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Chiral Amplification with a Stereodynamic Triaryl Probe: Assignment of the Absolute Configuration and Enantiomeric Excess of Amino Alcohols

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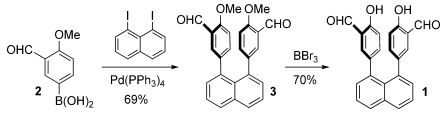
Chiroptical spectroscopy has been applied extensively in the stereochemical analysis of chiral compounds. In particular, the efficacy of methods based on circular dichroism has received increasing attention in recent years.[1] Induced circular dichroism (ICD) has been used to probe the orientation of guest molecules in cyclodextrin and calixarene inclusion complexes[2] or to analyze the structure of chiral ion pairs[3] and supramolecular assemblies.[4] The covalent linkage of a chiral compound to a porphyrin, phthalocyanine or other chromophoric moieties has been reported to generate strong Cotton effects,[5] which provides a means to determine the chirality of UV-silent substrates.[6] 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.[7] The formation of hydrogen bond adducts[8] and metal complexes[9] can provide an entry to in situ analysis that avoids elaborate workup procedures.

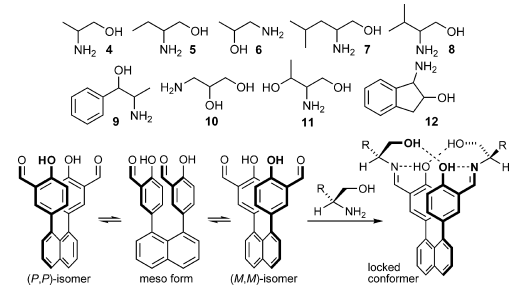
Compared to ICD analysis of amines, amino acids, carboxylic acids and alcohols, only few methods for the determination of both the absolute configuration and enantiomeric composition of amino alcohols have been developed.[10] Remaining drawbacks of some of these protocols are elaborate derivatization and purification steps prior to CD analysis, generation of modest Cotton effects at low wavelengths, and narrow application scope. Furthermore, the use of a stereodynamic chromophoric sensor that undergoes rapid racemization via rotation about a chiral axis for both quantitative ICD sensing of the ee and simultaneous determination of the absolute configuration of amino alcohols has not been reported to date. This may be partly attributed to the difficulty of designing a stereolabile probe that is suitable for distinct chiral amplification and predictable chiroptical properties upon binding to a chiral substrate.

Scheme 1. Synthesis of Stereodynamic Sensor **1**



We now introduce a simple, time-efficient CD method based on an axially chiral reporter molecule that provides information on the enantiomeric excess and the absolute configuration of amino alcohols. We realized that the unique structure of 1,8-diarylnaphthalenes provides an excellent opportunity to design a sensor that carries a chromophoric binding pocket and that has the ability to transform a binding event with a chiral substrate into a strong CD signal. In continuation of previously conducted studies with stereodynamic chiral biaryls and triaryls[11] and 1,8-diheteroarylnaphthalene-derived sensors,[12] we decided to prepare 1,8-bis(3′-formyl-4′-hydroxyphenyl)naphthalene, **1**.[13] Suzuki coupling of boronic acid **2** with 1,8-diiodonaphthalene gave **3** which was easily deprotected to afford **1** in 48% overall yield (Scheme 1).

Scheme 2. Central-to-Axial Chirality Induction Using Amino Alcohols **4**−**12** and Triaryl Probe **1**



In analogy to other 1,8-diarylnaphthalenes, **1** can be expected to undergo facile rotation about the two aryl−aryl bonds at room temperature.[14] Accordingly, the enantiomeric *anti*-isomers of this triaryl rapidly interconvert via the thermodynamically less stable meso *syn*-intermediate. We envisioned that imine formation with amino alcohols would disturb this equilibrium and strongly favor population of a single diastereomer by intramolecular hydrogen bonding (Scheme 2).

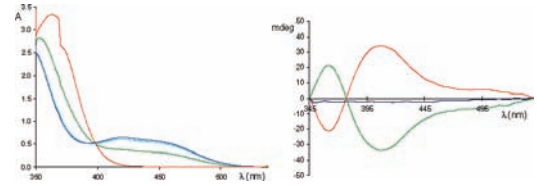


Figure 1. UV and CD analysis of the imines obtained with **4** using **1** and salicylaldehyde. (Left) UV plot of **1** titrated with (*R*)-**4** in $CHCl_3$, reaction concentration was 0.02 M, UV concentration was 10.0×10^{-3} M. Pure **1** (red), 1 equiv of **4** after 5 min (green), 2 equiv after 5 and 10 min (both light blue) and 18 equiv after 5 min (dark blue). (Right) CD plot of the diimine obtained from (*R*)-**4** in $CHCl_3$ (green) and (*S*)-**4** (red) both (5.0×10^{-4} M), and the (*R*)-**4** derived salicylidenimine (blue, 5.0×10^{-3} M).

Indeed, titration of **1** with either enantiomer of amino alcohol **4** showed a new characteristic UV absorption band above 400 nm and MS and NMR analysis proved quantitative diimine formation in chloroform within 5 min (see Figure 1 and Supporting Information).[15] 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 (see Supporting Information). Since it is known that salicylaldehyde can be used for CD analysis of the absolute configuration of amines and amino acids, we employed both **1** and free salicylaldehyde in CD sensing experiments of **4**.[16] CD and NMR analysis showed that the reaction with salicylaldehyde requires significantly more time and is still not complete after 90 min. The corresponding salicylidenimine remains CD silent above 300 nm in chloroform and ethanol even at 10-fold concentration. Apparently, the strong Cotton effect at high wavelengths and the short condensation reaction time are due to the unique structure of sensor **1**.

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We were able to grow single crystals of the diimines **13** and **14** produced from **1** and amino alcohols **4** and **5**. Crystallographic analysis of the orange crystals of **13** and **14** proved that the central chirality of the substrates induces a rigid, axially chiral triaryl scaffold. Condensation of **1** and the (*S*)-enantiomer of **4** and **5** 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 2 and Supporting Information). Importantly, we obtained (*R*,*R*,*M*,*M*)-**13** when (*R*)-**4** 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 (*R*,*R*,*M*,*M*)-**13** and (*S*,*S*,*P*,*P*)-**13** is 15.9°. The salicylidenimine rings are also not perfectly orthogonal to the naphthalene ring but afford a torsion angle of −52.6° and +52.1°, respectively. Finally, (*R*,*R*,*M*,*M*)-**13** and (*S*,*S*,*P*,*P*)-**13** 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 $\pi-\pi$-interactions between the two salicylidenimine units. The $C{=}N\cdots HOC_{phenyl}$ hydrogen bonding lengths are 1.692 and 1.649 Å and the $C_{aliph}OH\cdots OC_{phenyl}$ hydrogen bonds are 1.899 and 2.011 Å, respectively. The sense of asymmetric induction and the three-dimensional arrangement including bond angles and hydrogen bond lengths in (*S*,*S*,*P*,*P*)-**14**, which was obtained from (*S*)-**5**, closely match those discussed for (*S*,*S*,*P*,*P*)-**13** (see Supporting Information). This parallel behavior underscores the generality of the chiral amplification process shown in Scheme 2.

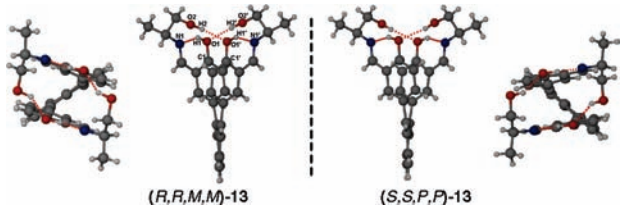

Figure 2. X-ray structures of (*R*,*R*,*M*,*M*)-**13** and (*S*,*S*,*P*,*P*)-**13**. Outside: view into the cleft; Inside: view along the naphthalene plane. Selected crystallographic separations [Å]: (*R*,*R*,*M*,*M*)-**13**: N1···H1 1.692, H2···O1′ 1.899; (*S*,*S*,*P*,*P*)-**13**: N1···H1 1.649, H2···O1′ 2.011.

This arrangement allows the two imino alcohol moieties in **13** and **14** 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 toward 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.[17] 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.[18] The sign of the CD spectrum can therefore be used to determine the absolute configuration of the amino alcohols shown in Scheme 2 (see Supporting Information).

To evaluate the practical use of our sensor, scalemic samples of 2-aminopropanol, 2-aminobutanol and 2-hydroxypropylamine, **4**−**6**, covering a wide ee range were analyzed (Supporting Information). In all cases, diimines were formed within 5 min and analyzed without further purification. The results obtained by our in situ CD sensing method were in excellent agreement with the theoretical ee's. This time-efficient ICD assay reveals the absolute configuration of the major enantiomer and gives accurate ee's that are generally within 6% of the actual values.

In conclusion, we have introduced sensor **1**, which can be easily prepared in two steps, for enantioselective CD analysis of chiral amino alcohols. This stereodynamic probe 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 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 toward 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.

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Supporting Information Available: Experimental procedures and CD, MS and X-ray analyses of the diimines. This material is available free of charge via the Internet at http://pubs.acs.org.

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