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Quantitative chirality sensing of amines and amino alcohols *via* Schiff base formation with a stereodynamic UV/CD probe†

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A stereodynamic chemosensor that can be used for simultaneous determination of the absolute configuration, enantiomeric composition and total concentration of chiral amines and amino alcohols based on two fast optical measurements was prepared and tested. The free sensor is CD-silent and produces characteristic blue-shifted UV and CD signals upon substrate binding *via* Schiff base formation. The potential in high-throughput screening applications and for rational sensor developments are discussed.

Introduction

The important role of asymmetric synthesis and stereochemical analysis of chiral compounds in the pharmaceutical, environmental and forensic sciences or other interdisciplinary research settings is staggering and continues to grow. The widespread availability of high-throughput equipment accelerates overall progress and it reduces labor and material costs, in particular when small-scale reactions are carried out. Today, the production of numerous chiral samples *via* automated parallel asymmetric synthesis is routine in many laboratories. Despite the efficient use of high-throughput technology in reaction discovery and development programs, the analysis of the absolute configuration and enantiomeric excess (ee) of chiral compounds has remained relatively time-consuming and laborious. Several groups have introduced robust GC and HPLC methods suitable for the study of one-pot multi-substrate reactions.[1] Some of the typical shortcomings of chiral chromatography, including time-inefficiency and solvent waste production, however, remain unless high-speed separations can be achieved.[2]

The mismatch in parallel synthesis and analysis capabilities has inspired the introduction of high-throughput screening (HTS) methodologies that enable simultaneous analysis of the enantiomeric composition of a large number of chiral samples. Optical chirality sensing with small molecular probes[3] and supramolecular systems[4] has been identified as a promising alternative to traditional enantioselective chromatography or electrophoresis. Because of the general significance of chiral amines, the development of chemosensors that utilize Schiff base formation to capture a chiral substrate for subsequent ee analysis has been of particular interest. Several probe designs exhibiting an aldehyde or ketone moiety for this purpose have been reported by Kim, Hong and Chin,[5] Anslyn,[6] Pu,[7] Joyce[8] and our group (Fig. 1).[9] Typically, the covalent binding of the chiral amine affects the circular dichroism or fluorescence readout of the chemosensor, and this change is then used to determine the enantiomeric composition of the target compound. Remaining drawbacks of some of these chemosensors are limited substrate scope and the formation of more than one reaction product which can complicate the ee analysis.

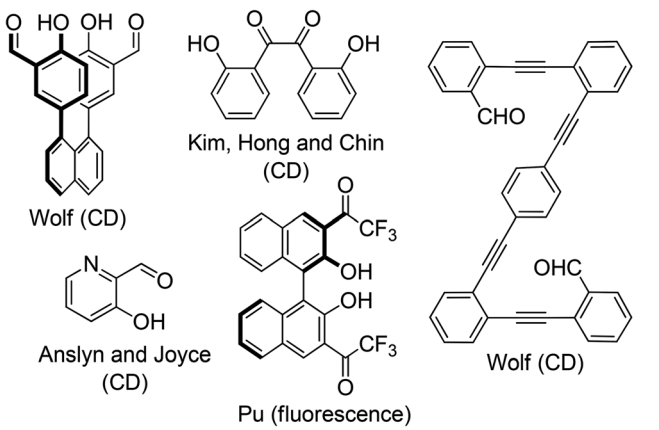

Fig. 1 Structures of optical sensors used for covalent binding and enantioselective detection of chiral amines, amino alcohols and amino acids.

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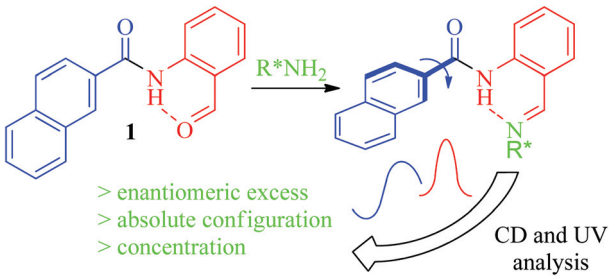
Results and discussion

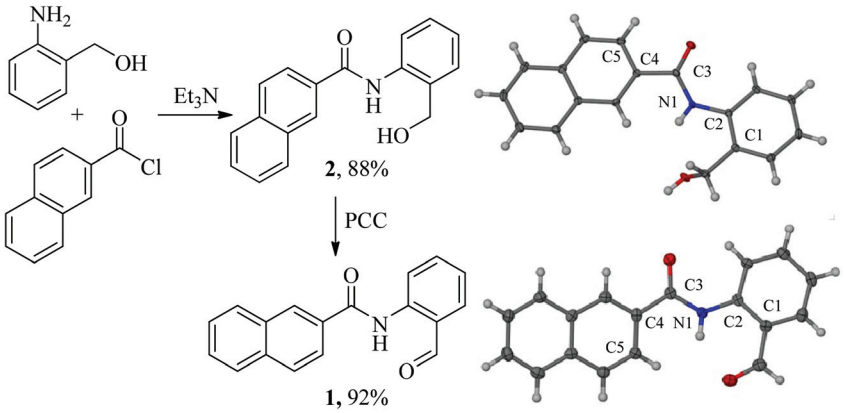
We now wish to report a readily available chiroptical sensor **1** that is designed to trap chiral amino compounds as Schiff base for quantitative ee and concentration determination. The receptor used in this study consists of a benzaldehyde unit and an adjacent naphthamide moiety which activates the formyl group toward imine formation by intramolecular hydrogen bonding (Scheme 1). At the onset of this study we hypothesized that the 2-amidobenzaldehyde component (red) would function as a rigid substrate binding site. Schiff base formation would then result in a nonenantioselective change in the UV absorption of **1** (to be used for total concentration analysis) and a stereochemical bias in the 2-naphthamide CD reporter unit (blue). This chirality imprinting from the bound amino compound onto the 2-naphthamide unit was expected to furnish a characteristic CD signal which would provide information about the absolute configuration and ee of the substrate.

We were able to prepare **1** in two high yielding steps (Scheme 2). Acylation of 2-amino benzylalcohol with 2-naphthoyl chloride gave direct access to amide **2** without the need to protect the primary alcohol. Oxidation with pyridinium chlorochromate (PCC) provided **1** in almost quantitative amounts. We were able to grow single crystals of **1** and **2** by slow evaporation of concentrated acetonitrile and chloroform solutions, respectively. As expected, crystallographic analysis confirmed that the amides exhibit a near planar structure and an intramolecular hydrogen bond in the case of **1**.[10] A closer look at the crystal structure of **2** revealed that the two aromatic moieties are coplanar with the amide unit being twisted out of that plane. Probably because of the intramolecular hydrogen bond, compound **1** shows less molecular twisting.

With sensor **1** in hand, we selected a series of 11 amines and amino alcohols **3–13** to evaluate the use of this readily available probe for chirality sensing (Fig. 2). We first investigated the imine formation which needs to be quantitative for the intended analytical purposes and should preferably occur under mild conditions. Proton NMR analysis using amine **6** showed complete reaction within 5 hours at room temperature. The time necessary for quantitative Schiff base formation can easily be reduced if necessary. For example, we found that the condensation reaction takes less than 40 minutes in the presence of $Ti(Oi\text{-}Pr)_4$ which may serve as both an activating Lewis acid and a hygroscopic reagent to accelerate the imine formation and favor quantitative conversion, respectively (ESI†). We were excited to observe strong CD readouts of the imines formed *in situ* above 300 nm at submillimolar concentrations. Representative examples obtained with the imines prepared from the enantiomers of **3** and **10** are shown in Fig. 3. Similar results were observed with the other amino compounds and we note that the free substrates are CD silent in the region of interest (ESI†). Interestingly, all imines derived from the (*R*)-enantiomers of the monoamines produce a negative CD signal while the (*S*)-enantiomers induce the opposite chiroptical sensor response. Because of the variations in the amino alcohol structures exhibiting either acyclic or cyclic scaffolds with one or two chiral centers a general relationship between the sign of the CD readout of **1** and the absolute configuration of the bound substrate cannot be construed at this point. In contrast to the strong CD signals obtained with sensor **1** we observed only a moderate chiroptical response with the corresponding 1-naphthamide derivative.[11]



Scheme 1 Structure of **1** and illustration of the chiroptical sensing concept.



Scheme 2 Synthesis and X-ray structures of **2** and sensor **1**. Selected torsion angles [°] and bond lengths [Å] for **1**: C1–C2–N1–C3 175.5, N1–C3–C4–C5: –15.3, hydrogen bond: 1.973. For **2**: C1–C2–N1–C3: 146.5, N1–C3–C4–C5: –150.1.

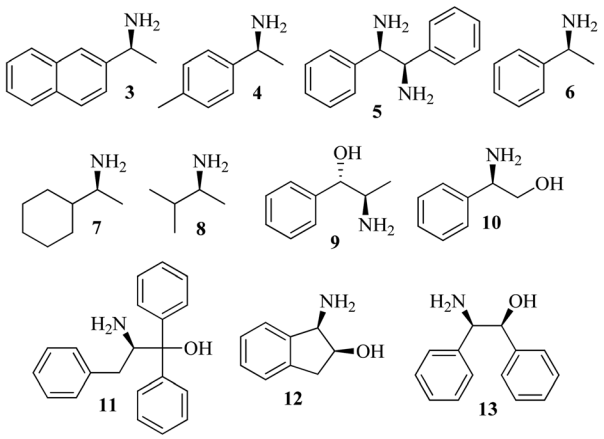


Fig. 2 Amines and amino alcohols tested (only one enantiomer is shown).

An important feature of the chiroptical analysis (CD and UV) with **1** is that purification of the imines or any work-up steps are not required and all measurements can be performed directly using the crude condensation product mixtures in acetonitrile. Further analysis with nonracemic samples of **3** showed a perfectly linear relationship between the amplitude of the CD signals of the imines of **1** and the ee of the free amine (Fig. 4). The change in the UV signature of **1** upon addition of varying amounts of **3** was then analyzed. We were pleased to find that the substrate fixation coincides with characteristic CD and UV changes. As shown in Fig. 4, the substrate binding event results in a hypsochromic shift and a linear increase in the UV absorption at 310 nm.

Having established that **1** undergoes smooth condensation with amino compounds yielding distinct CD and UV responses that change linearly with the ee and total amount of the substrate encouraged us to further test its value for quantitative stereochemical analysis. Five nonracemic samples of **3** were prepared and then treated with sensor **1** to generate the corresponding imine. Using the linear regression equation obtained from the calibration shown in Fig. 4 and the measured Cotton effect amplitude at 320 nm, the enantiomeric excess of these samples was determined (Table 1). Gratifyingly, the experimentally obtained sensing data were within a few percent of the actual values. Basically the same approach was applied to UV chemosensing of five solutions containing **3** at varying concentrations (Table 2). Again, the sensing results were of sufficient accuracy for HTS purposes. To prove the reproducibility and practicality, the concentration analysis of these samples was conducted with calibration curves obtained at different days. The sensing results show little variation which highlights that a single regression analysis suffices and recalibration is not necessary (ESI†).

A single crystal was obtained by slow evaporation of a concentrated solution of the imine derived from sensor **1** and (*R*)-**3** in CD_3CN (Fig. 5).[12] Crystallographic analysis confirmed the expected intramolecular hydrogen bonding motif between the imine nitrogen and the adjacent amide proton. Although solid state packing forces are likely to affect the conformational structures of the sensor and the imine derivative, it is noteworthy that the latter exhibits enhanced twisting on both sides of the amide function which might in part explain the distinct chiroptical readouts measured in solution. Comparison of the CD signals in acetonitrile, dichloromethane, diethyl ether and methanol, however, showed minor solvent effects (ESI†). The intensity of the CD readout of the imine of (*R*)-**3**, which can be used as a measurement of the chiral amplification process, remains almost unchanged and decreases by approximately 10% in methanol. This small variation indicates that the conformation in the crystal structure and the intramolecular hydrogen bonding motif might not be predominant in solution.

Finally, we decided to investigate if the rationale underlying the chiroptical amine and amino alcohol sensing with **1** could, in principle, be extended to aldehydes. To date, chirality sensing of aldehydes and ketones has remained very challenging.[13] We previously found that the concept of isostericity has remarkable potential in this regard.[13a] Accordingly, fixation of a chiral aldehyde such as citronellal, **14**, by the aniline deriva-

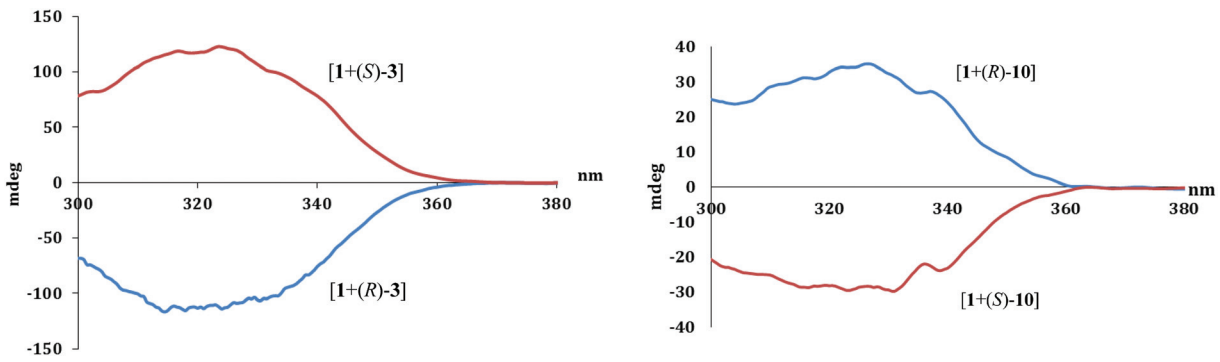


Fig. 3 CD Spectra of the imines derived from **1** and the enantiomers of **3** (left) and **10** (right). The CD analysis was conducted with sample concentrations of 3.0×10^{-4} M in CH_3CN. The chiroptical responses collected with the imines derived from the (*R*)-configured substrates are shown in blue and those from the (*S*)-enantiomers are in red.

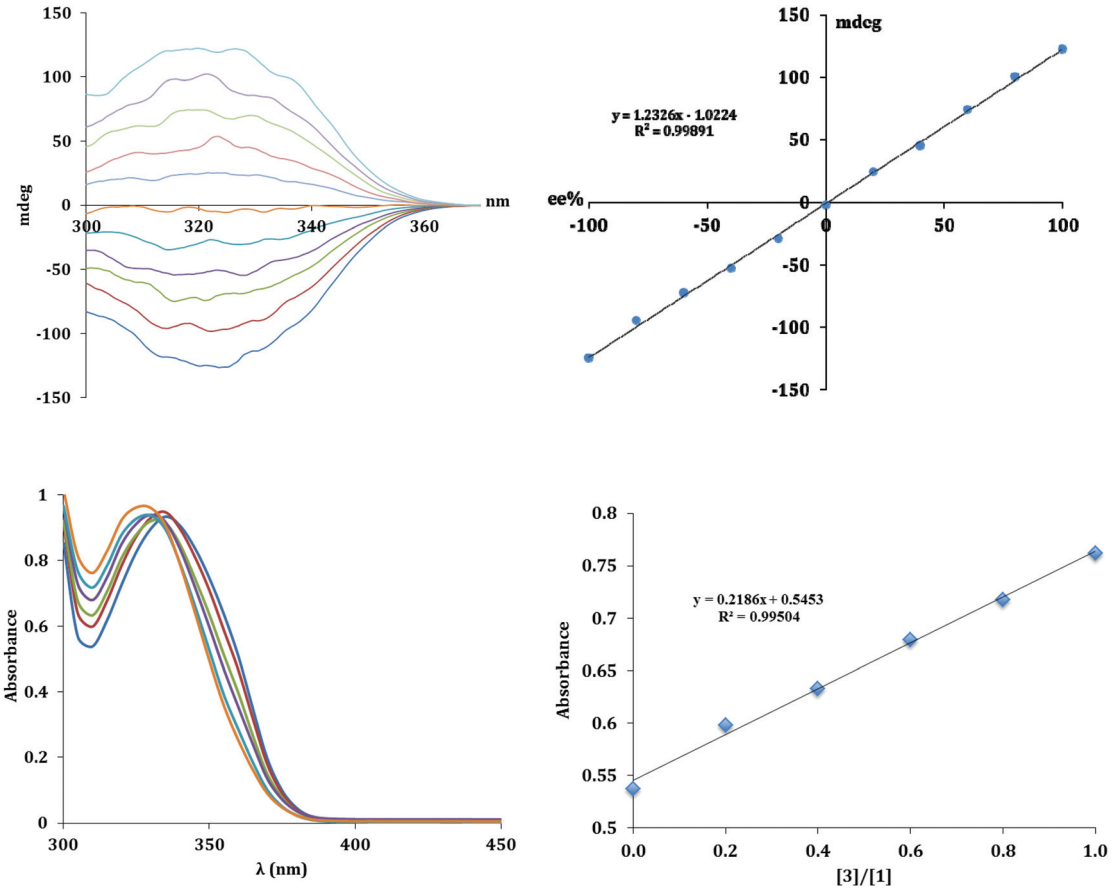


Fig. 4 Top: CD spectra of the imine obtained from **1** and varying ee compositions of **3** and linear relationship between the CD amplitude at 320 nm and the sample ee. Bottom: UV spectra of **1** upon addition of **3** in varying molar ratio and linear regression analysis of the UV change at 310 nm.

Table 1 Experimentally determined ee's of five nonracemic samples of **3** using the imine CD maximum at 320 nm

Sample composition		Chiroptical sensing results	
Abs. config.	Actual %ee	Abs. config.[a]	Calc. %ee[b]
R	87.0	*R*	87.6
R	76.0	*R*	72.3
R	12.0	*R*	8.4
S	26.0	*S*	20.7
S	68.0	*S*	66.9
S	89.0	*S*	89.1

[a] Based on the sign of the CD response. [b] Based on the amplitude of the CD response.

Table 2 UV sensing of the concentration of **3** [a]

Actual conc. (10^{-3} M)	UV sensing (**1**) (10^{-3} M)	UV sensing (**2**) (10^{-3} M)
1.5	1.3	1.6
5.5	5.6	5.7
7.0	6.1	6.1
8.5	8.3	8.3
9.0	8.9	8.8

[a] UV sensing data were calculated with two different calibration curves.

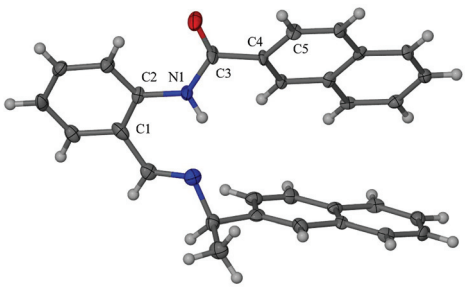
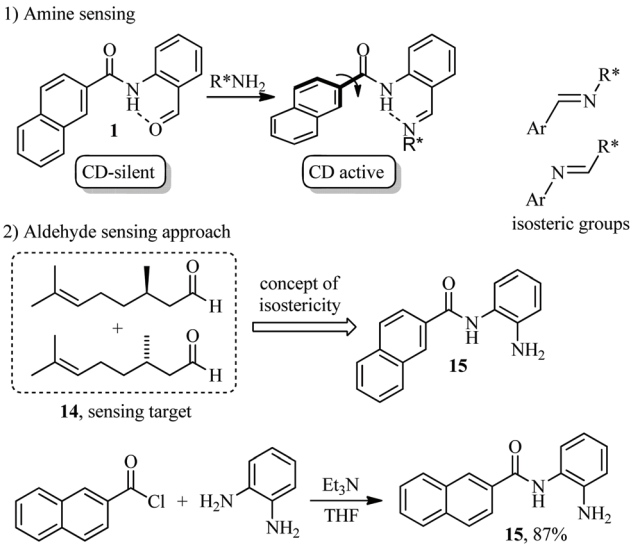


Fig. 5 Crystallographic analysis of the imine derived from sensor **1** and (*R*)-**3**. Selected torsion angles [°] and bond lengths [Å]: C1–C2–N1–C3: −162.2, N1–C3–C4–C5: 155.8, (CO)NH···N hydrogen bond: 2.018.

tive **15** would afford an isosteric Schiff base motif that in analogy to the sensing study described above with **1** could result in chirality imprinting onto the adjacent naphthamide unit and a chiroptical sensor readout (Scheme 1). Similarly to **1**, *N*-(2-aminophenyl)-2-naphthamide, **15**, is readily available and was prepared in one step in 87% yield. Condensation with the enantiomers of **14** required elevated temperatures. We were pleased, however, to observe a measurable chiroptical



Scheme 3 Chirality imprinting on **1** and rationale for the sensing of citronellal, **14**, with **15**.

response from **15** which proves the value of the isostericity concept for the development of new chirality sensors (ESI†) (Scheme 3).

Conclusions

In summary, we have demonstrated the usefulness of *N*-(2-formylphenyl)-2-naphthamide, **1**, for quantitative sensing of chiral amines and amino alcohols. Schiff base formation results in spontaneous chirality amplification yielding a distinct CD signal that is successfully correlated to the absolute configuration and ee of a series of compounds. The free sensor **1** is CD-silent and therefore does not generate any chiroptical background noise. The imine formation also coincides with a UV change that is nonenantioselective and can be used to determine the total amount of a chiral analyte. Altogether, this readily available chiroptical sensor allows simultaneous determination of the total concentration and enantiomeric composition of amines and amino alcohols. The potential of the binding motif and the architecture of this sensor for isosteric aldehyde sensing was confirmed and briefly discussed.

Acknowledgements

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10 CCDC numbers 1440658 and 1440660 contain the supplementary crystallographic data for this paper.

11 The CD response of **1** was about 10-fold stronger and the maximum was slightly red shifted. The importance of the naphthyl moiety was verified by using 2-aminobenzaldehyde as probe for the sensing of **6**. NMR analysis proved that quantitative imine formation was accomplished by stirring a solution of 2-aminobenzaldehyde (10 mg, 0.08 mmol), **6** (10 mg, 0.08 mmol) and $Ti(Oi\text{-}Pr)_4$ (23 mg, 0.08 mmol) in 4 mL of chloroform for 2 hours. The mixture was then diluted to a concentration of 2.0×10^{-4} M in $CHCl_3$ for CD analysis. The resultant imine was found to be CD-silent in the region of interest.

12 CCDC number 1440659 contains the supplementary crystallographic data for this paper.

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