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Chiroptical Asymmetric Reaction Screening via Multicomponent Self-Assembly

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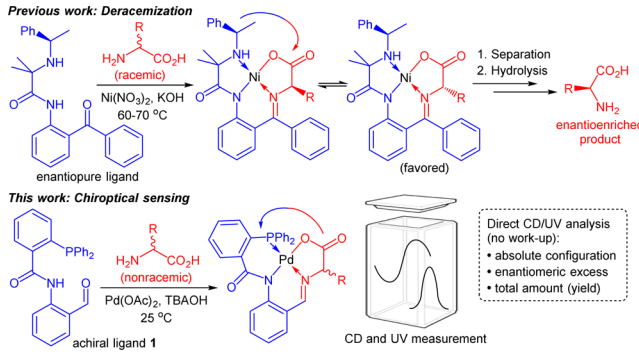
Supporting Information

ABSTRACT: Self-assembly of a stereodynamic phosphine ligand, Pd(II), and a chiral amine, amino alcohol, or amino acid generates characteristic UV and CD signals that can be used for quantitative stereochemical analysis of the bound substrate. A robust mix-and-measure chiroptical sensing protocol has been developed and used to determine the absolute configuration, ee, and yield of an amine produced by Ir-catalyzed asymmetric hydrogenation of an iminium salt. The analysis requires only 1 mg of the crude reaction mixture and minimizes cost, labor, time, and waste.

Asymmetric reaction discovery and development continue to be a top priority in the life sciences. Optimizing synthetic methods typically involves systematic variation of the catalyst structure and evaluation of the effects of temperature, solvent, and other reaction parameters on the product yield and enantiomeric excess (ee). The search for the most favorable protocol can be streamlined with the use of automated high-throughput (HT) experimentation equipment. Hundreds of microscale reactions can now be conducted in parallel, which greatly facilitates the testing of a large number of modifications. In contrast, determining the absolute configuration, ee, and yield has remained disproportionally time-consuming and costly. Analytical methods based on chromatography,[1] mass spectrometry,[2] fluorescence[3] and UV[4] spectroscopy, IR thermography,[5] NMR spectroscopy,[6] electrophoresis,[7] electrochemistry,[8] and biochemical assays[9] undoubtedly have great potential to address this bottleneck.[10] To this end, Berova,[11] Anslyn,[12] Borhan,[13] Canary,[12a,d] our group,[14] and others[15] have developed circular dichroism (CD) probes that can be used for stereochemical analysis of chiral compounds.[16]

A few years ago, Soloshonok et al. reported an efficient diastereomerization reaction in which a racemic amino acid bound as Schiff base to a chiral Ni(II) complex undergoes conversion to either the (*S*)- or the (*R*)-form during heating in the presence of excess of base.[17] Upon completion of the reaction, separation, and hydrolytic cleavage, this thermodynamically controlled process results in deracemization of the substrate and provides practical access to the desired amino acid enantiomer, Scheme 1. Inspired by Soloshonok's work, we now introduce a broadly useful chiroptical sensing method that can be used for quantitative stereochemical analysis of amino acids, amino alcohols, and amines. Our sensing strategy exploits the multicomponent self-assembly of the carefully selected *achiral* ligand **1**, palladium acetate, and an amino acid or generally a compound capable of Schiff base formation. The self-assembly occurs under mild conditions and is accompanied by imprinting of chirality from the sensing target onto the stereodynamic reporter unit in **1**. The sensing target does not racemize at room temperature (rt), and its enantiomeric composition remains unchanged. Amplification of chirality produces a characteristic CD signal and a UV change that can be used to determine the amount, absolute configuration, and ee of the substrate tested. Compared to the de-racemization procedure with a chiral Ni complex described above, we have thus reversed the direction of the asymmetric induction relay by using a supramolecular assembly that is formed from an achiral ligand, $Pd(OAc)_2$, and an amino acid, amino alcohol, or amine under conditions that do not affect the ee of the latter. Moreover, this sensing assay can be used for direct analysis of crude asymmetric reaction mixtures.

Scheme 1. Amino Acid De-racemization with an Enantiopure Ni(II) Complex and Chiroptical Sensing Using an Achiral Pd(II) Complex[a]



[a]The two-colored arrows denote the direction of the ligand to substrate (top) vs substrate to ligand (bottom) chirality induction.

We began our investigation with the synthesis of ligand **1**, Scheme 2. Quantitative protection of 2-nitrobenzaldehyde gave acetal **2**, which was hydrogenated to aniline **3** in 94% yield. Coupling of **3** and 2-(diphenylphosphanyl)benzoic acid in the presence of DCC and HOBt gave the desired amide **4**, which was directly deprotected to afford **1**. For the purpose of HT applications, it is important that the three-component assembly shown in Scheme 1 is complete within 1 h or preferentially within a few minutes at rt. Furthermore, the chiroptical analysis should operate with small sample amounts at mM concentrations to be fully adaptable to automated reaction screening setups that are

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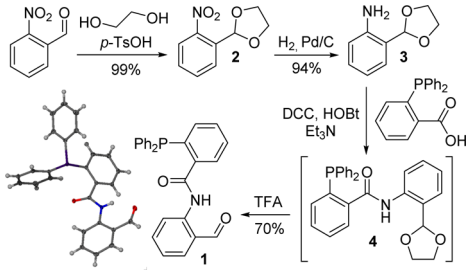
Scheme 2. Synthesis of Phosphine Ligand 1



often conducted on the milligram scale. We rationalized that a chirality probe that strongly binds the target compound and responds to the amount and ee with distinct chiroptical readouts at high wavelengths holds exceptional promise with regard to sensitivity and ruggedness. The latter is invaluable for direct sensing of crude asymmetric reaction mixtures, which typically contain impurities, starting materials, reagents, catalysts, etc. High accuracy of ee and concentration determination, however, is not necessarily a top priority in HT analysis, which aims to identify the best reaction conditions out of hundreds of variations tested in parallel; error margins up to 10% have been considered generally acceptable.[18]

These considerations were used as guidance for the design of ligand **1** and the sensing assay development. We installed the formyl group, which is significantly more reactive than a ketone unit, with the expectation to accomplish covalent substrate binding and assembly of a metal complex at rt within 1 h. The terminal phosphine propeller unit and the extended chromophoric system in **1** were selected to achieve effective chirality imprinting across the metal complex, resulting in characteristic chiroptical signals at high wavelengths, which is desirable to avoid interference with chiral impurities that may be present in reaction mixtures. Screening various combinations of ligand **1**, Ti, Ni, Pd, Pt, Cu, Au, and Zn salts and base additives in MeOH, ACN, $CHCl_3$, or DMSO revealed that the desired assembly with phenylalanine is complete within 15 min when $Pd(OAc)_2$ is used in chloroform in the presence of TBAOH. The stoichiometry and time required for quantitative assembly as well as the absence of amino acid racemization were confirmed by ESI-MS, ^1H and ^{31}P NMR, and CD spectroscopy, see the Supporting Information (SI).

When we applied a series of 12 amino acids **5**–**16** to our assay, we were pleased to find that strong CD signals are induced by both aromatic and aliphatic substrates, Figure 1. In all cases, the sensing of L-amino acids gave a positive Cotton effect at high wavelengths (typically around 420 nm), while the (*R*)-enantiomers induced the opposite chiroptical sensor response. Supramolecular sensing with **1** thus allows determination of the absolute configuration of small quantities of amino acids. We then continued with investigating the possibility of quantitative ee and concentration determination. CD analysis of the assemblies obtained with nonracemic **5** showed a linear relationship between the maxima at 310 and 420 nm and the % ee of the amino acid, Figure 2. We also observed a steady decrease in the UV absorbance. It is important to note that binding of chiral amino acids yields enantiomeric assemblies that produce opposite Cotton effects but have identical UV properties. In contrast to the CD readouts that correspond to the sample ee, the UV changes can thus be correlated to the concentration of the amino acid, regardless of the enantiomeric composition.

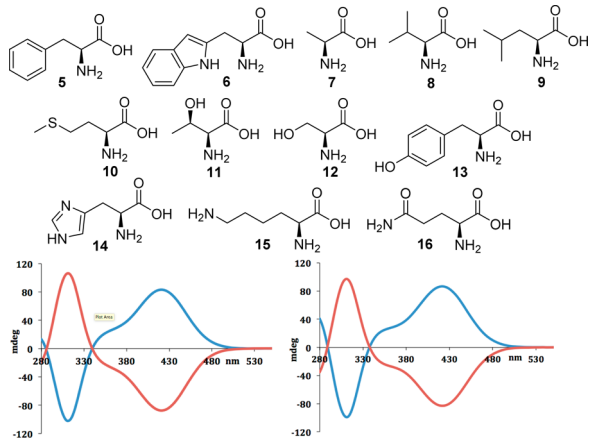


Figure 1. Structures of amino acids tested and CD effects obtained with Phe and Val (2.50×10^{-4} M in $CDCl_3$). The CD effects induced by L-**5** and L-**8** are shown in blue, and the CD responses to the D-enantiomers are shown in red.

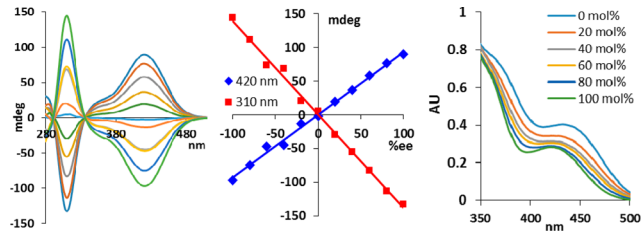


Figure 2. Left: Linear CD effects observed with nonracemic samples of Phe (2.50×10^{-4} M in $CHCl_3$). Right: UV change upon assembly with **1**, $Pd(OAc)_2$, and Phe.

With the quantified CD sensing responses in hand, we used our assay for chiroptical analysis of five nonracemic samples of phenylalanine. In all cases, the absolute configuration of the major enantiomer was correctly identified, and the ee's were calculated with an error margin <5%, Table 1. Knowledge of the UV change

Table 1. Chiroptical Sensing of Nonracemic Phe[a]

sample		chiroptical sensing			
			calcd %ee		
abs config	%ee	abs config	(310 nm)	(420 nm)	averaged %ee
L	76.0	L	77.6	77.7	77.6
L	12.0	L	6.6	7.6	7.1
D	26.0	D	31.5	30.3	30.9
D	68.0	D	71.3	71.2	71.3
D	89.0	D	88.3	88.1	88.2

[a]CD measurements were performed at 2.5×10^{-4} M in $CHCl_3$.

at 390 nm as a function of the relative amount of the sensing target allowed us to determine the concentration of solutions containing Phe at 1.5, 3.5, 5.5, and 8.5 mM. Quantification of the sensor UV responses gave 1.8, 3.5, 6.0, and 8.3 mM, respectively, which correspond well with the actual values, see SI. The amino acid sensing results prompted us to apply amino alcohols **17**–**20** and amines **21**–**25** in our chirality sensing assay, Figure 3. Again, distinct Cotton effects of the corresponding assemblies were observed with both aromatic and aliphatic compounds, which underscores the general utility of this sensing approach. As expected, the characteristic CD induction and UV change that occur as a result of the Pd(II)-centered assembly can be used for

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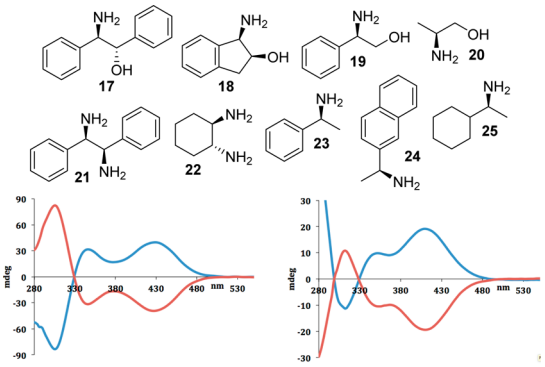


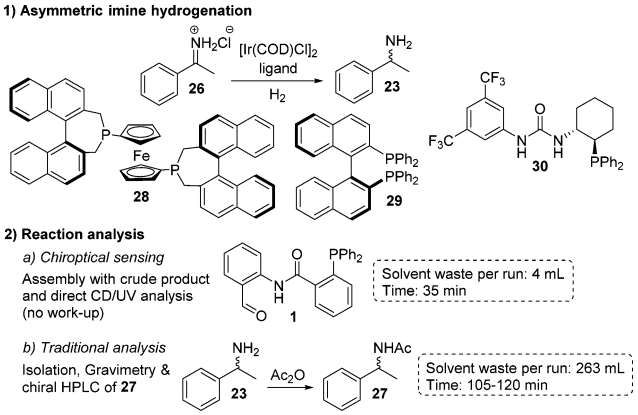
Figure 3. Structures of amino alcohols and amines tested and CDs obtained with the assemblies derived from **17** and **24**. CD measurements were conducted at 2.5×10^{-4} M in $CHCl_3$.

quantitative ee and concentration determination, which was verified with amine **23**, see SI.

The practicality, sensitivity, time efficiency, and wide application scope of chiroptical sensing via Schiff base formation and concomitant multicomponent assembly with the readily available ligand **1** and $Pd(OAc)_2$ compare well with many previously reported optical assays.[19] The ultimate test for any sensing method, however, is the direct analysis of asymmetric reactions, which has remained a major challenge to date. Very promising steps toward this goal have been made with a variety of optical sensors,[20] but lack of assay robustness, restriction to immobilized or labeled starting materials, need for product derivatization or isolation, and the supplementary use of chromatography to determine yield are typical limitations. We recently demonstrated that chiroptical sensing of crude product mixtures obtained by asymmetric dihydroxylation of alkenes or reduction of keto acids is possible with stereodynamic metal complexes and Bronsted/Lewis acid probes, respectively.[21] The chirality sensing discussed herein combines key features of these approaches by integrating metal complexation and covalent substrate binding in a supramolecular assembly.

The strong chiroptical signals above 400 nm of our chirality sensing assembly prompted us to test its value for asymmetric reaction analysis using the Ir-catalyzed asymmetric hydrogenation of the iminium chloride **26** to amine **23** as an example.[22] We expected that interference from the chiral catalyst or byproducts with the CD measurements would be minimal at 415 nm. We conducted five reactions with different phosphine ligands and catalyst loading, Scheme 3. The yield, ee, and absolute configuration of the major enantiomer of **23** were determined for each reaction using (a) the traditional approach based on gravimetric yield analysis and chiral HPLC ee determination with the *N*-acetyl amine **27** and (b) our chiroptical assay. For the latter, ~1 mg of the crude reaction mixture was directly employed in the assembly and then subjected to CD and UV analysis. This required 4 mL of solvents and a total of 35 min for the complex assembly and the two spectroscopic measurements per sample. Because the sensing experiments can, in principle, be conducted in parallel, the chiroptical analysis of many more samples could essentially be accomplished in the same time frame, and we point out that new calibration curves were not needed. For the traditional reaction analysis, purification of ~40 mg of the reduction product by automated flash chromatography and acetylation of **23** with acetic anhydride for chiral HPLC enantioseparation took 105–120 min and consumed about 260 mL of solvents per sample, see SI for details. Comparison of the

Scheme 3. Asymmetric Imine Hydrogenation and Reaction Analysis



results obtained by the traditional and the sensing analyses show that error margins are within the accuracy expected for HTS applications, Table 2. Our probe dramatically reduces labor, solvent waste, and analysis time and is suitable for direct asymmetric reaction analysis of mg amounts of crude materials.

Table 2. Results of the Reaction Analysis by Traditional and Chiroptical Sensing Methods[a]

asymmetric hydrogenation		traditional analysis		chiroptical sensing	
entry	ligand	yield (%)	%ee (*R*)	yield (%)	%ee (*R*)
1[b]	**28**	70.6	44.4	65.4	38.6
2[b]	**29**	52.7	33.8	59.4	37.8
3[c]	**28**	70.2	64.0	61.1	62.6
4[c]	**29**	72.4	10.2	78.2	12.5
5[d]	**30**	69.3	0.7	68.3	0.4

[a]Reaction conditions: iminium chloride **26** (0.25 mmol) and 5–10 mol% Ir catalyst in 4 mL of MeOH/DCM (2:1) at 25 °C; H_2 pressure was 150 psi; 24 h (entry 2, 48 h). [b]$[Ir(COD)Cl]_2$/ligand/**26** = 2.5/5/100. [c]$[Ir(COD)Cl]_2$/ligand/**26** = 5/10/100. [d]$[Ir(COD)Cl]_2$/ligand/**26** = 5/20/100.

In conclusion, a multicomponent metal-centered assembly was developed and used for chiroptical sensing of the absolute configuration, enantiomeric composition, and total amount of amino acids, amino alcohols, and amines. The general utility was successfully tested with—but is not limited to—21 chiral compounds. The ruggedness of the method was further verified by direct analysis of the sense of asymmetric induction, ee, and yield of the asymmetric hydrogenation of an imine. Excellent sensing results were obtained using just 1 mg of crude reaction mixtures. The elimination of cumbersome reaction workup, compatibility with a milligram reaction scale, and reduction of both the analysis time and waste are important advantages of this chiroptical sensing method over traditional techniques.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b08892.

Experimental procedures, compound characterization, and reaction analysis details (PDF)

X-ray crystallographic data (CIF)

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Notes

The authors declare no competing financial interest.

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