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Chiroptical sensing of citronellal: systematic development of a stereodynamic probe using the concept of isostericity†

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A rationally designed stereodynamic ICD probe carrying two terminal amino functions for chemo- and enantioselective sensing of citronellal is introduced. The sensor shows strong Cotton effects upon diimine formation which can be used for accurate ee determination.

The general importance of chiral pharmaceuticals, agrochemicals, flavors, nutrients and other fine chemicals has stimulated tremendous activity in asymmetric synthesis.[1] The introduction of high-throughput screening (HTS) technologies that allow parallel synthesis and time-efficient optimization of reaction conditions has further propelled progress in this field. Consequently, the development of enantioselective methods for HTS of the absolute configuration and ee of numerous samples of chiral compounds generated in parallel has become an increasingly important challenge. Although chiral chromatography has been successfully applied in the analysis of multi substrate reactions,[2] spectroscopic techniques are more easily tailored to HTS of large numbers of samples and have an inherent sustainability advantage by generating less solvent waste.[3,4]

Chiroptical spectroscopy is particularly well-suited for stereochemical analysis of chiral compounds and molecular recognition events.[5] Induced circular dichroism (ICD) measurements[6] with stereodynamic chromophoric probes that generate distinct Cotton effects upon interaction with a chiral substrate are frequently used for structural investigations of inclusion complexes,[7] chiral ion pairs[8] and supramolecular architectures.[9] The same principles have been introduced by us and others to determine the absolute configuration and enantiomeric composition of chiral compounds that lack a strong chromophore.[10] Rosini, Toniolo and others covalently attached a conformationally flexible biphenyl reporter moiety to chiral amino acids, carboxylic acids and alcohols and showed that the induced CD signals are directly related to the absolute configuration of the substrates used.[11] Berova and others demonstrated that configurational analysis can also be achieved with hydrogen bond adducts[12] and porphyrin-derived metal complexes.[13] Similarly, Anslyn and Kleij introduced exciton-coupled circular dichroism protocols that exploit zinc and copper complexes for quantitative ee determination of chiral compounds.[14] Despite all these efforts, optical sensing is still limited to few classes of compounds and the analysis of chiral aldehydes has remained particularly challenging.[15] The introduction of new effective ICD probes has proven to be quite difficult which has hampered the advance of this emerging field. We have therefore become interested in discovering a rational approach that would provide a practical venue for systematic sensor developments. We now wish to report such a case study using citronellal, arguably one of the most important biologically active chiral aldehydes, as a sensing target.

Our laboratory recently introduced **1** and similar stereodynamic arylacetylene-based dialdehyde probes that generate a strong ICD readout upon condensation with amines and amino alcohols.[16] The diimines obtained with **1** and simple aliphatic amines, such as 2-aminoheptane and 1-cyclohexylethylamine, have characteristic Cotton effects at high wavelengths. We envisioned that due to the rigidity of the imine bond, the underlying concept of central-to-axial chirality induction could lead to the development of an effective ICD sensor for citronellal (Fig. 1). Bisaniline **2** was expected to exist as a CD-silent mixture of rapidly interconverting conformations due to the facile rotation about the triple bond axes. Diimine formation between **2** and citronellal, **3**, would then disrupt this equilibrium and impose axial chirality on the previously fluxional polyarylacetylene scaffold, resulting in distinct amplification of chirality and induced Cotton effects.

We first prepared 1,4-bis((2-bromophenyl)ethynyl)benzene, **4**, *via* palladium catalyzed double Sonogashira coupling of 2-iodobromobenzene, **5**, and 1,4-diethynylbenzene, **6**, in quantitative amounts.

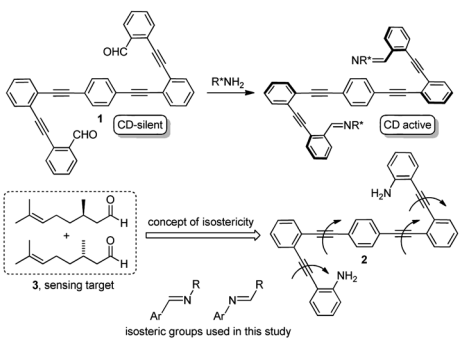

Fig. 1 Chirality imprinting on the arylacetylene scaffold of **1** with primary amines and sensing of the ICD target citronellal, **3**, using 1,4-bis(2(2-anilinylethynyl)phenylethynyl)benzene, **2**.

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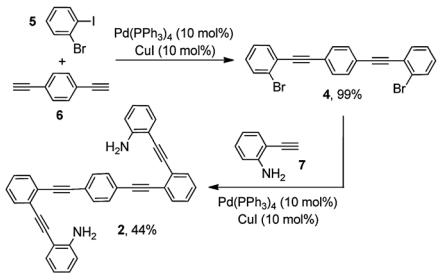
† Electronic supplementary information (ESI) available: Synthetic procedures, and spectroscopic, spectrometric and cystallographic details. CCDC 895201. For ESI and crystallographic data in CIF or other electronic format see 10.1039/c2cc36267h



Scheme 1 Synthesis of bisaniline **2**.

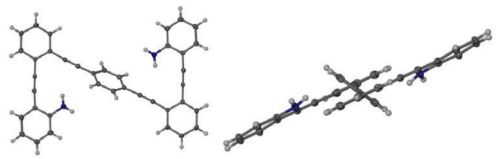


Fig. 2 Two views of the crystal structure of **2**. The dihedral angles between the central 1,4-disubstituted benzene ring and the adjacent 1,2-disubstituted arenes were calculated as 117.06° and 123.75°, respectively.

The coupling of **4** with 2-ethynylaniline, **7**, then gave 1,4-bis(2(2-anilinylethynyl)phenylethynyl)benzene, **2**, in 44% yield (Scheme 1). A single crystal of **2** suitable for X-ray diffraction was obtained by slow evaporation of a saturated solution in chloroform (Fig. 2). In the solid state, bisaniline **2** adopts an essentially flat structure that has the central benzene ring pointing out and lying about an inversion center. In solution, one would expect **2** to exist as a mixture of several conformers that undergo rapid rotation about all four triple bonds. Incorporation of an acetylene unit increases the aryl–aryl distance to approximately 4.0 Å. Accordingly, the energy barrier to rotation in diarylacetylenes is typically low and conformational isomers cannot be isolated at room temperature.[17] This high degree of rotational freedom is a vital property of diarylacetylene-derived molecular turnstiles[18] and gyroscopes.[19]

The condensation reaction between **2** and two equivalents of citronellal was monitored by ^{1}H-NMR, UV and IR spectroscopy (see ESI†). Formation of the expected diimine was evident by NMR and IR spectroscopy showing quantitative disappearance of the formyl protons and the characteristic carbonyl stretching of the aldehyde, respectively. ESI-MS analysis also confirmed conversion to the diimine showing the expected signal for m/z = 781.5 in the positive ion mode (Fig. 3). Interestingly, the reaction can be followed by colorimetric means. While the sensor is colorless the citronellal-derived diimine is light yellow due to a red shift in the UV spectrum (see ESI†).

As expected, the bisaniline **2** is CD-silent in solution because it adopts rapidly interconverting chiral (and achiral) conformations.

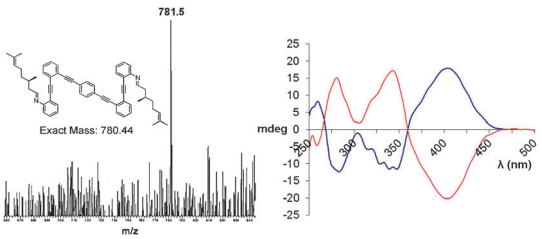


Fig. 3 Left: MS spectrum of the diimine obtained from **2** and **3**. Right: CD spectra of the diimine derived from (*R*)-**3** (blue) or (*S*)-**3** (red) at 9.38 × 10^{-5} M in $CHCl_3$.

By contrast, CD analysis proved that the diimine formed from **2** and citronellal, **3**, has distinct chiroptical properties and affords strong Cotton effects at high wavelengths even at high dilution (Fig. 3). Control experiments with free citronellal at 100 times higher concentrations showed that it is essentially CD-silent under otherwise the same conditions. In light of the distant location of the chiral center in **3** from the imine functions formed during the condensation reaction with **2**, the strong CD output is quite remarkable and indicates a pronounced imprinting of chiral information on the arylacetylene framework. The diimine formation with **3** occurs smoothly at room temperature and the condensation adduct can be analyzed *in situ*, thus eliminating any purification steps prior to the CD measurement.

Sensor **2** does not only provide a strong CD readout upon recognition of a chiral substrate with a remote chiral center, it also turned out to be chemoselective. We found that **2** does not react with α-branched substrates such as perillaldehyde and myrtenal even upon heating and prolonged reaction times. This unexpected selectivity is probably due to increased repulsion between the *ortho*-substituted aniline moieties and these sterically less accessible aldehydes. As a result, the presence of perillaldehyde and myrtenal does not affect the ICD analysis of citronellal.[20] In order to evaluate the practical use of the stereodynamic sensor **2** for quantitative ee determination of citronellal, a calibration curve was constructed using **3** in varying ee. The condensation reaction was carried out at 3.75 mM and the samples were diluted to 9.38 × 10^{-5} M for CD analysis. Plotting of the CD amplitudes at 400 nm *versus* % ee revealed a perfectly linear relationship (Fig. 4). Three scalemic samples of **3** covering a wide ee range (−90, 54 and 88% ee) were then prepared and treated with sensor **2** as described above. Using the linear regression equation calculated from the calibration experiment and the CD amplitudes measured at 400 nm, the enantiomeric excess of these samples was determined. Experimentally obtained data were within 3% of the actual values, see ESI.† To the best of our knowledge this is the first example of enantioselective sensing of the ee of a single chiral aldehyde.

The concept of isostericity applied in this work was inspired by the reciprocity concept used for the rational development of chiral stationary phases (CSPs) for chromatographic separation of enantiomers. A seminal example is the introduction of the Whelk-O HPLC column by Pirkle and coworkers.[21] Assuming reciprocal stereoselective interactions, enantiopure naproxen was immobilized on silica gel to screen racemic CSP candidates by HPLC. The enantiomer of a racemate that was separated with high enantioselectivity was then used to produce a new CSP. The well separated solute turned out to be the invaluable Whelk-O selector. The chiral naproxen based CSP was thus used to develop

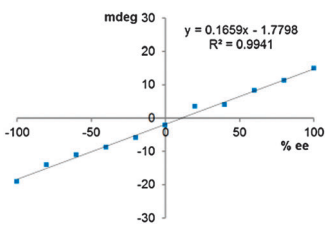


Fig. 4 Plot of the CD amplitude of the diimine at 400 nm *vs.* the ee of **3**. All measurements were conducted at 9.38 × 10^{-5} M in $CHCl_3$.

the Whelk-O column which indeed separates the enantiomers of naproxen and other profens with excellent selectivity. Our results with bisaniline **2** and citronellal demonstrate that a similar rationale, which exploits the central-to-axial chirality induction observed upon condensation between **1** and aliphatic amines, provides a systematic approach for the development of an ICD sensor applicable to enantioselective analysis of a chiral aldehyde.

In summary, the remarkable ICD signals generated upon diimine formation with the intrinsically stereodynamic sensor **2** allows unprecedented enantioselective detection of citronellal at micromolar concentrations and quantitative ee analysis with high accuracy. The use of **2**, which is readily prepared by two Sonogashira couplings, combines several attractive features: (1) The generation of intense Cotton effects at high wavelength reduces interference with chiral impurities and thus facilitates determination of the enantiomeric composition; (2) the *in situ* diimine formation and subsequent CD measurements eliminate elaborate purification steps; (3) the CD assay is operationally simple and requires only minute sample, sensor and solvent amounts which reduces waste production; (4) the sensor is highly selective for citronellal and other chiral aldehydes do not interfere with the chiral induction and chiroptical sensing processes and (5) this sensing method avoids the use of enantiopure derivatizing agents which are often more expensive. Moreover, this work shows that the concept of isostericity provides new means for the rational design of ICD probes or stereodynamic receptors used in chiral amplification processes.

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