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Chiroptical Sensing of Unprotected Amino Acids, Hydroxy Acids, Amino Alcohols, Amines and Carboxylic Acids with Metal Salts

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Optical chirality sensing of unprotected amino acids, hydroxy acids, amino alcohols, amines and carboxylic acids based on a practical mix-and-measure protocol with readily available copper, iron, palladium, manganese, cerium or rhodium salts is demonstrated. The generation of strong Cotton effects allows quantitative *ee* analysis of small sample amounts with high speed. In contrast to previously reported assays the use of chromophoric reporter ligands and the control of metal coordination kinetics and redox chemistry are not necessary which greatly simplifies the sensing procedure with the benefit of reduced waste production and cost.

Chirality plays a fundamental role in nature and across the chemical sciences. The analysis of the enantiomeric composition of chiral compounds has become a crucial task in countless endeavors aimed at developing pharmaceuticals, agrochemicals, materials, molecular devices and other products. For more than 50 years, this field has been dominated by chromatography on chiral stationary phases and by NMR analysis with chiral solvating or derivatizing agents.[1] Despite the introduction of powerful HPLC, SFC[2] and NMR[3] methods, the advance of automated instrumentation and high-throughput expectations in industrial and academic laboratories has shifted increasing attention toward time-efficient optical methods that are compatible with multi-well plate technology and parallel screening setups.[4] The development of metal coordination complexes carrying carefully designed chiral or stereodynamic ligands has led to a wide variety of broadly applicable NMR agents[5] and optical sensors[6] that, in principle, allow simultaneous determination of the enantiomeric excess (*ee*) of chiral compounds.

Optical chirality sensing with metal complexes typically relies on fast analyte coordination or incorporation of the target compound into a supramolecular assembly. These processes affect the photophysical properties of one or more than one chromophoric reporter unit in the sensor scaffold via intramolecular interactions and formation of distinct spatial arrangements. This affords induced or altered circular dichroism, fluorescence or UV signals that can be compared to a calibration curve to calculate the sample *ee* values.[7] A remaining drawback is that the required sensor scaffold may be expensive, moisture sensitive or not commercially available. We have recently reported that quantitative chirality sensing is possible with ligand-free, earth-abundant cobalt salts devoid of an organic reporter moiety.[8] To obtain complexes that are rapidly formed and produce stable CD signals we used Co(II) salts that were treated upon complexation with hydrogen peroxide to afford Co(III) complexes which can be conveniently handled under air. The introduction of inexpensive, readily available metal salts that can be directly applied to *ee* analysis streamlines the assay development because it obviates the need to optimize an organic ligand and it results in a simplified sensing protocol with reduced operational cost and waste. We now demonstrate that this is a generally useful concept and show a variety of examples using manganese, iron, palladium, copper, rhodium and cerium salts in a simple mix-and-measure protocol.

By screening $Pd(NO_3)_2$, $FeCl_2$, $FeCl_3$, $MnCl_2$, $CuCl_2$, $Ce(NO_3)_3$ and $RhCl_3$ we observed strong Cotton effects with a broad variety of chiral ligands (Figure 1). The metal salts and analytes **1**-**26** were simply combined in either MeOH, DMSO or water and then subjected to CD analysis after dilution to 0.5-1.8 mM solutions. In contrast to the chiroptical sensing with cobalt, the use of an oxidant is not necessary and we now extend the auxiliary-free chirality sensing to monofunctional compounds. The samples can be exposed to air and moisture and we believe that it is important to note that the inherent practicality of this sensing procedure greatly facilitates adaptation to automated high-throughput experimentation equipment.

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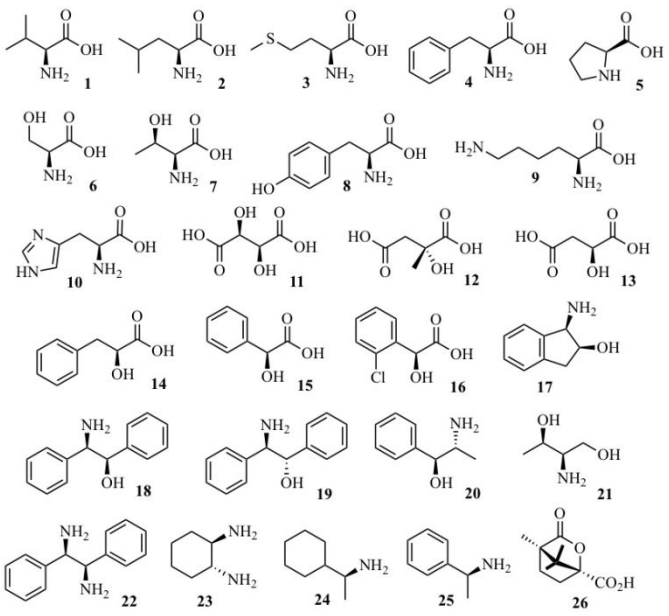

Fig. 1 Structures of chiral ligands tested. Only one enantiomer is shown.

The tested compounds include many examples of amino acids, amino alcohols, hydroxy acids, amines and carboxylic acids. The induced CD (ICD) effects typically have maxima above 300 nm which is advantageous for quantitative *ee* analysis because interference at lower wavelength arising from small amounts of CD-active impurities can typically be avoided. Importantly, the aliphatic and aromatic test compounds are CD-silent or exhibit very weak chiroptical activity in the region under observation in the absence of the metal salts under the same conditions. Representative CD spectra for the sensing of **1**, **8**, **15** and **17** using palladium, iron and copper salts are shown in Figure 2 (see ESI for all examples). It is noteworthy that the sensing with Cu(II) and Fe(III) salts is particularly broad in scope, covering all analytes tested (see ESI). The general simplicity of the sensing workflow originates from a true mix-and-measure procedure as shown below. The sensing also coincides with characteristic colorimetric changes that can be used for naked-eye detection and analyte classification.

Based on the distinct CD effects obtained with $FeCl_3$ and $CuCl_2$ we decided to use our simple mix-and-measure protocol for quantitative analysis of the enantiomeric composition of tartaric acid, **11**, and *cis*-aminoindanol, **17**. The stoichiometry and structures of ferric and cupric complexes carrying amino acid, hydroxy acid, or amine ligands have been reported based on spectrophotometric, potentiometric and mass spectrometric measurements to vary significantly with solvent, pH and other conditions, and several species can co-exist in solution.[9] It is expected that this is also the case for Fe(III) tartrates and Cu(II) aminoindanol complexes which may form mixtures of mono- and polynuclear species.[10] Interestingly, sensing of tartrate with ferric chloride, perchlorate and nitrate salts showed minor differences in the ICD intensities whereas the comparison of the chiroptical signals obtained with *cis*-aminoindanol and cupric chloride, acetate, trifluoroacetate, nitrate, sulfate and perchlorate revealed more significant counteranion effects on both the ICD shapes and intensities (ESI).[11]

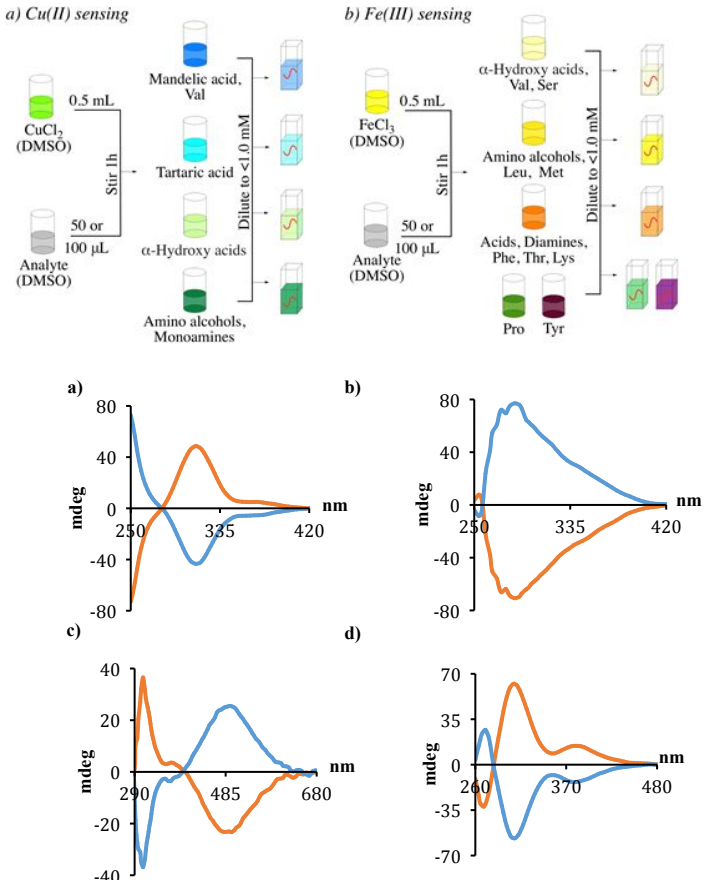

Fig. 2 General workflow of the CD sensing assay and examples of ICD effects obtained for **1** (a), **15** (b), **8** (c) and **17** (d) using $Pd(NO_3)_2$, $FeCl_2$, $FeCl_3$ and $CuCl_2$, respectively. The sensing with Pd(II) was conducted at 1.8 mM in MeOH. All other spectra were collected at 0.5 mM in DMSO.

Altogether, these results indicate that the UV and CD responses observed originate from complex equilibria between co-existing metal complexes. CD titration experiments showed that the addition of (*R,R*)-**11** and (*S,R*)-**17** to $FeCl_3$ and $CuCl_2$, respectively, in DMSO yields maximum Cotton effects at a 3:1 ratio (ESI). We constructed calibration curves with nonracemic tartraric acid samples and found a linear relationship between the induced CD maxima and the sample *ee* values (Figure 3). Using $FeCl_3$ as sensor, TBAOH as base and DMSO as solvent, we then analyzed the enantiomeric composition of 10 samples of **11**. The absolute configuration of the major enantiomer was assigned based on the sign of the ICD signal and the *ee* values were calculated from the amplitude of the measured CD signals at 288 and 338 nm. As is shown in Table 1, we tested samples covering a wide *ee* range with either the (*S,S*)- or the (*R,R*)-enantiomer in excess. In all cases, the absolute error margin is less than 10% which is acceptable for high-throughput screening applications. For example, the enantiomeric compositions of the samples containing (*R,R*)-**11** in 88.0% ee

and (*S,S*)-**11** in 16.0% ee, respectively, were determined as 85.0 and 14.1% ee (entries 1 and 6).

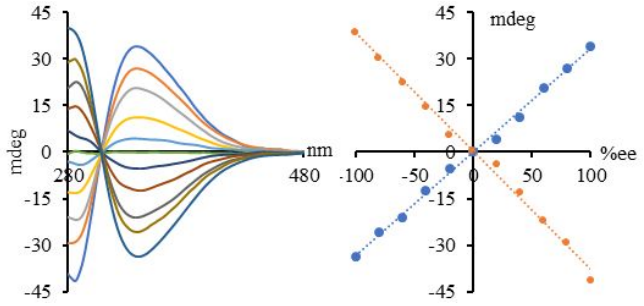

Fig. 3 ICD sensing of tartaric acid samples of varying enantiomeric composition with $FeCl_3$ and plot of the induced maxima at 288 (red) and 338 (blue) nm versus sample ee (0.5 mM, DMSO).

Table 1 Quantitative chirality sensing of tartaric acid samples with $FeCl_3$.

Sample Composition			Chiroptical Sensing Results			
Entry	Abs. Config.	*%ee*	Abs. Config.[a]	*%ee* (ICDs at 288 and 338 nm)[b]		Averaged *%ee*
1	*R,R*	88.0	*R,R*	85.2	84.8	85.0
2	*R,R*	82.0	*R,R*	80.3	83.8	82.0
3	*R,R*	61.0	*R,R*	59.0	59.1	59.1
4	*R,R*	46.0	*R,R*	38.6	34.5	36.5
5	*R,R*	27.0	*R,R*	22.4	17.9	20.1
6	*S,S*	16.0	*S,S*	15.3	12.8	14.1
7	*S,S*	33.0	*S,S*	27.5	29.7	28.6
8	*S,S*	57.0	*S,S*	66.3	64.4	65.4
9	*S,S*	76.0	*S,S*	75.3	72.6	74.0
10	*S,S*	94.0	*S,S*	97.2	98.5	97.9

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

Interestingly, the sensing of the amino alcohol **17** with copper(II) chloride in DMSO revealed a nonlinear relationship between the ICD maxima at 308 and 382 nm and the sample *ee*'s (Figure 4). This, however, does not affect the accuracy of the quantitative analysis. The determination of the absolute configuration and enantiomeric composition of 5 nonracemic samples is shown in Table 2.

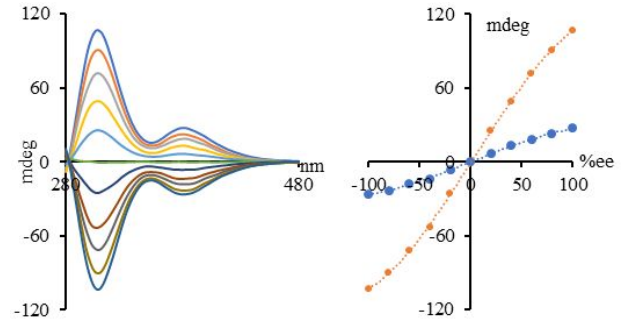

Fig. 4 ICD sensing of *cis*-aminoindanol samples of varying enantiomeric composition using $CuCl_2$ and plot of the induced maxima at 308 (red) and 382 (blue) nm versus sample ee (0.9 mM, DMSO).

Table 2 Quantitative chirality sensing of *cis*-aminoindanol samples with $CuCl_2$.

Sample Composition			Chiroptical Sensing Results			
Entry	Abs. Config.	*%ee*	Abs. Config.[a]	*%ee* (ICDs at 308 and 382 nm)[b]		Averaged *%ee*
1	*RS*	88.0	*RS*	88.1	87.1	87.6
2	*RS*	46.0	*RS*	48.3	48.2	48.2
3	*SR*	16.0	*SR*	14.2	14.3	14.3
4	*SR*	76.0	*SR*	75.0	73.3	74.2
5	*SR*	94.0	*SR*	95.2	88.6	91.9

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

The absolute configuration of the major enantiomer was correctly assigned in all cases and the averaged *%ee* values remained within a 3% absolute error margin. Additional CD studies with amino alcohols showed that simultaneous *ee* determination of mixtures containing two or more than two chiral substrates remains complicated. In such a case, we observed significant CD changes that may be attributed to the formation of interfering ternary complexes that are derived from both substrates.

In summary, we have shown that optical chirality sensing of 26 unprotected amino acids, hydroxy acids, amino alcohols, amines and carboxylic acids is possible with readily available copper, iron, palladium, manganese, cerium or rhodium salts. The broad scope of inexpensive Cu(II) and Fe(III) chlorides that have been successfully applied to chiroptical sensing of a variety of mono and multifunctional compounds is particularly attractive and we were able to determine *ee* values of nonracemic samples of tartaric acid and aminoindanol with good accuracy. This mix-and-measure method is very practical, fast and does not require anhydrous solvents or inert reaction conditions. The metal salt and the chiral sample are simply mixed, stirred for one hour and then subjected to CD analysis. A stoichiometric amount of TBAOH is added when acidic compounds are analyzed. The use of a chromophoric ligand or other reagents is not necessary and one can use MeOH, DMSO or water as solvent. We believe that the time efficiency, operational simplicity, solvent compatibility and the reduced cost are advantageous features of this optical sensing assay and we note that it can be easily adapted to high-throughput experimentation equipment for parallel *ee* analysis of hundreds of samples.

Conflicts of interest

There are no conflicts to declare.

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