.67 g (0.99 mmol, 74%) of 15 as a white solid.

$^1$H NMR: $\delta = 3.79$ (s, 6H), 6.26 (s, 2H), 6.35 (dd, $J = 2.7$ Hz, 8.5 Hz, 2H), 6.57 (d, $J = 8.5$ Hz, 2H), 7.29 (d, $J = 2.7$ Hz, 2H), 7.36 (dd, $J = 1.3$ Hz, 7.2 Hz, 2H), 7.56 (dd, $J = 7.2$ Hz, 8.2 Hz, 2H), 8.04 (dd, $J = 1.3$ Hz, 8.2 Hz, 2H). $^{13}$C NMR: $\delta = 40.4, 55.5, 114.4, 115.4, 125.1, 128.9, 129.8, 130.2, 130.4, 131.0, 131.4, 135.0, 135.7, 139.0$.

**V.4.2 Crystallization and X-Ray Diffraction**

Single crystal X-ray analysis was performed at 100 K using a Siemens platform diffractometer with graphite monochromated Mo-K$_\alpha$ radiation ($\lambda = 0.71073$ 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.
A crystal of enantiopure \((P,P)-5\) was obtained by slow evaporation of a solution of 10 mg of \((P,P)-5\) in 3 mL of CHCl₃. Crystal structure data for \((P,P)-5\): Formula C\(_{26}H_{20}O_4\), M= 396.43, crystal dimensions 0.15 x 0.10 x 0.05 mm, tetragonal, space group P\(_{4_3}\), \(a = 11.7955(17) \, \text{Å}, \ b = 11.7955 (17) \, \text{Å}, \ c = 28.4769(40) \, \text{Å}, \ V = 3962.10 \, \text{Å}^3, \ Z = 1, \ \rho_{\text{calc}} = 1.3290 \, \text{g cm}^{-3}.

<table>
<thead>
<tr>
<th>Phenyl-phenyl [Å] (centroid to centroid)</th>
<th>3.470</th>
</tr>
</thead>
<tbody>
<tr>
<td>Splaying angle between salicyldenimine planes [°]</td>
<td>20.51</td>
</tr>
<tr>
<td>Torsion angle [°]</td>
<td>5.32</td>
</tr>
</tbody>
</table>

The slow evaporation of a solution of 15 mg of 5 and 2 equivalents of \((R)-2\text{-amino-1-propanol in 3 mL of CHCl}_3\) afforded single crystals of \textit{syn-9}. Crystal structure data for \textit{syn-9}: Formula C\(_{32}H_{34}N_2O_4\), M=510.62, crystal dimensions 0.12 x 0.10 x 0.07 mm,
monoclinic, space group P2$_1$/c, $a = 22.3400(21)$ Å, $b = 6.8469$ (6) Å, $c = 17.6753$ (16) Å, $eta = 100.956$ (1), $V = 2654.33$ Å$^3$, $Z = 4$, $\rho_{\text{calc}} = 1.2751$ g cm$^{-3}$.

Figure V.14. Different views of the crystal structure of syn-9.

| Phenyl-phenyl [Å] (centroid to centroid) | 3.518 |
| Splaying angle between salicylideneimine planes [°] | 21.09 |
| Torsion angle [°] | 18.33 |
A crystal of \((P,P,R,R)-10\) was obtained by crystallization of 100 mg of \((P,P,R,R)-10\) from 15 mL of hexanes. Crystal structure data for \((P,P,R,R)-10\): Formula C\(_{32}\)H\(_{34}\)N\(_2\)O\(_4\), M=566.73, crystal dimensions 0.10 x 0.10 x 0.05 mm, orthorhombic, space group P2\(_1\), \(a = 10.8469(44)\) Å, \(b = 21.3655\) (86) Å, \(c = 13.6440\) (55) Å, \(V = 3161.99\) Å\(^3\), \(Z = 2\), \(\rho_{\text{calc}} = 1.1903\) g cm\(^{-3}\).

![Figure V.15. Different views of the crystal structure of \((P,P,R,R)-10\).](image)

<table>
<thead>
<tr>
<th>Bond Description</th>
<th>Length [Å]</th>
</tr>
</thead>
<tbody>
<tr>
<td>C=N···HOC(_{\text{phenyl}}) hydrogen bond</td>
<td>1.861</td>
</tr>
<tr>
<td>C(<em>{\text{aliph}})OH···OC(</em>{\text{phenyl}}) hydrogen bond</td>
<td>2.178</td>
</tr>
<tr>
<td>Phenyl-phenyl [Å] (centroid to centroid)</td>
<td>3.326</td>
</tr>
<tr>
<td>Splaying angle between salicyldenimine planes [°]</td>
<td>13.46</td>
</tr>
<tr>
<td>Torsion angle [°]</td>
<td>18.17</td>
</tr>
</tbody>
</table>
V.5. References


VI. Synthesis and Characterization of 1,8-Bis(2’-methyl-4’-hydroxy-5’-phenylphenyl)naphthalene and Other Atropisomeric Analogues

VI. Introduction

Based on the analysis of the chiroptical and stereochemical properties of 1,8-bis(2’-methyl-4’-hydroxy-5’-formylphenyl)naphthalene (see Chapter V) and in continuation of previous studies with 1,8-diarylnaphthalenes,\(^1\) analogues featuring other functionalities than a formyl group at the 5’-position were anticipated to exhibit similar stability towards atropisomerization and present new opportunities for enantioselective sensing and asymmetric catalysis (Figure VI.1).\(^2\)

![Structure of atropisomeric 1,8-bis(2’-methyl-4’-hydroxy)naphthalenes.](image)

A wide range of phenol and naphthol-derived compounds, in particular BINOL, have successfully been used for enantioselective sensing and catalysis.\(^3\) For example, Pu and co-workers have examined a variety of BINOL derivatives and employed these successfully in the stereoselective sensing of amino alcohols and hydroxy acids.\(^4\) Helically chiral 2,15-dihydroxyhexahelicene has also been reported to effectively differentiate between enantiomers of amino alcohols and amines.\(^5\) However, several classes of chiral substrates, such as ketones and esters, still pose a significant challenge to currently available enantioselective sensing assays.
Various modifications that would ultimately allow fine-tuning of the acidity and both the stereochemical and chiroptical properties of atropisomeric 1,8-bis(2’-methyl-4’-hydroxy)naphthalene were considered. Introduction of electron-rich aryl or electron-deficient 3,5-trifluoromethylphenyl groups should alter the acidity of the phenol groups. Anticipating a use as hydrogen-bond donating enantioselective sensor, a small change in acidity might be useful for optimization of stereoselective interactions with hydrogen-bond accepting substrates. The introduction of a triple bond spacer (see compounds 3 and 4) would place the bulk of the aromatic substituents further away from the phenol functionality, and allow more space for coordination to a metal center. This may prove important for possible applications in asymmetric catalysis or enantioselective sensing based on ligand displacement. To date, few sensor molecules have been reported carrying large aromatic groups connected through a triple bond spacer. Pu et al. showed the effect of the presence\(^6\) or absence\(^7\) of acetylene units on the enantioselectivity of various sensors (Figure VI.3). Upon incorporation of acetylene units into a dendrimer structure,
the new set of BINOL sensors obtained showed the same sense of enantiodiscrimination and comparable Stern-Volmer ratios, but gave a five-fold enhancement in sensitivity.

Figure VI.3. BINOL core-based phenylene (left) and phenylacetylene (right) dendrimers.

An important characteristic of a UV or fluorescent sensing assay is the wavelength at which it is conducted. Higher wavelengths are more desirable in order to minimize interferences with aromatic substrates and impurities. In addition, large extinction coefficients are advantageous since they often lead to more sensitive assays that require smaller amounts of sensor. The introduction of large chromophores (see compounds 4 and 5) should cause a UV redshift and an increase in absorption. As shown previously in Chapter II.1, Pu and others have reported on the attachment of light harvesting dendrimers onto a BINOL core. As the dendrimer generation increases, the fluorescence intensity and the association constants with α-amino alcohols improve.
In addition to the parameters discussed above, a better control of the separation between the phenyl groups may prove important for future applications of 1,8-bis(2’-methyl-4’-hydroxy)naphthalene derivatives. An asymmetric atropisomer carrying an electron-rich and an electron-poor substituent at the 5’-positions (see compound 6) might have a smaller distance between the neighboring phenols, possibly through increased charge-transfer interactions. This may facilitate bidentate metal coordination and provide a better basis for understanding the mechanism of chiral recognition. Finally, analogue 7 possesses two secondary amine functionalities in addition to the phenol groups. Many organocatalysts featuring secondary amine functionalities such as proline, have been successfully used in enantioselective Michael additions, Diels-Alder and Aldol reactions, as well as other transformations. Structures similar to 7 also have potential applications as asymmetric ligands for the atroposelective synthesis of chiral biaryl compounds and in asymmetric bimetallic catalysis.

Based on experience with the preparation of similar 1,8-diarylnaphthalenes, the synthesis of compounds 1-7 was expected to be possible via Suzuki or Sonogashira couplings of 1,8-bis(2’-methyl-4’-hydroxy-5’-iodophenyl)naphthalene 10 and the corresponding boronic acid or terminal alkyne. The backbone of 10 could be constructed as shown in Chapter V via the Suzuki coupling of 4-methoxy-2-methylphenylboronic acid, 8, and 1,8-dibromonaphthalene.

Scheme VI.1. General retrosynthetic scheme of 1-7.
VI.2. Results and Discussion

VI.2.1. Synthesis and Enantioseparation of 1

The first member of the structures shown above, 1,8-bis(2’-methyl-4’-hydroxy-5’-phenylphenyl)naphthalene, 1, was synthesized via the Suzuki coupling of 1,8-dibromonaphthalene and commercially available 4-methoxy-2-methylphenylboronic acid, 8 (Scheme VI.2). 1,8-Bis(2’-methyl-4’-methoxyphenyl)naphthalene, 9, was obtained in quantitative amounts using Pd(PPh₃)₄ and K₃PO₄ in toluene. The electrophilic aromatic substitution of 9 with 2.2 equivalents of benzyltrimethylammonium dichloroiodate and zinc chloride in glacial acetic acid furnished 1,8-bis(2’-methyl-4’-methoxy-5’-iodophenyl)naphthalene, 10, in 67% yield. A second set of Suzuki couplings followed, this time using phenylboronic acid under the same conditions described above to give 11 in 87% yield. Finally, deprotection of 11 with boron tribromide gave 1 in 85% yield.

The stereoisomers of 1 were separated on a CHIRALPAK AD column using hexanes:IPA (9:1) as mobile phase (Figure VI.4). The first eluting enantiomer elutes at 7.2 minutes, while the second elutes at 8.9 minutes. The syn-intermediate elutes at 10.5 minutes.
Figure VI.4. HPLC chromatogram of racemic 1 (1mg/mL in hexanes:IPA (9:1)) using a CHIRALPAK AD column with hexanes:IPA (9:1) as the mobile phase, and a detection wavelength of 240 nm.

The ratio of the absorption coefficient of the *syn*-diastereomer to that of the *anti*-isomer was determined as 0.699 in hexanes:IPA 9:1. Although chiral chromatography presented the opportunity for a semi-preparative separation of stereoisomers, a method allowing for the large scale resolution of enantiomers was desired. After the examination of several chiral auxiliaries, *N*-Boc tryptophan was found to form a chromatographically separable diastereomeric mixture 12 that was later hydrolyzed to afford enantiopure 1.

Scheme VI.3. Resolution of 1 through the formation of diastereomeric intermediate 12.
VI.2.2. Synthesis of 2-7

Additional analogues of 1 were then synthesized. Initially, we were interested in converting the two phenol rings into anilines, thiophenols and aryl phosphoric acids. The formation of the bistriﬂate of 1 was successful, but palladium catalyzed aminations and amidations using benzylamine or benzamide, with various palladium sources, ligands, bases and solvents as described in the literature did not occur, probably because of steric hindrance. Amidation was successful when the phenyl group in position 5’ was not present, affording the bisacetamide analogue 14 in 85% yield (Scheme VI.4). Bromination of the latter proceeded in 77% yield, but neither 16 nor its hydrolyzed form 17 underwent Suzuki coupling.

The introduction of aryl and alkynyl substituents in the 5’-positions of 1 proved more successful (Schemes VI.5 and VI.6). It is noted here that yields for the syntheses of 2-5 are not optimized. The Suzuki coupling of 10 and electron-deﬁcient 3,5-bis(triﬂuoromethyl)phenylboronic acid using Pd(PPh3)4 and K3PO4 in toluene proceeded...
in 11% yield, and was followed by the methyl ether deprotection to afford 2 in 85% yield. The introduction of a triple bond spacer in the 5'-position was also investigated. The Sonogashira coupling of 10 and phenylacetylene using Pd(PPh₃)₄, copper iodide and triethylamine proceeded in 70% yield, and was followed by BBr₃ deprotection to give 3 in 12% yield. In contrast to the results obtained with 10, all Sonogashira couplings conducted with compound 18 were unsuccessful (Scheme VI.6). Coupling of 10 with 1-ethynylpyrene using PdCl₂(PPh₃)₂, copper iodide and triethylamine proceeded in 60% yield, and was followed by ether deprotection to give 4 in 24% yield. The Suzuki coupling of 10 and commercially available 2-anthraceneboronic acid proceeded in 16% yield. Finally, methyl ether deprotection afforded 5 in 18% yield.

Scheme VI.5. Synthesis of 2-5.

Following the synthesis of a series of C₂ symmetric structures, we were interested in developing an asymmetric atropisomer carrying both electron-rich and electron-poor substituents to evaluate if possible charge-transfer interactions between the cofacial arenes would reduce the O-O distance from 4.2 Å as observed in the crystal structure of 1 (see chapter VI.2.5). Selective monoarylation of 10 was not successful, and it was concluded that the Caryl-I bond is not suitable for this transformation since it is readily cleaved through oxidative addition with palladium. Therefore, 9 was brominated using N-bromosuccinimide to give 1,8-bis(2'-methyl-4'-methoxy-5'-bromophenyl)naphthalene,
18, in 60% yield (Scheme VI.6). Careful Suzuki coupling using one equivalent of 3,5-bis(trifluoromethyl)phenylboronic acid, Pd(PPh₃)₄ and K₃PO₄ in toluene afforded monosubstituted 19 in 16% yield, along with 40% of recovered starting material. A second Suzuki coupling using 19 and 3,5-dimethylphenylboronic acid proceeded in 46% yield, and was followed by BBr₃ deprotection to give 6 in 32% yield.


It was expected that the reductive amination using previously synthesized 1,8-bis(2’-methyl-4’-methoxy-5’-formylphenyl)naphthalene and benzylamine would produce 7, an interesting candidate for a variety of applications including enantioselective sensing and asymmetric catalysis. The use of five equivalents of benzylamine allowed for complete condensation towards the corresponding diimine. The latter was isolated and then resuspended with sodium borohydride in DCM:EtOH (1:2) to afford 66% of the diamine. Finally, BBr₃ deprotection gave 7 in 75% yield (Scheme VI.7).

Scheme VI.7. Synthesis of 7.
VI.2.3. Chiroptical Properties and Crystallographic Analysis

Having developed a practical method providing enantiopure 1, the chiroptical properties of this new bisphenol atropisomer were investigated. The CD instrument was purged with nitrogen for 20 minutes. Spectra were collected at room temperature between 270 and 390 nm with a standard sensitivity of 100 mdeg, a data pitch of 0.5 nm, a band width of 1 nm, a scanning speed of 500 nm/s and a response of 0.5 s using a quartz cuvette (1 cm path length). Polarimetric measurements were conducted at 21.5 °C and 589 nm. The first eluting enantiomer of 1 has an optical rotation of 247.8°, and the value for the enantiomer that is more strongly retained on the CHIRALPAK AD column was determined as -248.8° (1 mg/mL in hexanes:IPA 1:1).

![UV Spectrum and CD Spectra](image)

Figure VI.5. Top: UV Spectrum of 1 (1.02 x 10^{-3} M, hexanes:IPA 1:1). Bottom: CD Spectra of dextrorotatory (blue) and levorotatory (orange) enantiomers of 1.
A comparison of the absorbance and emission wavelengths of some of the synthesized diarylnaphthalenes is presented in Table VI.1. As expected, replacing the phenyl group on the 5'-position of 1 by ethynylbenzene (3), 1-ethynylpyrene (4) and 2-anthracene (5) shifts the corresponding $\lambda_{\text{max}}$ from 290 nm to 330, 397 and 360 nm, respectively.

Table VI.1. Summary of the absorbance maximum, excitation and emission wavelengths of selected compounds (5.0 x $10^{-5}$ M in ACN).

<table>
<thead>
<tr>
<th>Compound</th>
<th>$\lambda_{\text{max}}$ (nm)</th>
<th>$\lambda_{\text{excitation}}$ (nm)</th>
<th>$\lambda_{\text{emission}}$ (nm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>290</td>
<td>320</td>
<td>430</td>
</tr>
<tr>
<td>3</td>
<td>330</td>
<td>330</td>
<td>380</td>
</tr>
<tr>
<td>4</td>
<td>397</td>
<td>nd</td>
<td>nd</td>
</tr>
<tr>
<td>5</td>
<td>360</td>
<td>nd</td>
<td>nd</td>
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<tr>
<td>7</td>
<td>290</td>
<td>340</td>
<td>545</td>
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</table>

nd = not determined

Slow evaporation of a solution of 1 or 2 in dichloromethane gave single crystals suitable for X-ray studies (Figures VI.6 and VI.7). As expected, crystallographic analysis shows that the two phenol rings reside in almost perfectly perpendicular orientation relative to the naphthalene backbone, exhibiting a C$_2$-symmetric structure with a small torsion angle of 0.28°. The splaying between the two phenyl rings was determined as 19.48° which results in a centroidal phenyl-to-phenyl separation of 3.50 Å, and an O-O distance of 4.37 Å.
Figure VI.6. Different views of the crystal structure of 1.

Compared to 1, 2 exhibits slightly larger torsion (1.02°) and splaying (27.13°) angles, as well as phenyl-to-phenyl (3.61 Å) and O-O (4.77 Å) distances. Attempts to grow single crystals of 3-7 were unsuccessful.

Figure VI.7. Different views of the crystal structure of 2.
VI.2.4. Kinetic Studies

VI.2.4.1. Isomerization Experiments

Several solutions of the levorotatory enantiomer of \( \text{I} \) (4.06 µmol, hexanes:IPA 9:1) were prepared in separate vials and stirred at 77.1 °C (±0.4 °C). The temperature was continuously monitored using a calibrated digital thermometer. At various times, the stereoisomeric composition was determined using a rapidly cooled vial. From this vial, 50 µL were diluted with 1 mL of 9:1 hexanes:IPA, and then analyzed by chiral chromatography on CHIRALPAK AD and UV detection at 240 nm.

![Figure VI.8. Change of the %ee of \( \text{I} \) at 77.1 °C. Inset: HPLC chromatograms showing the change in the relative amounts of the stereoisomers of \( \text{I} \).](image-url)
VI.2.4.2. Determination of the Rate Constants for the Isomerization of 1

Interconversion of the stereoisomers of 1 requires one phenyl ring to rotate about the chiral naphthyl-phenyl axis (Scheme VI.8). Accordingly, the edge of the rotating ring points towards the adjacent phenyl moiety in the transition state to afford the meso intermediate.

Scheme VI.8. Interconversion of the stereoisomers of 1.
Figure VI.9 shows the decrease of the mol fraction of (-)-1 as a function of time. The mathematical solution for the kinetics of consecutive, first-order, reversible reactions involving 3 species such as the syn/anti-interconversion of 1 has been reported by Vriens.\textsuperscript{14} Curve fit analysis using equation 1 allows for the determination of the rate constant for the anti- to syn-isomerization, $k_1$.

$$x = C_1e^{D_1kt} + C_2e^{D_2kt} + \frac{\alpha}{K_1K_2E_2}$$  \hspace{1cm} (1)

$k_1$ = rate constant of the anti$\rightarrow$syn interconversion, $K_1$ = equilibrium constant for the formation of the syn-isomer, $K_2$ = equilibrium constant for the formation of either anti-isomer, $\alpha$ = ratio of forward rate constants ($k_2/k_1$) for the consecutive, reversible, first-order reactions, $k_2$ = rate constant for syn$\rightarrow$anti interconversion, $C_1$, $C_2$, $D_1$, $D_2$, $E_2$ are constants defined below. Curve fitting of the decay of (-)-1 to $y = A1*exp(-x/t1) + A2*exp(-x/t2) + y0$ was performed using OriginPro 8.1, with $A1 = 0.40745$, $A2 = 0.11968$, $t1 = 77.31456$, $t2 = 8.33489$, $y0 = 0.40745$, $R^2=0.9999$.

The syn/anti-ratio of 1 at equilibrium was determined as 0.46 by HPLC using individual response factors. The mixture consists of 81.4\% of racemic anti-1 and 19.1\% of syn-1.

\begin{align*}
E_1 &= 1 + \frac{1}{K_1} + \alpha + \frac{\alpha}{K_2} \\
E_2 &= \alpha \left(1 + \frac{1}{K_1K_2} + \frac{1}{K_2}\right) = D_1D_2 \\
D_1 &= -E_1 + \sqrt{E_1^2 - 4E_2} \\
D_2 &= -E_1 - \sqrt{E_1^2 - 4E_2} \\
C_1 &= \frac{-1 - D_2 + \frac{\alpha}{K_1K_2D_1}}{D_1 - D_2} \\
C_2 &= \frac{1 + D_1 - \frac{\alpha}{K_1K_2D_2}}{D_1 - D_2}
\end{align*}
\[ K_1 = 0.46 \text{ and } K_2 = 1/K_1 = \alpha = 2.15. \]

Using the above equations, the remaining constants can now be calculated.

\[ E_1 = 6.29, \ E_2 = 5.29 \]

\[ D_1 = -1.00, \ D_2 = -5.29 \]

\[ C_1 = 0.500, \ C_2 = 0.094 \]

\[ D_2k_1 = -1/t2 = -0.1199, \ k_1 = 0.0003778 \text{ s}^{-1} \]

\[ K^{\#}_{\text{anti} \rightarrow \text{syn}} = k_1h/k_bT = 5.18 \times 10^{-17} \]

\[ \Delta G^{\#}_{\text{anti} \rightarrow \text{syn}} = -RT\ln K^{\#}_{\text{anti} \rightarrow \text{syn}} = 109.2 \text{ kJ/mol.} \]

Also, \( D_1k_1 = -1/t1 = -0.01293, \ k_1 = 0.00021557 \text{ s}^{-1} \)

\[ K^{\#}_{\text{anti} \rightarrow \text{syn}} = k_1h/k_bT = 2.95 \times 10^{-17} \]

\[ \Delta G^{\#}_{\text{anti} \rightarrow \text{syn}} = -RT\ln K^{\#}_{\text{anti} \rightarrow \text{syn}} = 110.8 \text{ kJ/mol.} \]

Averaging of these two values gives \( \Delta G^{\#}_{\text{anti} \rightarrow \text{syn}} = 110.0 \text{ kJ/mol.} \)

Since \( k_2 = k_1/K_1, \ k_2 = 0.0006373 \text{ s}^{-1} \)

\[ K^{\#}_{\text{syn} \rightarrow \text{anti}} = k_2h/k_bT = 8.73 \times 10^{-17} \]

\[ \Delta G^{\#}_{\text{syn} \rightarrow \text{anti}} = -RT\ln K^{\#}_{\text{syn} \rightarrow \text{anti}} = 107.7 \text{ kJ/mol.} \]

As shown in Chapter V, the presence of methyl groups in the \textit{ortho}-positions of these atropisomeric structures produces conformational isomers that are stable to interconversion and separable at room temperature. This moderate bulk adjacent to the chiral axes is sufficient to isolate and characterize the stereoisomers of 1. HPLC analysis gave a Gibbs activation energy for atropisomerization of 110.0 (107.7) kJ/mol for the conversion of the \textit{anti-(syn-)} to the \textit{syn-(anti-)} isomer.
VI.3. Conclusions

The synthesis and structural examination of several atropisomeric compounds featuring a 1,8-bis(2'-methyl-4'-hydroxy-5'-arylphenyl)naphthalene backbone and 5'-arylalkynyl derivatives have been accomplished. Several substituents such as phenyl, 3,5-bis(trifluoromethyl)phenyl, ethynylbenzene, 1-ethynylpyrene, 2-anthracence, and benzylaminomethyl have been successfully introduced to the 5’-position. The conversion of the two phenol rings of 1 into anilines, thiophenols and aryl phosphoric acids was unsuccessful probably due to steric hindrance. An alternative strategy based on Suzuki coupling of 17 with arylboronic acids also did not provide the desired atropisomeric 1,8-dianilinonaphthalenes. As anticipated, the synthesized compounds are stable towards atropisomerization at room temperature (kinetic studies revealed a Gibbs activation energy for atropisomerization of 110.0 (107.7) kJ/mol for the conversion of the \textit{anti-(syn-)} to the \textit{syn-(anti-)isomer}), while isomerization occurs upon heating. In particular, compounds 3-5 have great promise as UV and fluorescent probes for enantioselective sensing of several classes of chiral substrates such as amino alcohols, ketones, esters and acids.

VI.4. Experimental Section

VI.4.1. Synthetic Procedures

All reagents and solvents were used without further purification. All reactions were carried out under nitrogen atmosphere and anhydrous conditions. Products were purified by flash chromatography on SiO\textsubscript{2} (particle size 0.032-0.063 mm). NMR spectra were
obtained at 400 MHz (\(^1\)H NMR) and 100 MHz (\(^{13}\)C NMR) using CDCl\(_3\) as solvent. Chemical shifts are reported in ppm relative to TMS.

1,8-Bis(2’-methyl-4’-hydroxy-5’-phenylphenyl)naphthalene (1)
To a solution of 1,8-bis(2’-methyl-4’-methoxy-5’-phenylphenyl)naphthalene, 11, (0.14 g, 0.28 mmol) in 10 mL of anhydrous CH\(_2\)Cl\(_2\) at 0 °C, BBr\(_3\) (1.67 mL, 1.67 mmol) was added dropwise and the mixture was stirred for sixteen hours at room temperature. The reaction was carefully quenched with isopropyl alcohol followed by addition of 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\(_2\)) afforded 0.12 g of 1 (0.24 mmol, 85%) as a white solid.

\(^1\)H NMR: \(\delta = 1.66\) (s, 6H), 5.01 (s, 2H), 6.45 (s, 2H), 6.89 (s, 2H), 7.25 (d, \(J = 7.0\) Hz, 2H), 7.36 (dd, \(J = 6.8\) Hz, 7.2 Hz, 2H), 7.42-7.51 (m, 10H), 7.91 (d, \(J = 8.1\) Hz, 2H). \(^{13}\)C NMR: \(\delta = 20.3, 115.9, 124.2, 125.0, 127.5, 128.6, 128.8, 129.2, 129.9, 130.3, 130.9, 150.7\). Anal. Calcd. for C\(_{36}\)H\(_{28}\)O\(_2\): C, 87.78; H, 5.73. Found: C, 88.04; H, 5.79.

1,8-Bis(2’-methyl-4’-hydroxy-5’-(3,5-bistrifluoromethylphenyl))naphthalene (2)
A solution of 10 (0.20 g, 0.32 mmol), 3,5-bis(trifluoromethyl)phenylboronic acid (0.25 g, 0.97 mmol), Pd(PPh\(_3\))\(_4\) (0.056 g, 0.048 mmol) and K\(_3\)PO\(_4\), (0.31 g, 1.45 mmol) in 10 mL of anhydrous toluene was stirred at 100 °C for 24 hours. The resulting mixture was allowed to cool to room temperature, quenched with water, extracted with CH\(_2\)Cl\(_2\) and washed with brine. 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 0.028 g (0.035 mmol, 11%) of a white solid.

$^1$H NMR: $\delta$ = 1.81 (s, 6H), 3.68 (s, 2H), 6.50 (s, 2H), 6.97 (s, 2H), 7.22-7.29 (m, 2H), 7.57 (dd, $J$ = 7.3 Hz, 8.1 Hz, 2H), 7.83 (s, 2H), 7.95 (s, 4H), 8.06 (d, $J$ = 8.1 Hz, 2H).

To this solid (0.028 g, 0.035 mmol) in 4 mL of anhydrous CH$_2$Cl$_2$ at 0 °C, BBr$_3$ (0.22 mL, 0.22 mmol) was added dropwise and the mixture was stirred for 15 hours at room temperature. The reaction was carefully quenched with isopropyl alcohol followed by addition of 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$_2$) afforded 0.0023 g of 2 (0.030 mmol, 85%) as a white solid.

$^1$H NMR: $\delta$ = 1.70 (s, 6H), 6.44 (s, 2H), 6.95 (s, 2H), 7.28 (d, $J$ = 7.0 Hz, 2H), 7.61 (dd, $J$ = 7.0 Hz, 7.8 Hz, 2H), 8.04 (bs, 2H), 8.08 (d, $J$ = 8.2 Hz, 2H), 8.16 (s, 4H), 9.66 (s, 2H).

$^{13}$C NMR: $\delta$ = 20.6, 116.6, 120.9, 125.3, 125.5, 129.0, 129.4, 130.2, 130.5, 130.8, 134.6, 135.2, 137.2, 138.5, 141.4, 153.2.

1,8-Bis(2'-methyl-4'-hydroxy-5'-phenylethynyl)naphthalene (3)

A solution of 10 (0.30 g, 0.48 mmol), phenylacetylene (0.25 g, 2.42 mmol), Pd(PPh$_3$)$_4$ (0.14 g, 0.12 mmol), CuI (0.046, 0.24 mmol) and TEA (0.20 g, 1.93 mmol) in 5 mL of THF was stirred at 80 °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 1:2) afforded 0.19 g (0.39 mmol, 70%) of a white solid. This material (0.19 g, 0.39 mmol) was dissolved in 5 mL of anhydrous
CH₂Cl₂ at 0 °C. Then, BBr₃ (2.15 mL, 2.15 mmol) was added dropwise, and the mixture was stirred for 16 hours at room temperature. The reaction was carefully quenched with isopropyl alcohol followed by addition of 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 1:4) afforded 0.025 g of 3 (0.047 mmol, 12%) as a white solid.

¹H NMR: δ = 1.85 (s, 6H), 6.62 (s, 2H), 6.66 (s, 2H), 6.94 (s, 2H), 7.14-7.30 (m, 8H), 7.45 (dd, J = 7.0 Hz, 8.3 Hz, 2H), 7.59 (dd, J = 1.3 Hz, 8.2 Hz, 2H), 7.88 (dd, J = 1.3 Hz, 8.3 Hz, 2H).

1,8-Bis(2'-methyl-4'-hydroxy-5'-(1-ethynylpyrene))naphthalene (4)

A solution of 10 (0.21 g, 0.33 mmol), 1-ethynylpyrene (0.38 g, 1.67 mmol), PdCl₂(PPh₃)₂ (0.070 g, 0.10 mmol), CuI (0.032, 0.17 mmol) and TEA (0.17 g, 1.67 mmol) in 5 mL of dioxane was stirred at 100 °C for 45 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 2:5) afforded 0.16 g (0.20 mmol, 60%) of a white solid. This material (0.16 g, 0.20 mmol) was dissolved in 3 mL of anhydrous CH₂Cl₂ at 0 °C. Then, BBr₃ (2.00 mL, 2.00 mmol) was added dropwise and the mixture was stirred for 20 hours at room temperature. The reaction was carefully quenched with isopropyl alcohol followed by addition of water, and extracted with CH₂Cl₂. The combined organic layers were dried over MgSO₄ and concentrated in vacuo. Purification
by flash chromatography on silica gel (CH$_2$Cl$_2$:hexanes 2:1) afforded 0.038 g of 4 (0.048 mmol, 24%) as a white solid.

$^1$H NMR: δ = 2.12 (s, 6H), 5.86 (s, 2H), 6.76 (s, 2H), 7.13 (s, 2H), 7.30 (d, $J$ = 7.0 Hz, 2H), 7.56 (dd, $J$ = 7.4 Hz, 7.8 Hz, 2H), 7.98-8.23 (m, 18H), 8.62 (d, $J$ = 9.1 Hz, 2H).

**1,8-Bis(2'-methyl-4'-hydroxy-5'-(2-anthracenyl))naphthalene (5)**

A solution of 10 (0.15 g, 0.24 mmol), 2-anthraceneboronic acid (0.19 g, 0.85 mmol), Pd(PPh$_3$)$_4$ (0.056 g, 0.048 mmol) and K$_3$PO$_4$, (0.23 g, 1.09 mmol) in 6 mL of dioxane:DMF:EtOH (1:1:1) was stirred at 100 °C for 48 hours. The resulting mixture was allowed to cool to room temperature, quenched with water, extracted with CH$_2$Cl$_2$ and washed with brine. 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 2:5) afforded 0.028 g (0.039 mmol, 16%) of a white solid. This material (0.028 g, 0.039 mmol) was dissolved in 2.5 mL of anhydrous CH$_2$Cl$_2$ at 0 °C. Then, BBr$_3$ (0.23 mL, 0.23 mmol) was added dropwise and the mixture was stirred for 15 hours at room temperature. The reaction was carefully quenched with isopropyl alcohol followed by addition of 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$_2$:ethyl acetate 75:2) afforded 0.003 g of 5 (0.0047 mmol, 18%) as a white solid.

$^1$H NMR: δ = 1.70 (s, 6H), 5.29 (s, 2H), 6.56 (s, 2H), 7.03 (s, 2H), 7.29 (d, $J$ = 7.0 Hz, 2H), 7.45-7.54 (m, 6H), 7.59 (dd, $J$ = 1.3 Hz, 8.6 Hz, 2H), 7.94 (d, $J$ = 8.2 Hz, 2H), 8.01-8.16 (m, 8H), 8.49 (s, 1H), 8.52 (s, 1H).
1,8-Bisphenol (6)

A solution of 19 (0.10 g, 0.15 mmol), 3,5-dimethylphenylboronic acid (0.068 g, 0.45 mmol), Pd(PPh₃)₄ (0.026 g, 0.023 mmol) and K₃PO₄, (0.14 g, 0.68 mmol) in 8 mL of toluene was stirred at 115 °C for 15 hours. The resulting mixture was allowed to cool to room temperature, quenched with water, extracted with CH₂Cl₂ and washed with brine. The combined organic layers were dried over MgSO₄ and concentrated in vacuo. Purification by flash chromatography on silica gel (CH₂Cl₂:hexanes 1:4) afforded 0.048 g (0.070 mmol, 46%) of a white solid.

This material (0.048 g, 0.070 mmol) was dissolved in 4 mL of anhydrous CH₂Cl₂ at 0 °C. Then, BBr₃ (0.42 mL, 0.42 mmol) was added dropwise and the mixture was stirred for 20 hours at room temperature. The reaction was carefully quenched with isopropyl alcohol followed by addition of 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:ethyl acetate 75:2) afforded 0.015 g of 6 (0.022 mmol, 32%) as a white solid.

¹H NMR: δ = 1.71 (s, 3H), 1.74 (s, 3H), 2.35 (s, 6H), 3.08 (bs, 1H), 5.01 (bs, 1H) 6.37 (s, 1H), 6.43 (s, 1H), 6.90 (s, 1H), 6.93 (s, 1H), 6.95 (s, 1H), 7.05 (s, 2H), 7.21-7.28 (m, 2H), 7.50 (dd, J = 4.1 Hz, 8.3 Hz, 2H), 7.78 (s, 1H), 7.94 (m, 4H).

1,8-Bis(2’-methyl-4’-methoxy-5’-((benzylamino)methyl)phenyl)naphthalene (7)

1,8-Bis(2’-methyl-4’-methoxy-5’-formylphenyl)naphthalene ¹ (0.20 g, 0.47 mmol) was dissolved in 10 mL of DCM:EtOH (1:1). Molecular sieves (4 Å, beads, 8-12 mesh) were added and the mixture was stirred with benzylamine (0.25 g, 2.36 mmol) for 24 hours at

¹ For the synthetic procedure concerning this compound, see Chapter V.4.1.
65 °C. The resulting mixture was cooled to room temperature, quenched with 10 % NaOH, extracted with CH₂Cl₂ and washed with brine. The combined organic layers were dried over MgSO₄ and concentrated in vacuo. The residue was then resuspended in 3 mL of DCM:EtOH (1:2), and NaBH₄ (0.090 g, 2.36 mmol) was added. The mixture was stirred at 85 °C for 24 hours, after which it was cooled 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 (EtOAc:EtOH 99.5:0.5) afforded 0.19 g (0.31 mmol, 66%) of a white solid. This material (0.19 g, 0.31 mmol) was dissolved in 10 mL of anhydrous CH₂Cl₂ at 0 °C. Then, BBr₃ (1.87 mL, 1.87 mmol) was added dropwise and the mixture was stirred for 20 hours at room temperature. The reaction was carefully quenched with isopropyl alcohol followed by addition of 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:ethyl acetate 7:1) afforded 0.14 g of 7 (0.23 mmol, 75%) as a white solid.

1H NMR: δ = 1.63 (s, 6H), 3.64 (m, 4H), 3.87 (m, 4H), 6.28 (s, 2H), 6.38 (s, 2H), 6.80 (bs, 2H), 7.10 (d, J = 6.8 Hz, 2H), 7.25-7.38 (m, 10H), 7.44 (dd, J = 6.8 Hz, 7.9 Hz, 2H), 7.87 (d, J = 7.9 Hz, 2H).

1,8-Bis(2'-methyl-4'-methoxyphenyl)naphthalene (9)

A solution of 1,8-dibromonaphthalene, (1.29 g, 4.5 mmol), 2-methyl-4-methoxyphenylboronic acid, 8, (2.24 g, 13.5 mmol), Pd(PPh₃)₄ (0.78 g, 0.68 mmol) and K₃PO₄, (4.30 g, 20.0 mmol) in 50 mL of toluene was stirred at 110 °C for 18 hours. The resulting mixture was allowed to come 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 2:3) afforded 1.66 g (4.5 mmol, >99%) of off-white crystals containing syn- and anti-isomers of 9.

¹H NMR: δ = 1.76 (s, 4.6H), 1.83 (s, 1.4H), 3.69 (s, 4.4H), 3.71 (s, 1.4H), 6.28-6.39 (m, 4H), 6.66 (d, J = 8.2 Hz, 0.5H), 6.87 (d, J = 8.2 Hz, 1.5H), 7.16 (d, J = 6.8 Hz, 2H), 7.46 (dd, J = 6.8 Hz, 8.0 Hz, 2H), 7.89 (d, J = 8.0 Hz, 2H). ¹³C NMR: δ = 20.9, 21.0, 55.1, 55.2, 109.9, 110.3, 114.3, 114.4, 124.8, 125.0, 128.5, 129.0, 130.2, 130.4, 131.0, 131.6, 132.3, 134.8, 134.9, 135.2, 135.4, 136.5, 136.9, 139.5, 157.6, 158.1. Anal. Calcld. for C₂₆H₂₄O₂: C, 84.75; H, 6.57. Found: C, 84.74; H, 6.61.

1,8-Bis(2'-methyl-4'-methoxy-5'-iodophenyl)naphthalene (10)

To a solution of 9 (0.18 g, 0.49 mmol) in 8 mL of glacial acetic acid, benzyltrimethylammonium dichloroiodate (0.38 g, 1.08 mmol) and zinc dichloride (0.15 g, 1.08 mmol) dissolved in 8 mL of acetic acid were added dropwise over 30 minutes, and the mixture was stirred at 55 °C for 20 hours. It was then cooled to 0 °C, carefully quenched with water and extracted with CH₂Cl₂. The combined organic layers were washed with 1 M sodium thiosulfate, dried over MgSO₄ and concentrated in vacuo. Purification by flash chromatography on silica gel (hexanes:CH₂Cl₂ 3:1) afforded 0.20 g (0.33 mmol, 67%) of 10 as a white solid.

¹H NMR: δ = 1.86 (s, 6H), 3.83 (s, 6H), 6.41 (s, 2H), 7.15 (d, J = 6.9 Hz, 2H), 7.27 (s, 2H), 7.48 (dd, J = 6.9 Hz, 8.1 Hz, 2H), 7.92 (d, J = 8.1 Hz, 2H). ¹³C NMR: δ = 20.7,
1,8-Bis(2'-methyl-4'-methoxy-5'-phenylphenyl)naphthalene (11)

A solution of 10 (0.20 g, 0.32 mmol), phenylboronic acid (0.12 g, 0.96 mmol), Pd(PPh₃)₄ (0.055 g, 0.048 mmol) and K₂PO₄, (0.31 g, 1.44 mmol) in 5 mL of toluene was stirred at 110 °C for 18 hours. The resulting mixture was allowed to come 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 1:2) afforded 0.14 g (0.28 mmol, 87%) of 11 as a white solid.

¹H NMR: δ = 1.70 (s, 6H), 3.67 (s, 6H), 6.36 (s, 2H), 7.00 (s, 2H), 7.21-7.31 (m, 4H), 7.38 (dd, J = 7.5 Hz, 7.7 Hz, 4H), 7.45-7.52 (m, 6H), 7.92 (d, J = 8.2 Hz, 2H). ¹³C NMR: δ = 20.7, 55.5, 125.1, 126.3, 126.5, 127.9, 128.6, 129.2, 130.2, 130.6, 130.9, 134.8, 135.3, 136.4, 138.6, 139.1, 154.7. Anal. Calcd. for C₃₈H₃₂O₂: C, 87.66; H, 6.19. Found: C, 87.42; H, 6.47.

1,8-Bis(2'-methyl-4'-(N-Boc tryptophan ester)-5' phenylphenyl)naphthalene (12)

A solution of racemic 1 (0.17 g, 0.35 mmol), N-Boc (S)-tryptophan (0.23 g, 0.76 mmol), dicyclohexylcarbodiimide (0.16 g, 0.79 mmol) and DMAP (0.05 g, 0.41 mmol) was stirred in 15 mL of dichloromethane for 23 hours at room temperature. The resulting suspension was filtered, dried over MgSO₄, and then concentrated in vacuo. The crude was carefully subjected to flash chromatography on silica gel (gradient elution
DCM:EtOAc 70:1 to 60:1) to afford two fractions with a combined weight of 0.33 g (0.31 mmol, 91%) of 12 as a white powder.

The first eluted fraction (0.17 g, 0.16 mmol) was dissolved in 10 mL of 0.38 M KOH dissolved in 4:1 EtOH:H₂O, and stirred for 15 minutes at room temperature. The solution was carefully quenched at 0 °C with 0.2 mL of concentrated HCl, and extracted with CH₂Cl₂. The combined organic layers were dried over MgSO₄ and concentrated in vacuo. Purification by flash chromatography on silica gel (CH₂Cl₂) afforded 0.078 g of enantiopure 1 (0.16 mmol, 100%) as a white solid. The enantiopurity of the fraction was confirmed as 100 %ee by the HPLC method described in Chapter VI.2.1, and the fraction corresponded to the enantiomer more strongly retained on the CHIRALPAK AD column. The same hydrolysis procedure was then applied to the second eluting diastereomer of 12, which affords the other enantiomer of 1 in 100% yield, but only 95% ee. To further improve enantiopurity, this fraction was dissolved in hexanes:IPA (9:1) and subjected to preparative HPLC on CHIRALPAK AD, to collect the first eluting enantiomer in 100% ee.

**1,8-Bis(2′-methyl-4′-triflatephenyl)naphthalene (13)**

To a solution of 9, (1.03 g, 2.78 mmol) in 40 mL of anhydrous CH₂Cl₂ at 0 °C, BBr₃ (16.7 mL, 16.7 mmol) was added dropwise and the mixture was stirred for sixteen hours at room temperature. The reaction was carefully quenched with isopropyl alcohol followed by addition of water, and extracted with CH₂Cl₂. The combined organic layers were dried over MgSO₄ and concentrated in vacuo. Purification by flash chromatography on silica gel (EtOAc:CH₂Cl₂ 1:7) afforded 0.91 g of a white solid (2.67 mmol, 96%).
To this solid (0.91 g, 2.67 mmol) in 22 mL of toluene, trifluoromethanesulfonic anhydride (4.5 mL, 26.7 mmol) and TEA (1.1 g, 10.7 mmol) were added at 0 °C. The temperature was gradually increased to 95 °C over a period of one hour and stirred for 19 hours. It was cooled to 0 °C, carefully 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 (hexanes:CH$_2$Cl$_2$ 3:1) afforded 1.60 g (2.64 mmol, 99%) of 13 as a white solid.

$^1$H NMR: $\delta = 2.10$ (s, 6H), 6.70-7.00 (m, 6H), 7.34 (dd, $J = 1.2$ Hz, 7.1 Hz, 2H), 7.52 (dd, $J = 7.1$ Hz, 8.0 Hz, 2H), 7.98 (dd, $J = 1.2$ Hz, 8.0 Hz, 2H).

**1,8-Bis(2’-methyl-4’-acetamidophenyl)naphthalene (14)**

To acetamide (0.26 g, 4.4 mmol), tris(dibenzylideneacetone)dipalladium (0.20 g, 0.22 mmol), potassium phosphate (0.69 g, 3.3 mmol) and 2-di-tert-butylphosphino-2’,4’,6’-triisopropylbiphenyl (0.46 mg, 1.1 mmol), a solution of 13 (0.65 g, 1.1 mmol) in 15 mL of nitrogen-purged isopropyl alcohol was added, and the mixture was stirred at 90 °C for 19 hours. The resulting mixture was allowed to come 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 (EtAOC to EtOAc:EtOH 90:10) afforded 0.35 g (0.84 mmol, 78%) of 14 as a yellow paste.

$^1$H NMR: $\delta = 1.87$ (s, 6H), 2.18 (s, 6H), 6.40 (s, 2H), 6.66-6.84 (m, 2H), 7.04-7.11 (m, 2H), 7.38 (d, $J = 7.0$ Hz, 2H), 7.50 (dd, $J = 7.3$ Hz, 7.9 Hz, 2H), 7.86 (s, 1H), 7.92 (d, $J = 8.1$ Hz, 2H).
1,8-Bis(2'-methyl-4'-anilino)naphthalene (15)

To a solution of 1,8-bis(2'-methyl-4'-acetamidophenyl)naphthalene, 14, (0.27 g, 0.64 mmol) in 8 mL of ethanol, 3M HCl (4.3 mL, 12.7 mmol) was added and the mixture was stirred at 95 °C for 24 hours. The resulting mixture was allowed to come to room temperature, basified with a stoichiometric amount of 28% NH₄OH, and extracted with CH₂Cl₂. The combined organic layers were dried over MgSO₄ and concentrated in vacuo. Purification by flash chromatography on silica gel (EtOAc:EtOH 97.5:2.5) afforded 0.20 g (0.59 mmol, 92%) of 15 as a yellowish powder.

¹H NMR: δ = 1.90 (s, 6H), 3.18 (s, 4H), 6.20–6.90 (m, 6H), 7.39 (dd, J = 1.2 Hz, 7.0 Hz, 2H), 7.49 (dd, J = 7.2 Hz, 8.0 Hz, 2H), 7.87 (dd, J = 1.2 Hz, 8.1 Hz, 2H).

1,8-Bis(2’-methyl-4’-acetamido-5’-bromophenyl)naphthalene (16)

To a solution of 14 (0.28 g, 0.66 mmol) in 10 mL of chloroform, bromine (0.12 mL, 2.28 mmol) in 5 mL of chloroform was added dropwise over 30 minutes, and the mixture was stirred at room temperature for 48 hours. It was then quenched with 10% Na₂S₂O₃, basified with 2M KOH, and extracted with CH₂Cl₂. The combined organic layers were dried over MgSO₄ and concentrated in vacuo. Purification by flash chromatography on silica gel (EtOAc:CH₂Cl₂ 1:5) afforded 0.30 g (0.51 mmol, 77%) of 16 as a white solid.

¹H NMR: δ = 1.96 (s, 6H), 2.21 (s, 6H), 7.03 (s, 2H), 7.18 (d, J = 7.0 Hz, 2H), 7.50 (dd, J = 7.0 Hz, 8.0 Hz, 4H), 7.94 (d, J = 8.0 Hz, 2H).
1,8-Bis(2’-methyl-4’-anilino-5’-bromophenyl)naphthalene (17)

To a solution of 1,8-bis(2’-methyl-4’-acetamidophenyl)naphthalene, 16, (0.27 g, 0.64 mmol) in 8 mL of ethanol, 3M HCl (4.3 mL, 12.7 mmol) was added and the mixture was stirred at 95 °C for 24 hours. The resulting mixture was allowed to come to room temperature, basified with a stoichiometric amount of 28% NH₄OH, and extracted with CH₂Cl₂. The combined organic layers were dried over MgSO₄ and concentrated in vacuo. Purification by flash chromatography on silica gel (EtOAc:EtOH 97.5:2.5) afforded 0.20 g (0.59 mmol, 92%) of 17 as a white powder.

¹H NMR: δ = 1.80 (s, 6H), 3.82 (s, 4H), 6.43 (s, 2H), 6.83 (s, 2H), 7.17 (dd, J = 1.1 Hz, 7.0 Hz, 2H), 7.46 (dd, J = 7.0 Hz, 8.0 Hz, 2H), 7.88 (dd, J = 1.1 Hz, 8.0 Hz, 2H).

1,8-Bis(2’-methyl-4’-methoxy-5’-bromophenyl)naphthalene (18)

To a solution of 9 (0.20 g, 0.54 mmol) in 10 mL of DMF, N-bromosuccinimide (0.20 g, 1.14 mmol) was added in three portions over 30 minutes, and the mixture was stirred at 60 °C for 24 hours. It was then cooled to 0 °C, 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 (hexanes:CH₂Cl₂ 2:1) afforded 0.17 g (0.33 mmol, 60%) of 18 as a white solid.

¹H NMR: δ = 1.86 (s, 6H), 3.83 (s, 6H), 6.46 (s, 2H), 7.04 (s, 2H), 7.18 (d, J = 7.0 Hz, 2H), 7.50 (dd, J = 7.0 Hz, 8.0 Hz, 2H), 7.92 (d, J = 8.0 Hz, 2H). ¹³C NMR: δ = 20.8, 56.1, 108.0, 112.2, 125.3, 129.3, 130.4, 132.8, 135.9, 136.9, 137.8, 137.9, 155.2.
Monosubstituted 1,8-(Bisphenol)naphthalene (19)

A solution of 1,8-bis(2’-methyl-4’-methoxy-5’-bromophenyl)naphthalene (0.44 g, 0.84 mmol), 3,5-bis(trifluoromethyl)phenylboronic acid (0.22 g, 0.87 mmol), Pd(PPh₃)₄ (0.068 g, 0.059 mmol) and K₃PO₄, (0.36 g, 1.67 mmol) in 14 mL of toluene was stirred at 115 °C for 24 hours. The resulting mixture was allowed to cool to room temperature, quenched with water, extracted with CH₂Cl₂ and washed with brine. The combined organic layers were dried over MgSO₄ and concentrated in vacuo. Purification by flash chromatography on silica gel (CH₂Cl₂:hexanes 1:2) afforded 0.088 g (0.139 mmol, 16%) of 19 as a white solid, while 40% of starting material was recovered.

¹H NMR: δ = 1.67 (s, 3H), 1.96 (s, 3H), 3.69 (s, 3H), 3.80 (s, 3H), 6.30 (s, 1H), 6.65 (s, 1H), 6.86 (s, 1H), 7.11 (s, 1H), 7.15 (dd, J = 1.2 Hz, 6.8 1H), 7.25 (dd, J = 1.2Hz, 6.8 1H), 7.45-7.55 (m, 2H), 7.78 (bs, 1H), 7.89 (bs, 2), 7.94 (dd, J = 1.4 Hz, 1.7 Hz, 2H).
VI.4.2. Crystallization and X-Ray Diffraction

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.

A crystal of 1 was obtained by slow evaporation of a solution of 10.0 mg of 1 in 5 mL of CH₂Cl₂. Crystal structure data for 1: Formula C₃₆H₂₈O₂, M= 492.61, crystal dimensions 0.15 x 0.15 x 0.15 mm, monoclinic, space group P21/c, a = 11.3010 (23) Å, b = 11.8081 (24) Å, c = 19.1846 (40) Å, β = 96.897 (3), V = 2541.53 Å³, Z = 4, ρ_calc = 1.2872 g cm⁻³.

| Phenyl-phenyl [Å] (centroid to centroid) | 3.498 |
| O-O distance [Å] | 4.373 |
| Splaying angle between phenol planes [°] | 19.48 |
| Torsion angle [°] | 0.28 |
A crystal of 2 was obtained by slow evaporation of a solution of 10.0 mg of 2 in 5 mL of CH₂Cl₂. Crystal structure data for 2: Formula C₄₀H₂₄F₁₂O₂, M = 764.60, crystal dimensions 0.01 x 0.01 x 0.05 mm, monoclinic, space group C2/c, \( a = 19.6587 (37) \, \text{Å}, b = 24.5343 (46) \, \text{Å}, c = 8.2961 (16) \, \text{Å}, \beta = 107.758 (2), V = 3810.66 \, \text{Å}^3, \, Z = 4, \, \rho_{\text{calcd}} = 1.5387 \, \text{g cm}^{-3}.

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<td>Splaying angle between phenol planes [°]</td>
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</tr>
<tr>
<td>Torsion angle [°]</td>
<td>1.02</td>
</tr>
</tbody>
</table>
VI.5. References


VII. Stereocontrolled Photodimerization with Congested 1,8-Bis(4’-anilino)naphthalene Templates

VII.1. Introduction

The chiral pool of natural products contains numerous compounds having a cyclobutane ring including sugars, steroids and terpenes. In many cases, the cyclobutane motif has proven to play an important role for the biological activity of these compounds. For example, the antinociceptive potency of incarvillateine has been attributed to the tetrasubstituted cyclobutane core, since related compounds lacking this four-membered ring exhibit no activity (Figure VII.1).

Figure VII.1. Structures of pharmaceuticals and natural products displaying the cyclobutane motif. From left to right: an agonist of the mGluR5a receptor, agent for imaging brain tumors and incarvillateine, a potent analgesic.

Specifically, β-truxinic acid (1) and its derivatives have been demonstrated to possess significant anti-inflammatory activities against pain resulting from tissue injury, while the corresponding trans-cinnamic acid monomer (4) showed weak or no activity (Figure VII.2). Four-membered rings carrying phenyl, carboxyl or cyano groups such as 1 have

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been found to form selective inclusion complexes with an array of 168 uncharged species like methanol, acetonitrile and DMSO.\(^8\)

![Image of structures](image_url)

Figure VII.2. Structures of \(\beta\)-truxinic (1), \(\delta\)-truxinic (2), \(\alpha\)-truxillic (3) and \(\text{trans}\)-cinnamic acid (4).

These host-guest complexes can have several important applications as selective carriers for various substrates or in molecular machines, as discussed by Jean-Marie Lehn in his Nobel lecture.\(^9\) The cyclobutane ring may be an essential component of drugs and other chemicals as described above, but it is also a versatile intermediate in ring opening reactions, ring contractions, ring expansions to five, six, seven, eight or nine-membered rings, and most importantly in natural product synthesis.\(^10\) Enantiopure cyclobutane derivatives have also been used as chiral ligands in asymmetric catalytic reactions (Scheme VII.1).\(^11\)

![Image of reaction](image_url)

Scheme VII.1. Asymmetric allylic substitution using a cyclobutane bisphosphine ligand.

The four-membered ring is synthetically challenging partly because of the angle and torsional strains that can add up to 110.4 kJ/mol in unsubstituted cyclobutane.\(^12\) The introduction of substituents and functional groups to the ring increases the complexity of
the synthesis with the possibility for several different stereoisomers. Methods to prepare a
cyclobutane ring include the [2+2] cycloaddition of two olefins or one olefin and an
aromatic system, an enone, and a ketene. Other common strategies include the 1,4-
cyclization of disubstituted substrates such as δ-chloroesters through nucleophilic
substitutions, intramolecular Michael-aldol condensation, radical reactions or acyloin
condensations (Scheme VII.2). Alternatively, one can utilize the ring expansion of
cyclopropylcarbinyl precursors, or the ring contraction of cyclopentane and furanose
derivatives to generate a substituted four-membered ring.

Scheme VII.2. Krohn’s intramolecular cyclization of a dithianyl epoxide.

Some of these transformations proceed with high enantioselectivity. Diastereoselective
reactions of prochiral cyclobutane enolates with activated pyridinium salts, kinetic
resolution of racemic cyclobutanes or conventional resolution of racemates have also
been reported (Scheme VII.3).

Scheme VII.3. Diastereoselective cyclobutane synthesis with a chiral pyridinium salt.
One can divide dimerization reactions of olefinic compounds to cyclobutane derivatives into template-assisted and non-assisted methodologies. The latter involves systems in which a crystal lattice is anticipated to provide the proper packing for a successful photoreaction, as described further below. The dimerization of olefinic compounds to cyclobutane derivatives in solution faces many problems including isomerization of the starting materials and the formation of a complex mixture of regio- and stereoisomers resulting from the large number of possible relative orientations. Regarding template-assisted methods, one can envisage either a covalent or non-covalent approach to preorganize the substrates. The advance of supramolecular chemistry has fueled the development of intriguing templates that utilize non-covalent interactions such as hydrogen bonding, halogen bonding, \( \pi-\pi \) interactions, cation-\( \pi \) interactions, and transition metal coordination to affect the relative orientation of \( \alpha,\beta \)-unsaturated compounds.\(^{24}\) The adducts that result from non-covalent preorganization are generally irradiated in the solid state, while those realized through covalent attachments can also be used in solution.

**VII.2. Non-assisted Approach**

Schmidt and coworkers have investigated \([2+2]\) photocycloadditions of \textit{trans}-cinnamic acids in the crystalline state and showed that these reactions are controlled by the packing arrangement of the molecules.\(^{25}\) Empirically developed topochemical rules state that neighboring double bonds ought to lie in parallel planes, with a common direction and a separation of less than 4.2 Å. It was postulated that under these circumstances, dimerization occurs with a minimum of molecular motion. Interestingly,
trans-cinnamic acid crystallizes in α-, β- and γ-forms, and photoirradiation of these polymorphs produces different isomers (Scheme VII.4).

Scheme VII.4. Dimerization of trans-cinnamic acid in the solid state and cis/trans-isomerization in solution.

It is noteworthy that many exceptions to the topochemical rules outlined by Schmidt have been found. A crystal consisting of p-formylcinnamic acid monomers separated by more than 4.825 Å has been shown to quantitatively form the corresponding dimer. Several reports on unreactive crystals showing suitable distances and arrangements between monomers have occurred in the literature. For instance, trans,trans-muconic acid forms a crystal lattice that satisfies all the above mentioned topological requirements for a [2+2]cycloaddition (separation of parallel double bonds of 3.737 Å, Figure VII.3). However, UV irradiation of the trans,trans-muconic acid crystals has been found to give the divinyl substituted cyclobutanedicarboxylic acid (5) and various amounts of oligomers (Scheme VII.5). Upon formation of 5, the vinylic double bonds are situated further apart than in the original trans,trans-muconic acid crystal, and thus cannot undergo another cycloaddition.
Figure VII.3. Crystal structure of *trans,trans*-muconic acid.\textsuperscript{30} Copyrights reserved by IUCr.

Scheme VII.5. Products obtained from irradiation of crystals of *trans,trans*-muconic acid.

The principles developed by Schmidt and coworkers still have value for predicting whether a dimerization might occur. In any case, a major challenge is to accomplish the desired crystal packing. The architecture of crystals is a result of a delicate balance between several intermolecular forces and there is no foolproof systematic approach for tailored crystal packing. Moreover, some suitably packed crystals are reactive and others are not.\textsuperscript{31} Alternatively, templates can be used to extend the scope of [2+2]photodimerizations to substrates that (a) do not crystallize with the desired geometry or (b) that do not react in the solid state as expected.
VII.3. Template-assisted Approach

VII.3.1. Non-covalent Preorganization

Supramolecular self-assembly through well-defined non-covalent interactions between complementary building blocks has been exploited to preorganize olefinic substrates for subsequent cycloaddition. Olefinic substrate alignment has been controlled by inclusion in cucurbiturils, cyclodextrins and organometallic hosts, association with biomolecules, in micellar environments, self-assembly by complementary cation-π-interactions, rotaxane formation, or with small molecular templates. Ito et al. have utilized several dicarboxylic acids to ensure the orientational control of two trans-cinnamamide molecules via hydrogen-bonding for their subsequent dimerization. The use of oxalic acid as template provided access to the cis,trans,cis-stereoisomer in 86% yield (not isolated) and 97% de. Several cases of photochemical and γ-radiation-induced topochemical polymerization of unsaturated ammonium carboxylates are also known. Ammonia or imidazole salts of trans-cinnamic acid have been reported to produce a crystal lattice that gives truxinic acids upon UV irradiation with high stereoselectivity. Nishikubo et al. derivatized trans-cinnamic acid to a p-nitrophenyl ester which was crystallized and then irradiated for six hours in a hexane suspension at 30°C; after hydrolysis, β-truxinic acid was obtained in 99% yield. An example of covalent bond formation between substrate and template followed by solid-state irradiation has been presented by Ito et al. N-Cinnamoyl-substituted dopamine gave a single stereoisomer with 66% conversion (Scheme VII.6).
Scheme VII.6. Ito’s stereoselective synthesis of a cyclobutane derivative using dopamine.

In another case reported by Feldman et al., hydrogen bonding enforced packing in the crystal ensures proper orientation and dimerization after covalent attachment of the olefinic portion to scaffold (6) (Scheme VII.7). A drawback of this approach is that the template cannot be recovered since it remains incorporated in the final structure.


MacGillivray et al. have presented several examples of solid-state [2+2]photodimerizations of hydrogen-bonded self-assemblies. The cocrystallization of trans-1,2-bis(4-pyridyl)ethylene and resorcinol resulted in an intermolecular olefin separation of ∼4 Å which quantitatively yielded one stereoisomer upon irradiation (Scheme VII.8).
Scheme VII.8. MacGillivray’s use of a resorcinol template for the preorganization of trans-1,2-bis(4-pyridyl)ethylene and subsequent photodimerization.

The introduction of a modified resorcinol template allowed the proper packing of all-trans-poly-m-enes (m=2, 3), and the corresponding ladderanes were obtained stereoselectively after 120 and 78 hours respectively in 85% yield (Scheme VII.9).\(^{45}\) Compared to unassisted trans,trans-muconic acid dimerization attempts described earlier (Chapter VII.2.), strong O-H···N hydrogen bonds will force the newly formed vinylic groups from the first photoaddition into the proper orientation for a second photoaddition to the ladderane. A review describing the use of several small molecules to direct the packing of olefinic substrates in the solid for dimerization has recently appeared.\(^{46}\)

Scheme VII.9. Preorganization of trans-poly-m-enes with a 5-methoxyresorcinol template and subsequent photodimerization.

1,8-Dipyridylnapthalene (7) has been used by Wolf et al. to preorganize several unsaturated dicarboxylic acids.\(^{47}\) This template can be synthesized in a single step through Stille coupling of 1,8-dibromonaphthalene and 4-(tributylstannyl)pyridine with a yield of 76% (Scheme VII.10). Alternatively, Stille coupling using 1,8-diiodonaphthalene
gives 7 in 42% yield, while Suzuki coupling with 4-pyridylboronic acid and either 1,8-dibromo- or diiodonaphthalene were unsuccessful.

Scheme VII.10. Synthesis of the 1,8-dipyridynaphthalene 7.

Cocrystallization of 7 and fumaric acid resulted in the formation of tetrameric arrangements that are stabilized by eight hydrogen bonds and enforced by face-to-face pyridyl π-stacking (Figure VII.4). The resulting cocrystal displayed parallel packing of the substrates with a separation distance of less than 4.2 Å. Photochemical irradiation gave quantitative amounts of cis,trans,cis-cyclobutanetetracarboxylic acid, and the template was fully recovered by extraction with dichloromethane.

Figure VII.4. Crystal structures showing the preorganization of fumaric acid with 7, and the single stereoisomer obtained after irradiation.47
To examine the scope of this template, other unsaturated dicarboxylic acids were investigated. The structures of several unsaturated mono- and dicarboxylic acid and amide substrates screened for preorganization and subsequent photodimerization with template 7 are shown in Figure VII.5.

![Chemical structures](image)

Figure VII.5. Structures of the unsaturated substrates screened for cocrystallization with 7.

4,4'-Stilbenedicarboxylic acid and fumaramide were insoluble in all of the common organic solvents screened including alcohols, DMF, ACN and DMSO, while others like cis,cis-muconic acid and dihydroxy fumaric acid precipitated upon mixing with 7. A cocrystal of 7 and mesaconic acid was obtained through slow evaporation of an equimolar mixture in a tetrahydrofuran/methanol (1:1) solution. While each pyridyl ring of 7 showed hydrogen bonding with one diacid molecule, the substrate arrangement did not obey any of the topochemical rules developed by Schmidt and thus showed no desirable overlap between the olefinic bonds (Figure VII.6).
Under the same conditions, a cocrystal of 7 and \textit{trans,trans}-muconic acid was obtained. Crystallographic analysis revealed three different packing arrangements of proximate acid molecules of which only one seemed suitable for two [2+2]photodimerizations to a [3]-ladderane. This eight hydrogen bond-four component cocrystal exhibits enforced face-to-face pyridyl $\pi$-stacking and parallel packing of the olefinic substrates separated by 3.652-3.757 Å (Figure VII.7).
Two other packing modes with a nonlinear topology were also present; the two olefinic pairs obeyed the distance requirement, and lay in parallel planes. But the substrates were not collinear and had crossing angles of up to 76° (Figure VII.8). We realize that this does not necessarily disqualify the systems for dimerization since an angle of nearly 56° between reacting double bonds has previously been reported.48

![Figure VII.8. Packing modes in the cocrystal of trans,trans-muconic acid with 7 that do not obey the topochemical requirements postulated by Schmidt.](image)

However, numerous attempts at the photodimerization of trans,trans-muconic acid cocrystals did not produce the desired compound. A close look revealed a subtle but important difference between the expected and observed packing motifs (Scheme VII.11). It was anticipated that the cocrystal would be stabilized by a set of four OH⋯N and parallel CH⋯O hydrogen bonds. While the first interaction occurred as predicted, the weaker CH⋯O bond involved o-hydrogens on either side of the template, thus resulting in a crossed orientation of the substrates. Following irradiation, NMR analysis of the product mixture suggested the formation of a wide range of different oligomers. This can be attributed to the fact that separations of adjacent tetrameric assemblies were less than 4.2 Å in some cases. Neither the divinyl substituted cyclobutanedicarboxylic acid (5) nor its Cope rearrangement product were detected.
Scheme VII.11. Expected (left) and observed (right) packings of trans,trans-muconic acid with 7.

Another cocrystal was obtained by slow evaporation of an ethanol solution containing equimolar amounts of template 7 and trans-cinnamic acid 4. We found that only one pyridyl ring of 7 would participate in hydrogen bonding, resulting in an offset head-to-tail packing arrangement of the unsaturated acid molecules with essentially no double bond overlap (Figure VII.9).

Figure VII.9. Structure of the cocrystal of 7 and trans-cinnamic acid.
The cocrystallization experiments using 7 and trans-cinnamic, mesaconic or trans,trans-muconic acids clearly reveal an important limitation of the solid state approach. Despite the overall success with solid-state photodimerizations, the packing motif and the relative orientation of olefinic substrates in the presence of 7 or other templates remain difficult to control. As a result, the application spectrum of solid-state synthesis is often rather narrow and may not be extended to a wide range of substrates.

**VII.3.2. Covalent Bond Preorganization**

Preorganization through covalent bonds provides another way to force unsaturated substrates into proper orientation for cycloaddition in solution or in the solid state. A bis-stilbene macrocycle presented by Shimizu et al.\textsuperscript{49} reacts as expected both in solution and in the solid state (Scheme VII.12). Following a four-step attachment of the scaffold to cis-stilbene (8) (8% overall yield), the unprotected urea macrocycle undergoes cis/trans-photoisomerization and then an intramolecular [2+2]cycloaddition to afford a single product (9) in quantitative amounts. The urea scaffold remains a part of the final structure.
Scheme VII.12. Shimizu’s synthesis of 9 through the insertion of urea groups.

Akabori et al. showed that the incorporation of the olefinic bonds into diazacrown ethers allows stereoselective intramolecular [2+2] photocycloadditon in solution but not in the solid state.50 Yuasa et al. employed a sugar template to preorganize unsaturated carboxylic acid substrates, but irradiation in solution was accompanied by cis/trans-isomerization and resulted in the formation of several cyclobutane isomers (Scheme VII.13).51

Scheme VII.13. Yuasa’s synthesis of a cyclobutane derivative using a sugar template.
A prime example of a template-controlled stereoselective photodimerization in solution has been presented by Hopf and coworkers.\textsuperscript{52} They prepared 4,15-diamino[2.2]paracyclophane, 10, from [2.2]paracyclophane in eight steps with 14% overall yield. Diamide formation with cinnamoyl chloride then allowed photochemical cycloaddition to the corresponding cyclobutane 11 with 76% yield. Acidic cleavage gave β-truxinic acid, 1, and the free template in almost quantitative amounts (Scheme VII.14).


This result encouraged us to develop a rigid template for the in-solution photoaddition of covalently attached substrates that would overcome the limitations of 7 and provide synthetic access to polysubstituted cyclobutanes other than 1. We rationalized that a template should exhibit two parallel functionalities having a separation of approximately 4.0 Å, combined with a certain degree of rigidity and flexibility. In solution, the strict distance requirement of <4.2 Å in the solid state becomes less important due to enhanced molecular flexibility. Based on our experience with the structure and conformational flexibility of 1,8-diarylnaphthalenes,\textsuperscript{53} we initially investigated the use of 1,8-bis(4’-hydroxyphenyl)naphthalene (12) and 1,8-bis(4’-methoxycarbonylphenyl)naphthalene (15) templates for the preorganization of olefinic groups. The 1,8-bis(4’-hydroxyphenyl)naphthalene template (12) was successfully synthesized in two high
yielding steps and then derivatized to the corresponding diallyl ether (13) and diacyloyl ester (14) (Scheme VII.15). While 13 was photostable upon UV irradiation in acetone, 14 showed photochemical Fries rearrangement rather than [2+2]cycloaddition. Efforts to grow suitable crystals of compounds 13 and 14 for their dimerization in the solid state were not successful. Also, attempts to grow cocrystals of 12 and fumaric, mesaconic and trans,trans-muconic acids yielded only crystals of the template (Figure VII.10).

Scheme VII.15. Synthesis of 1,8-bis(4’-hydroxyphenyl)naphthalene 12, and derivatives 13 and 14.

Figure VII.10. Different views of the crystal structure of template 12.

To avoid Fries rearrangement, 1,8-bis(4’-methoxycarbonylphenyl)naphthalene template 15 was synthesized in one step and then converted to the corresponding 1,8-bis(4’-N-allylbenzamide)naphthalene 16. However, 16 was stable to UV irradiation in several solvents (dimethyl sulfoxide, acetonitrile and chloroform).

We then decided to prepare 1,8-bis(3’-methyl-4’-anilino)naphthalene (22) (Scheme VII.17). Suzuki coupling of boronic acid 17 and 1,8-dibromonaphthalene gave 1,8-bis(3’-methyl-4’-methoxyphenyl)naphthalene, 18, in 96% yield. Deprotection with boron tribromide and treatment of 19 with trifluoromethanesulfonic anhydride provided 20 in almost quantitative amounts. We first used 20 to make template 22 via palladium catalyzed amidation and subsequent hydrolysis of 1,8-bis(3’-methyl-4’-acetamidophenyl)naphthalene, 21. As a result, 22 was prepared in 5 steps from 17 with an overall yield of 65%. Attachment of two cinnamoyl units followed by photodimerization of 1,8-bis(3’-methyl-4’-cinnamamidophenyl)naphthalene, 23, and cleavage of the cycloadduct from the template gave β-truxinic acid, 1, in high yields while 22 was quantitatively recovered. The [2+2]photodimerization apparently proceeds with excellent stereocontrol, and the formation of configurational isomers of 1 was not observed. We then realized that trans-cinnamamidine can be used to prepare 23 directly from 20 in 90% yield, which eliminates two steps and further enhances the efficiency of the template-assisted stereoselective synthesis of 1.
Scheme VII.17. Synthesis of $\beta$-truxinic acid $1$ via template $22$. 

A closer look at the cycloaddition product by NMR analysis revealed the presence of two diastereomers that apparently vary by the orientation of the methyl groups in the template. We were able to separate the syn- and anti-isomers of $24$ by chromatography and found that both form the desired product upon acidic cleavage. Slow evaporation of a solution of $24$ in chloroform gave single crystals of the anti-isomer suitable for X-ray diffraction. Crystallographic analysis proved that $24$ has a cis,trans,cis-cyclobutane ring and opposite orientation of the carbonyl groups of the neighboring amide functionalities (Figure VII.11). Both NMR and X-ray analysis suggest that the bridging of the cofacial 2-methylaniline rings in $24$ by the cyclobutane moiety generates a congested framework that does not show rotation about the aryl-aryl bonds, thus giving rise to syn/anti-atropisomers that can be separated at room temperature.
Originally, we assumed that template 22 and its diamide analogue 23 would favorably populate the anti-conformation and thus generate the C$_2$-symmetric δ-truxinic acid 2 (Figure VII.2). However, crystallographic analysis of 24 and the exclusive formation of β-truxinic 1 after hydrolysis of the photodimer suggested that the presence of the methyl groups in the template does not affect the stereochemical outcome of the cycloaddition. We therefore decided to prepare 1,8-bis(4’-anilino)naphthalene, 27, in two high yielding steps from 4-acetamidophenylboronic acid 25 (Scheme VII.18). This readily available template then gave access to cyclobutane 1 in just 3 steps with an overall yield of 69%. We then applied our template-assisted cycloaddition strategy in the stereoselective synthesis of cis,trans,cis-3,4-bis(3,4-dimethylphenyl)cyclobutane-1,2-dicarboxylic acid, 32. Coupling of 27 and (E)-3-(3,4-dimethylphenyl)acrylic acid in the presence of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) gave 1,8-bis(4’-(3,4-
dimethylcinnamidophenyl)naphthalene, 30, in 80% yield. As expected, photochemical cycloaddition and hydrolysis with concentrated HCl gave cyclobutane-1,2-dicarboxylic acid 32 in excellent yields. The stereochemistry of 1 and 32 was confirmed by NMR comparison with the literature,\textsuperscript{51} and template 27 was quantitatively recovered by acidic hydrolysis.

Scheme VII.18. Synthesis of 1 and 32 using template 27.

In order to assess the importance of the 4’-anilino rings on the naphthalene, 1,8-diaminonaphthalene 33 was derivatized to the corresponding trans-cinnamoyl diamide 34 in 50% yield (Scheme VII.19). The subsequent dimerization to the cyclobutane adduct 35 proceeded only in 6% yield indicating the importance of a balance between conformational flexibility and rigidity of the template.
Scheme VII.19. Stereoselective dimerization of cinnamic acid with template 33.

Finally, we successfully synthesized diamides of 27 using trans-acryloyl chloride, 4-vinylbenzoic acid, 2- and 9-anthracenecarboxylic acid, and 3-(4-biphenyl)acrylic acid. However, these compounds did not undergo the expected cycloadditions under similar irradiation conditions in solution.

VII.4. Conclusions

1,8-Dipyridynaphthalene (7) can be used to preorganize fumaric acid and provide quantitative amounts of cis,trans,cis-cyclobutanetetracarboxylic acid via [2+2]photoaddition. Extensive substrate screening and crystallographic analysis of cocrystals formed by 7 and trans-cinnamic, mesaconic or trans,trans-muconic acids clearly revealed major limitations of this non-covalent solid-state synthesis approach. First, the majority of olefinic substrates tested did not form a cocrystal with template 7. Second, most cocrystals obtained were not suitable for photochemical cyclobutane synthesis. In an effort to circumvent these problems, a series of templates for the covalent attachment and preorganization of olefinic substrates was synthesized. Immobilization of two trans-cinnamic acid molecules to 1,8-bis(3’-methyl-4’-anilino)naphthalene 22 provided a means for a stereoselective photodimerization with high yield. Through the careful examination of stable diastereomers, the template design was simplified to 1,8-
bis(4'-anilino)naphthalene, 27. The template structure affords two cofacial aniline rings that favor a proximate, parallel arrangement of covalently attached cinnamoyl units. The use of template 27 effectively biased the [2+2]dimerization of trans-cinnamic and trans-3-(3,4-dimethylphenyl)acrylic acids towards one of several possible stereoisomers. This [2+2]cycloaddition proceeds with high yield and excellent stereoselectivity and the \textit{cis,trans,cis-cyclobutane-1,2-dicarboxylic acid} formed is readily cleaved by acidic hydrolysis which also allows quantitative recovery of the template. This approach overcomes limitations experienced with 1,8-bis(4’-pyridyl)naphthalene, and provides a new venue for stereoselective dimerization of olefinic substrates.

\section*{VII.5. Experimental Section}
\subsection*{VII.5.1. Synthetic Procedures}

All reagents and solvents were used without further purification. Reactions were carried out under nitrogen atmosphere and under anhydrous conditions. Products were purified by flash chromatography on SiO$_2$ (particle size 0.032-0.063 mm). NMR spectra were obtained at 400 MHz ($^1$H NMR) and 100 MHz ($^{13}$C NMR) using CDCl$_3$ as solvent unless otherwise specified. Chemical shifts are reported in ppm relative to TMS. UV irradiation experiments were conducted using a 400 W Mercury lamp positioned 1 cm away form the quartz reaction vessel. A fan was used to keep the solution at room temperature.
1,8-Bis(4’-pyridyl)naphthalene (7)

1,8-Diiodonaphthalene (0.73 g, 1.83 mmol), 4-trimethylstannylpyridine (2.6 g, 7.30 mmol), tetrakis(triphenylphosphane)palladium(0) (527 mg, 25 mol%) and copper oxide (0.29 g, 3.65 mmol) were dissolved in 4 mL of anhydrous DMF and refluxed for 18 hours. The reaction mixture was allowed to cool to room temperature, poured into 10% NH₄OH, and extracted with CH₂Cl₂. The combined organic layers were washed with water, dried over MgSO₄ and solvents were removed in vacuo. Purification by flash chromatography on silica gel (ethyl acetate:ethanol 9:1) afforded 0.39 g (1.39 mmol, 76%) of 1 as a yellow solid. \(^1\)H NMR: \(\delta = 6.93\) (dd, \(J = 1.7\) Hz, \(J = 4.4\) Hz, 4H), 7.43 (dd, \(J = 1.1\) Hz, \(J = 7.2\) Hz, 2H), 7.62 (dd, \(J = 1.1\) Hz, \(J = 8.2\) Hz, 2H), 8.04 (dd, \(J = 7.2\) Hz, \(J = 8.2\) Hz, 2H), 8.23 (dd, \(J = 1.7\) Hz, \(J = 4.4\) Hz, 4H). \(^1\)C NMR: \(\delta = 14.4, 125.5, 128.0, 129.7, 131.1, 135.2, 137.0, 148.8, 150.3\).

1,8-Bis(4’-allyloxyphenyl)naphthalene (13)

1,8-Bis(4’-hydroxyphenyl)naphthalene (12) (0.40 g, 1.29 mmol), allyl bromide (0.28 mL, 3.2 mmol) and potassium carbonate (1.3 g, 9.65 mmol) were stirred in 4 mL of acetone at reflux for 14 hours. The resulting mixture was quenched with water and extracted with dichloromethane. The combined organic layers were dried over MgSO₄ and concentrated in vacuo. The crude was then subjected to flash chromatography on silica gel (CH₂Cl₂:hexanes 1:1) to afford 0.41 g (1.06 mmol, 82%) of 13 as a white powder. \(^1\)H NMR: \(\delta = 4.41\) (d, \(J = 5.2\) Hz, 4H), 5.27 (dd, \(J = 1.2\) Hz, 10.5 Hz, 2H), 5.38 (dd, \(J = 1.2\) Hz, 17.3 Hz, 2H), 6.02 (m, 2H), 6.49 (d, \(J = 8.6\) Hz, 4H), 6.83 (d, \(J = 8.6\) Hz, 4H), 7.39 (d, \(J = 7.1\) Hz, 2H), 7.51 (dd, \(J = 7.1\) Hz, 8.2 Hz, 2H), 7.91 (d, \(J = 8.2\) Hz, 2H). \(^1\)C
NMR: δ 68.8, 113.6, 117.3, 125.0, 128.3, 129.6, 130.7, 130.8, 133.5, 135.5, 136.0, 140.1, 156.7.

1,8-Bis(4’-acryloylphenyl)naphthalene (14)

1,8-Bis(4’-hydroxyphenyl)naphthalene (12) (0.07 g, 0.22 mmol), acryloyl chloride (0.22 mL, 2.6 mmol) and triethylamine (0.16 mL, 1.1 mmol) were stirred in 2 mL of toluene at 60 °C for 20 hours. The resulting mixture was quenched with water and extracted with dichloromethane. The combined organic layers were dried over MgSO₄ and concentrated in vacuo. The crude was then subjected to flash chromatography on silica gel (CH₂Cl₂:hexanes 3:1) to afford 0.06 g (0.14 mmol, 64%) of 14 as a white powder.

¹H NMR: δ = 5.97 (d, J = 10.4 Hz, 2H), 6.30 (dd, J = 10.4 Hz, 17.3 Hz, 2H), 6.56 (d, J = 17.3 Hz, 2H), 6.77 (d, J = 8.4 Hz, 4H), 6.96 (d, J = 8.4 Hz, 4H), 7.42 (d, J = 7.0 Hz, 2H), 7.55 (dd, J = 7.0 Hz, 8.1 Hz, 2H), 7.96 (d, J = 8.1 Hz, 2H).

1,8-Bis(4’-methoxycarbonylphenyl)naphthalene (15)

A solution of 1,8-diiodonaphthalene, (0.60 g, 1.5 mmol), 4-methoxycarbonylphenylboronic acid, (0.68 g, 3.8 mmol), Pd(PPh₃)₄ (0.43 g, 0.38 mmol) and Cs₂CO₃, (1.97 g, 6.1 mmol) in 40 mL of toluene was stirred at reflux for 18 hours. The resulting mixture was allowed to come 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 (hexanes:CH₂Cl₂ 1:1) afforded 0.53 g (1.3 mmol, 88%) of 15 as an off-white solid.
H NMR: $\delta = 3.86$ (s, 6H), 7.13 (d, $J = 8.2$ Hz, 4H), 7.43 (d, $J = 7.1$ Hz, 2H), 7.57 (m, 6H), 7.98 (d, $J = 8.2$ Hz, 2H).

**1,8-Bis(4'-N-allylbenzamide)naphthalene (16)**

A solution of 1,8-bis(4'-methoxycarbonylphenyl)naphthalene (15), (0.09 g, 0.24 mmol) and allyl amine (0.4 mL, 4.8 mmol) in 1.5 mL of DMF was stirred in a pressure vessel at 200 °C for 24 hours. The resulting mixture was allowed to come 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 (ethyl acetate:ethanol 9:1) afforded 0.03 g (0.067 mmol, 28%) of 16 as a white solid.

H NMR: $\delta = 4.03$ (m, 4H), 5.15 (dd, $J = 1.4$ Hz, 10.2 Hz, 1H), 5.20 (dd, $J = 1.4$ Hz, 17.2 Hz, 1H), 5.93 (m, 2H), 6.68 (m, 2H), 6.95 (d, $J = 8.1$ Hz, 4H), 7.20 (d, $J = 8.1$ Hz, 4H), 7.41 (d, $J = 7.2$ Hz, 2H), 7.56 (dd, $J = 7.2$ Hz, 8.2 Hz, 2H), 7.98 (d, $J = 8.2$ Hz, 2H).

**1,8-Bis(3'-methyl-4'-methoxyphenyl)naphthalene (18)**

A solution of 1,8-dibromonaphthalene, (1.20 g, 4.2 mmol), 3-methyl-4-methoxyphenylboronic acid, 17, (2.10 g, 12.7 mmol), Pd(PPh$_3$)$_4$ (0.74 g, 0.64 mmol) and K$_3$PO$_4$, (4.05 g, 19.1 mmol) in 40 mL of toluene was stirred at reflux for 24 hours. The resulting mixture was allowed to come 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 (hexanes:CH$_2$Cl$_2$ 3:1) afforded 1.50 g (4.1 mmol, 96%) of 18 as off-white crystals.
\(^1\)H NMR: \(\delta = 1.91 \text{ (s, 3H)}, 2.02 \text{ (s, 3H)}, 3.73 \text{ (s, 6H)}, 6.30-6.90 \text{ (m, 6H)}, 7.38 \text{ (dd, } J = 1.2 \text{ Hz, 7.0 Hz, 2H)}, 7.48 \text{ (dd, } J = 7.3 \text{ Hz, 7.9 Hz, 2H)}, 7.89 \text{ (dd, } J = 1.0 \text{ Hz, 8.0 Hz, 2H}). \(^{13}\)C NMR: \(\delta = 15.9, 55.3, 108.6, 108.9, 124.8, 124.9, 127.6, 127.9, 128.2, 130.3, 130.5, 132.4, 132.8, 135.4, 135.4, 135.4, 135.5, 140.4, 155.7.\) Anal. Calcd. for \(\text{C}_{26}\text{H}_{24}\text{O}_2\): C, 84.75; H, 6.57. Found: C, 84.74; H, 6.61.

**1,8-Bis(3'-methyl-4'-hydroxyphenyl)naphthalene (19)**

To a solution of 1,8-bis(3'-methyl-4'-methoxyphenyl)naphthalene, \(18\), (1.50 g, 4.1 mmol) in 40 mL of anhydrous \(\text{CH}_2\text{Cl}_2\) at 0 °C, \(\text{BBr}_3\) (24.4 mL, 24.4 mmol) was added dropwise and the mixture was stirred for six hours. The reaction was carefully quenched with isopropyl alcohol followed by addition of water and extraction with \(\text{CH}_2\text{Cl}_2\). The combined organic layers were dried over \(\text{MgSO}_4\) and concentrated in vacuo. Purification by flash chromatography on silica gel (\(\text{CH}_2\text{Cl}_2\):EtOAc 7:1) afforded 1.33 g of \(19\) (3.92 mmol, 97%) as a white solid.

\(^1\)H NMR: \(\delta = 1.98 \text{ (s, 3H)}, 2.10 \text{ (s, 3H)}, 4.95 \text{ (s, 2H)}, 6.35-6.90 \text{ (m, 6H)}, 7.39 \text{ (dd, } J = 1.3 \text{ Hz, 7.0 Hz, 2H)}, 7.51 \text{ (dd, } J = 7.1 \text{ Hz, 8.1 Hz, 2H)}, 7.91 \text{ (dd, } J = 1.3 \text{ Hz, 8.2 Hz, 2H}). \(^{13}\)C NMR: \(\delta = 15.44, 15.61, 113.3, 113.9, 121.8, 122.0, 125.0, 127.8, 128.3, 129.7, 130.4, 132.6, 132.8, 135.4, 136.1, 140.1, 151.6.\) Anal. Calcd. for \(\text{C}_{24}\text{H}_{20}\text{O}_2\): C, 84.68; H, 5.92. Found: C, 84.69; H, 5.92.

**1,8-Bis(3'-methyl-4'-trifluoromethanesulfonatophenyl)naphthalene (20)**

To a solution of 1,8-bis(3'-methyl-4'-hydroxyphenyl)naphthalene, \(19\), (1.33 g, 3.9 mmol) and triethylamine (2.2 mL, 15.7 mmol) in 25 mL of toluene, trifluoromethanesulfonic
anhydride (6.6 mL, 39.2 mmol) was added at 0 °C. The temperature was gradually increased to 95 °C over a period of one hour, and the reaction mixture was then allowed to stir for 14 hours. The mixture was cooled 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 (hexanes:CH₂Cl₂ 4:1) afforded 2.30 g of 20 (3.8 mmol, 98%) as a yellow oil.

¹H NMR: δ = 2.09 (s, 3H), 2.18 (s, 3H), 6.70-7.00 (m, 6H), 7.34 (dd, J = 1.1 Hz, 7.1 Hz, 2H), 7.52 (dd, J = 7.2 Hz, 8.1 Hz, 2H), 7.98 (dd, J = 1.1 Hz, 8.2 Hz, 2H). ¹³C NMR: δ = 15.8, 16.0, 118.5 (q, J_C-F = 320.0 Hz), 120.0, 123.3, 125.3, 127.8, 128.5, 128.8, 129.2, 129.3, 129.5, 131.1, 133.1, 133.5, 135.3, 137.9, 143.0, 146.5. Anal. Calcd. for C₂₆H₁₈F₆O₆S₂: C, 51.66; H, 3.00. Found: C, 51.51; H, 2.98.

1,8-Bis(3'-methyl-4'-acetamidophenyl)naphthalene (21)

To acetamide (0.26 g, 4.4 mmol), tris(dibenzylideneacetone)dipalladium (0.20 g, 0.22 mmol), potassium phosphate (0.69 g, 3.3 mmol) and 2-di-tert-butylphosphino-2',4',6'-triisopropylbiphenyl (0.46 mg, 1.1 mmol), a solution of 20 (0.65 g, 1.1 mmol) in 15 mL of nitrogen-purged isopropyl alcohol was added, and the mixture was stirred at 90 °C for 19 hours. The resulting mixture was allowed to come 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 (EtAOc to EtOAc:EtOH 90:10) afforded 0.35 g (0.84 mmol, 78%) of 21 as a yellow paste. This material was used in the following step without further purification.
$^1$H NMR: $\delta = 1.87$ (s, 3H), 1.97 (s, 3H), 2.15 (s, 6H), 6.40 (s, 1H), 6.66-6.84 (m, 2H), 7.04-7.11 (m, 2H), 7.38 (d, $J = 7.0$ Hz, 2H), 7.50 (dd, $J = 7.3$ Hz, 7.9 Hz, 2H), 7.70 (s, 1H), 7.86 (s, 1H), 7.92 (d, $J = 8.1$ Hz, 2H). $^{13}$C NMR: $\delta = 17.5, 17.9, 23.6, 23.7, 124.6, 125.1, 125.4, 126.6, 127.5, 128.7, 129.4, 129.5, 130.4, 131.1, 132.2, 132.4, 132.6, 133.0, 133.0, 135.3, 135.4, 139.7, 141.0, 141.4, 169.3.

1,8-Bis(3'-methyl-4'-anilino)naphthalene (22)

To a solution of 1,8-bis(3'-methyl-4'-acetaminophenyl)naphthalene, 21, (0.27 g, 0.64 mmol) in 8 mL of ethanol, 3M HCl (4.3 mL, 12.7 mmol) was added and the mixture was stirred at 95 °C for 24 hours. The resulting mixture was allowed to come to room temperature, basified with a stoichiometric amount of 28% NH$_4$OH, 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 (EtOAc:EtOH 97.5:2.5) afforded 0.20 g (0.59 mmol, 92%) of 22 as a yellow powder.

$^1$H NMR: $\delta = 1.85$ (s, 3H), 1.98 (s, 3H), 3.18 (s, 4H), 6.20-6.90 (m, 6H), 7.39 (dd, $J = 1.2$ Hz, 7.0 Hz, 2H), 7.49 (dd, $J = 7.2$ Hz, 8.0 Hz, 2H), 7.87 (dd, $J = 1.2$ Hz, 8.1 Hz, 2H). $^{13}$C NMR: $\delta = 17.1, 17.7, 113.4, 114.1, 120.8, 124.9, 126.5, 127.9, 129.7, 130.3, 132.1, 134.2, 135.5, 140.8, 142.0. Anal. Calcd. for C$_{24}$H$_{22}$N$_2$: C, 85.17; H, 6.55; N, 8.28. Found: C, 85.08; H, 7.13; N, 7.87.

1,8-Bis(3'-methyl-4'-cinnamamidophenyl)naphthalene (23)

A) From 20: To trans-cinnamamide (0.75 g, 5.1 mmol), tris(dibenzylideneacetone)dipalladium (0.22 g, 0.24 mmol), potassium phosphate (0.81 g,
3.82 mmol) and 2-di-tert-butylphosphino-2’,4’,6’-triisopropylbiphenyl (0.54 mg, 1.3 mmol), a solution of 20 (0.77 g, 1.3 mmol) in 35 mL of nitrogen-purged isopropyl alcohol was added, and the mixture was stirred at 90 °C for 19 hours. The resulting mixture was allowed to come to room temperature, quenched with water and extracted with THF. The combined organic layers were dried over MgSO₄ and concentrated in vacuo. The material was suspended in 10 mL of CH₂Cl₂ and filtered to isolate the precipitate (0.39 g, 0.65 mmol). The filtrate was subjected to flash chromatography on silica gel (CH₂Cl₂:EtOAc 15:1) to afford another 0.30 g (0.50 mmol, 40%) of 23 as a white powder, which was combined with the precipitate to give a total of 0.69 g (1.15 mmol, 90%).

B) From 22: To 22 (0.20 g, 0.59 mmol) in 18 mL of THF was added a solution of cinnamoyl chloride (0.24 g, 1.4 mmol) in 5 mL of THF at 0 °C, and allowed to stir for 24 hours at room temperature. The resulting mixture was quenched with 1 M NaOH and extracted with THF. The combined organic layers were dried over MgSO₄ and concentrated in vacuo. The residue was suspended in 10 mL of CH₂Cl₂ and filtered to isolate the precipitate (0.22 g, 0.38 mmol). The filtrate was then subjected to flash chromatography on silica gel (CH₂Cl₂:EtOAc 95:5) to afford another 0.11 g (0.17 mmol, 29%) of 23 as a white powder, which was combined with the precipitate to give a total of 0.33 g (0.55 mmol, 94%).

¹H NMR: δ = 2.02 (s, 3.7H), 2.16 (s, 2.3H), 6.47 (s, 1H), 6.60-6.85 (m, 1H), 6.95 (d, J = 8.0 Hz, 1H), 7.13 (d, J = 8.1 Hz, 1H), 7.20-7.58 (m, 16H), 7.70 (s, 1H), 7.78 (d, J = 6.6, 1H), 7.82 (d, J = 6.6, 1H), 7.95 (d, J = 8.0, 2H). ¹³C NMR: δ = 17.7, 18.1, 121.2, 123.9, 125.1, 126.7, 127.6, 127.9, 128.7, 128.8, 128.9, 129.5, 130.3, 130.5, 132.3, 132.7, 132.9,
133.0, 134.7, 134.8, 135.4, 139.8, 140.8, 141.4, 141.8, 164.8. Anal. Calcd. for C₄₂H₃₄N₂O₂: C, 84.25; H, 5.72; N, 4.68. Found: C, 84.43; H, 6.07; N, 4.49.

**Cyclobutane derivative (24)**

A suspension of 23 (0.53 g, 0.88 mmol) in 120 mL of nitrogen-purged acetone was placed in a quartz vessel and subjected to 48 hours of irradiation from a 400 W medium pressure wide band mercury lamp placed 1 cm away. A fan was used to maintain the solution at room temperature. The solvent was then removed, and purification by flash chromatography on silica gel (CH₂Cl₂) afforded 0.45 g (0.77 mmol, 86%) of 24 as a white solid (mixture of two isomers that can be isolated).

First eluting isomer (*anti*-24): ¹H NMR: δ = 2.09 (s, 3H), 2.16 (s, 3H), 3.75 (dd, J = 2.0 Hz, 9.6 Hz, 1H), 4.32-4.48 (m, 2H), 4.60 (dd, J = 2.0 Hz, 9.6 Hz, 1H), 6.41 (d, J = 8.1 Hz, 2H), 6.95-7.20 (m, 13H), 7.45-7.58 (m, 5H), 7.94 (d, J = 8.0 Hz, 2H), 8.17 (d, J = 8.3 Hz, 1H), 8.24 (d, J = 8.3 Hz, 1H). ¹³C NMR: δ = 17.2, 17.4, 43.9, 45.0, 48.4, 49.4, 117.2, 117.4, 124.6, 124.7, 125.0, 126.7, 126.8, 127.3, 128.2, 128.4, 128.5, 128.7, 129.8, 129.9, 130.0, 132.5, 134.5, 135.6, 137.5, 137.7, 138.9, 139.7, 168.5, 169.8.

Second eluting isomer (*syn*-24): ¹H NMR: δ = 2.03 (s, 3H), 2.17 (s, 3H), 3.70 (dd, J = 9.2 Hz, 11.1 Hz, 1H), 3.96 (m, 1H), 4.10 (dd, J = 7.8 Hz, 9.9 Hz, 1H), 4.60 (m, 1H), 6.38 (s, 1H), 6.43 (s, 1H), 6.84 (d, J = 8.3 Hz, 1H), 6.90 (s, 1H), 6.96 (d, J = 8.4 Hz, 1H), 7.27-7.51 (m, 15H), 7.64 (s, 1H), 7.88 (d, J = 8.3 Hz, 1H), 7.92 (m, 1H), 8.18 (d, J = 8.4 Hz, 1H). ¹³C NMR: δ = 17.3, 17.4, 44.8, 46.4, 49.7, 51.9, 116.6, 118.4, 124.5, 124.6, 124.9, 125.0, 126.5, 126.6, 126.8, 127.5, 128.3, 128.6, 129.0, 129.7, 129.9, 130.1, 132.2, 132.3, 134.1, 134.8, 135.5, 138.7, 138.9, 139.4, 139.7, 140.8, 167.7, 168.9.
Anal. Calcd. for C_{42}H_{34}N_{2}O_{2} (syn/anti- mixture of 24): C, 84.25; H, 5.72; N, 4.68. Found: C, 83.90; H, 6.04; N, 4.46.

**β-Truxinic acid (1)**

A suspension of a mixture of syn- and anti-24 (0.050 g, 0.084 mmol) in 5 mL of 30 % aqueous hydrochloric acid was stirred at 110 °C for 24 hours in a closed vessel. The resulting mixture was allowed to come to room temperature, basified with NH_{4}OH, and extracted with chloroform to quantitatively recover 22. The aqueous layer was then acidified to pH 2 with concentrated hydrochloric acid, and extracted with EtOAc. The combined organic layers were washed with brine, dried over MgSO_{4} and concentrated in vacuo. The residue was then crystallized from acetic acid, filtered, washed with 10 % hydrochloric acid and freeze-dried, to afford 0.020 g of 1 (0.068 mmol, 81%) as a white powder.

{\textsuperscript{1}}H NMR (DMSO): δ = 3.77 (d, J = 5.9 Hz, 2H), 4.18 (d, J = 5.8 Hz, 2H), 6.94-7.09 (m, 10H), 12.38 (s, 2H). {\textsuperscript{13}}C NMR (DMSO): δ = 43.0, 44.9, 126.3, 128.1, 128.3, 139.7, 174.4.

**1,8-Bis(4′-acetamidophenyl)naphthalene (26)**

A solution of 1,8-diiodonaphthalene (0.57 g, 1.4 mmol), 4-acetamidophenylboronic acid, 25, (0.64 g, 3.6 mmol), Pd(PPh_{3})_{4} (0.41 g, 0.36 mmol), and K_{2}CO_{3} (0.89 g, 6.5 mmol) in 21 mL of nitrogen-purged ethanol:toluene:water (1:1:1) was stirred at 95 °C for 20 hours. The resulting mixture was allowed to come to room temperature, quenched with water and extracted with EtOAc and THF (1:1). The combined organic layers were washed
with brine, dried over MgSO₄ and concentrated in vacuo. Purification by flash chromatography on silica gel (EtOAc:EtOH 95:5 to 4:1) afforded 0.51 g (1.3 mmol, 90%) of 26 as a light brown powder.

1H NMR (DMSO): δ = 1.97 (s, 5.2 H), 2.03 (s, 0.8 H), 6.82 (d, J = 8.2 Hz, 4H), 7.17 (d, J = 8.3 Hz, 4H), 7.33 (d, J = 6.8 Hz, 2H), 7.56 (dd, J = 7.4 Hz, 7.8 Hz, 2H), 7.98 (d, J = 8.0 Hz, 2H), 9.69 (s, 1.8 H), 9.97 (s, 0.2H). 13C NMR (DMSO): δ = 24.5, 117.9, 119.8, 125.7, 126.8, 128.6, 129.0, 129.9, 131.1, 134.7, 135.7, 137.7, 138.8, 140.1, 168.3, 168.7. Anal. Calcd. for C₂₆H₂₂N₂O₂: C, 79.16; H, 5.62; N, 7.10. Found: C, 79.42; H, 5.96; N, 7.19.

1,8-Bis(4'-anilino)naphthalene (27)

To a solution of 1,8-bis(4'-acetamidophenyl)naphthalene, 26, (0.31 g, 0.79 mmol) in 12 mL of ethanol, 3M HCl (2.4 mL, 7.1 mmol) was added and the mixture was stirred at 95 °C for 24 hours. The resulting mixture was allowed to come to room temperature, basified with 28% NH₄OH, and extracted with CH₂Cl₂. The combined organic layers were dried over MgSO₄ and concentrated in vacuo. Purification by flash chromatography on silica gel (EtOAc:EtOH 97.5:2.5 to 95:5) afforded 0.25 g (0.79 mmol, 100%) of 27 as an off-white powder.

1H NMR: δ = 2.76 (bs, 4H), 6.33 (d, J = 8.2 Hz, 4H), 6.74 (d, J = 8.2 Hz, 4H), 7.38 (d, J = 7.0 Hz, 2H), 7.50 (dd, J = 7.3 Hz, 7.8 Hz, 2H), 7.87 (d, J = 8.1 Hz, 2H). 13C NMR: δ = 114.0, 125.0, 127.9, 129.6, 130.5, 130.7, 134.1, 135.6, 140.7, 144.2. Anal. Calcd. for C₂₂H₁₈N₂: C, 85.13; H, 5.85; N, 9.03. Found: C, 85.39; H, 6.12; N, 8.77.
1,8-Bis(4'-cinnamidophenyl)naphthalene (28)

To **27** (0.049 g, 0.16 mmol) in 5 mL of THF was added a solution of cinnamoyl chloride (0.05 g, 0.33 mmol) in 2 mL of THF at 0 °C, and allowed to stir for 22 hours at room temperature. The resulting mixture was quenched with 1 M NaOH and extracted with EtOAc. The combined organic layers were dried over MgSO₄ and concentrated in vacuo. The residue was suspended in 10 mL of CH₂Cl₂ and filtered twice to recover desired product (0.05 g, 0.10 mmol), and the filtrate was then subjected to flash chromatography on silica gel (hexanes:THF 2:1) to afford a total of 0.074 g (0.15 mmol, 93%) of **28** as a white powder.

¹H NMR (DMSO): δ = 6.73 (d, J = 15.7 Hz, 2H), 6.87 (d, J = 8.0 Hz, 4H), 7.25-7.60 (m, 20H), 8.0 (d, J = 7.8 Hz, 2H), 9.99 (s, 2H). ¹³C NMR (DMSO): δ = 122.9, 125.8, 128.0, 128.8, 129.1, 129.3, 130.0, 130.1, 131.1, 135.2, 135.7, 137.6, 138.1, 140.1, 140.2, 163.7.

Anal. Calcd. for C₄₀H₃₀N₂O₂: C, 84.19; H, 5.30; N, 4.91. Found: C, 84.56; H, 5.60; N, 4.80.

Cyclobutane derivative (29)

A suspension of **28** (0.22 g, 0.39 mmol) in 54 mL of nitrogen-purged acetone was placed in a quartz vessel and subjected to 48 hours of UV irradiation using a 400 W, medium pressure wide band mercury lamp placed 1 cm away. A fan was used to maintain the solution at room temperature. The solvent was then removed. Purification of the residue by flash chromatography on silica gel (CH₂Cl₂) afforded 0.18 g (0.32 mmol, 82%) of **29** as a white solid.
\[ \text{H NMR: } \delta = 3.78 \text{ (d, } J = 9.7 \text{ Hz, 1H), 4.36 \text{ (dd, } J = 10.6 \text{ Hz, 11.2 Hz, 1H), 4.50-4.64 \text{ (m, 2H), 6.31 \text{ (d, } J = 7.8 \text{ Hz, 2H), 6.48 \text{ (d, } J = 7.1 \text{ Hz, 1H), 6.54 \text{ (d, } J = 7.7 \text{ Hz, 1H), 6.98 \text{ (d, } J = 7.6 \text{ Hz, 2H), 7.05-7.20 \text{ (m, 10H), 7.42 \text{ (bs, 1H), 7.50-7.60 \text{ (m, 5H), 7.82 \text{ (d, } J = 7.4 \text{ Hz, 1H), 7.85 \text{ (d, } J = 7.9 \text{ Hz, 1H), 7.97 \text{ (dd, } J = 1.4 \text{ Hz, 7.8 Hz, 2H).}} \]
\[ \text{C NMR: } \delta = 43.4, 44.8, 47.4, 48.4, 119.2, 119.4, 119.5, 119.8, 125.1, 126.7, 127.3, 128.2, 128.4, 128.8, 129.0, 129.8, 130.1, 130.4, 130.9, 131.2, 135.6, 135.8, 137.6, 138.0, 139.1, 139.2, 139.4, 139.5, 168.9, 170.4. \text{ Anal. Calcd. for C}_{40}\text{H}_{30}\text{N}_{2}\text{O}_{2}: C, 84.19; H, 5.30; N, 4.91. \text{ Found: C, 84.42; H, 5.59; N, 4.76.} \]

\text{β-Truxinic acid (1)}^{52}

A suspension of 29, (0.054 g, 0.094 mmol), in 6 mL of 30 % aqueous hydrochloric acid was stirred at 110 °C for 24 hours in a closed vessel. The resulting mixture was allowed to come to room temperature, basified with NH\textsubscript{4}OH, and extracted with chloroform to quantitatively recover 27. The aqueous layer was then acidified to pH 2 with concentrated hydrochloric acid, and extracted with EtOAc. The combined organic layers were washed with brine, dried over MgSO\textsubscript{4} and concentrated in vacuo. The residue was then crystallized from acetic acid, filtered, washed with 10 % hydrochloric acid and freeze-dried, to afford 0.025 g of 1 (0.085 mmol, 90%) as a white powder.

\[ \text{H NMR (DMSO): } \delta = 3.77 \text{ (d, } J = 5.9 \text{ Hz, 2H), 4.18 \text{ (d, } J = 5.8 \text{, 2H), 6.94-7.09 \text{ (m, 10H), 12.38 \text{ (s, 2H).}} \]
\[ \text{C NMR (DMSO): } \delta = 43.0, 44.9, 126.3, 128.1, 128.3, 139.7, 174.4. \]
1,8-Bis(4’-(3,4-dimethylcinnamidophenyl)naphthalene (30)

A solution of 27 (0.12 g, 0.38 mmol), (E)-3-(3,4-dimethylphenyl)acrylic acid (0.14 g, 0.81 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (0.16 g, 0.85 mmol) and DMAP (0.07 g, 0.58 mmol) was stirred in 6 mL of toluene for 23 hours at room temperature. The resulting suspension was filtered twice to collect the desired product (0.05 g, 0.10 mmol), and the filtrate was subjected to flash chromatography on silica gel (hexanes:THF 2:1) to afford a total of 0.19 g (0.31 mmol, 80%) of 30 as a white powder.

$^1$H NMR (DMSO): $\delta = 2.11$ (s, 6H), 2.17 (s, 6H), 6.33 (d, $J = 15.7$ Hz, 2H), 6.84 (d, $J = 8.4$ Hz, 4H), 7.02 (d, $J = 7.6$ Hz, 2H), 7.14 (d, $J = 8.0$ Hz, 2H), 7.17 (s, 2H), 7.28 (d, $J = 8.4$ Hz, 4H), 7.37 (d, $J = 15.5$ Hz, 2H), 7.37 (d, $J = 7.0$ Hz, 2H), 7.57 (dd, $J = 7.4$ Hz, 7.6 Hz, 2H), 7.99 (d, $J = 8.0$ Hz, 2H), 9.86 (s, 2H). $^{13}$C NMR (DMSO): $\delta = 19.7$, 118.1, 121.7, 125.6, 125.7, 128.8, 128.9, 129.1, 130.1, 130.3, 131.0, 132.8, 135.6, 137.0, 137.7, 137.9, 138.5, 140.1, 140.2, 163.9. Anal. Calcd. for C$_{44}$H$_{38}$N$_2$O$_2$: C, 84.31; H, 6.11; N, 4.47. Found: C, 84.67; H, 6.16; N, 4.82.

Cyclobutane derivative (31)

A suspension of 30 (0.10 g, 0.16 mmol) in 54 mL of nitrogen-purged acetone was placed in a quartz vessel and subjected to 48 hours of UV irradiation using a 400 W, medium pressure wide band mercury lamp placed 1 cm away. A fan was used to maintain the solution at room temperature. The solvent was then removed, and the residue was purified by flash chromatography on silica gel (CH$_2$Cl$_2$) to give 0.08 g (0.13 mmol, 82%) of 31 as a white solid.
H NMR: δ = 2.13 (s, 12H), 3.72 (d, J = 10.2 Hz, 1H), 4.36 (dd, J = 10.2 Hz, 10.8 Hz, 1H), 4.40-4.54 (m, 2H), 6.31 (d, J = 7.8 Hz, 2H), 6.48 (d, J = 7.4 Hz, 1H), 6.54 (d, J = 7.4 Hz, 1H), 6.69 (d, J = 7.6 Hz, 1H), 6.76 (bs, 1H), 6.82-6.94 (m, 4H), 7.06 (d, J = 8.2 Hz, 1H), 7.11 (d, J = 8.0 Hz, 1H), 7.46-7.58 (m, 6H), 7.82 (d, J = 8.4 Hz, 1H), 7.86 (d, J = 8.2 Hz, 1H), 7.96 (dd, J = 1.4 Hz, 7.4 Hz, 1H). 13C NMR: δ = 19.3, 19.7, 43.0, 44.4, 48.0, 48.5, 119.3, 124.7, 125.0, 125.7, 128.5, 129.0, 129.4, 129.6, 129.8, 130.0, 130.8, 131.0, 134.8, 135.2, 135.5, 136.2, 136.3, 139.0, 139.6, 169.3, 170.1. Anal. Calcd. for C_{44}H_{38}N_{2}O_{2}: C, 84.31; H, 6.11; N, 4.47. Found: C, 84.00; H, 6.28; N, 4.80.

3,4-Bis(3,4-dimethylphenyl)cyclobutane-1,2-dicarboxylic acid (32)

A suspension of 31, (0.06 g, 0.096 mmol), in 6 mL of 30% aqueous hydrochloric acid was stirred at 110 °C for 24 hours in a closed vessel. The resulting mixture was allowed to come to room temperature, basified with NH₄OH, and extracted with chloroform to quantitatively recover 27. The aqueous layer was then acidified to pH 2 with concentrated hydrochloric acid, and extracted with EtOAc. The combined organic layers were washed with brine, dried over MgSO₄ and concentrated in vacuo. The residue was then crystallized from acetic acid, filtered, washed with 10% hydrochloric acid and freeze-dried, to afford 0.031 g of 32 (0.088 mmol, 92%) as a white solid.

H NMR: δ = 2.10 (s, 6H), 2.11 (s, 6H), 3.85 (d, J = 6.1 Hz, 2H), 4.31 (d, J = 6.1 Hz, 2H), 6.60-6.90 (m, 6H). 13C NMR: δ = 19.3, 19.7, 44.0, 44.4, 125.2, 129.2, 129.3, 134.5, 135.7, 136.0, 179.7. Anal. Calcd. for C_{22}H_{24}O_{4}: C, 74.98; H, 6.86. Found: C, 75.11; H, 7.05.
Cyclobutane derivative (35)

A suspension of 34 (0.10 g, 0.24 mmol) in 20 mL of nitrogen-purged acetone was placed in a quartz vessel and subjected to 48 hours of UV irradiation using a 400 W, medium pressure wide band mercury lamp placed 1 cm away. A fan was used to maintain the solution at room temperature. The solvent was then removed, and the residue was purified by flash chromatography on silica gel (CH$_2$Cl$_2$) to give 0.006 g (0.014 mmol, 6%) of 35 as a white solid.

$^1$H NMR: δ = 3.77 (m, 1H), 3.99 (m, 1H), 4.33 (m, 2H), 6.98-7.18 (m, 11H), 7.32-7.42 (m, 3H), 7.50 (d, $J$ = 8.4 Hz, 1H), 8.40 (d, $J$ = 7.7 Hz, 1H). $^{13}$C NMR: δ = 40.5, 42.3, 47.6, 48.7, 109.6, 119.1, 119.8, 123.7, 123.9, 126.6, 126.7, 127.3, 127.9, 128.0, 128.1, 128.2, 132.6, 134.4, 137.9, 138.0, 140.0, 158.9, 175.4.

VII.5.2. Crystallization and X-Ray Diffraction

Single crystal X-ray 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 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.

A cocrystal of 7 and mesaconic acid was obtained through the slow evaporation of an equimolar solution of 7 and the diacid in a 1:1 tetrahydrofuran and methanol solution. Crystal structure data: Formula C$_{50}$H$_{40}$N$_4$O$_8$, $M = 824.17$, crystal dimensions 0.60 x 0.40 x 0.30 mm, monoclinic, space group P21/c, $a = 12.0081$ (8) Å, $b = 34.5867$ (24) Å, $c = 9.6806$ (7) Å, $\beta = 90.908$ (1)$^\circ$, $V = 4020.05$ Å$^3$, $Z = 4$, $\rho_{\text{calc}} = 1.3611$ g cm$^{-3}$. 
A cocrystal of 7 and trans,trans-muconic acid was obtained through the slow evaporation of an equimolar solution of 7 and trans,trans-muconic acid in a 1:1 tetrahydrofuran and methanol solution. Crystal structure data: Formula C$_{156}$H$_{117}$N$_{12}$O$_{24}$, M = 2543.17, crystal dimensions 0.50 x 0.30 x 0.30 mm, monoclinic, space group P21/n, 

\[ a = 21.9636 \text{ (26) Å}, \ b = 20.7916 \text{ (24) Å}, \ c = 29.6572 \text{ (35) Å}, \ \beta = 109.188 \text{ (2)}^0, \ V = 12790.82 \text{ Å}^3, \ Z = 4, \ \rho_{\text{calc}} = 1.3207 \text{ g cm}^{-3}. \]

A cocrystal of 7 and trans-cinnamic acid was obtained by slow evaporation of a solution of 20 mg of equimolar 1 and trans-cinnamic acid from 5 mL of ethanol. Crystal structure data: Formula C$_{29}$H$_{22}$N$_{2}$O$_{2}$, M = 430.49, crystal dimensions 0.40 x 0.40 x 0.10 mm, monoclinic, space group P-1, 

\[ a = 9.5279 \text{ (15) Å}, \ b = 10.4512 \text{ (16) Å}, \ c = 12.1116 \text{ (19) Å}, \ \alpha = 100.867 \text{ (3)}^0, \ \beta = 110.309 \text{ (3)}^0, \ \gamma = 98.418 \text{ (3)}^0, \ V = 1081.01 \text{ Å}^3, \ Z = 2, \ \rho_{\text{calc}} = 1.3224 \text{ g cm}^{-3}. \]

A crystal of 1,8-bis(4’-hydroxyphenyl)naphthalene template 12 and fumaric acid was obtained by slow evaporation of a solution of 20 mg of equimolar 12 and fumaric acid from 5 mL of ethanol. Crystal structure data: Formula C$_{22}$H$_{16}$O$_{2}$, M = 312.36, crystal dimensions 0.40 x 0.30 x 0.10 mm, triclinic, space group P-1, 

\[ a = 8.4615 \text{ (76) Å}, \ b = 9.5887 \text{ (86) Å}, \ c = 10.8753 \text{ (19) Å}, \ \alpha = 104.925 \text{ (3)}^0, \ \beta = 92.533 \text{ (1)}^0, \ \gamma = 115.941 \text{ (4)}^0, \ V = 754.10 \text{ Å}^3, \ Z = 1, \ \rho_{\text{calc}} = 1.3755 \text{ g cm}^{-3}. \]

A crystal of anti-24 was obtained by slow evaporation of a solution of 5.0 mg of anti-24 in 5 mL of CHCl$_3$. Crystal structure data for anti-24: Formula C$_{42}$H$_{32}$N$_{2}$O$_{2}$, M = 482.57, crystal dimensions 0.15 x 0.10 x 0.05 mm, monoclinic, space group P2$_1$/c, 

\[ a = 13.591 \text{ (22) Å}, \ b = 7.7942 \text{ (13) Å}, \ c = 31.3246 \text{ (5) Å}, \ \alpha, \gamma = 90^0, \ \beta = 96.566 \text{ (2)}^0, \ V = 3296.48 \text{ (3)} \text{ Å}^3, \ Z = 4, \ \rho_{\text{calc}} = 1.2062 \text{ g cm}^{-3}. \]
VII.6. References


