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Chirality Sensing of Amines, Diamines, Amino Acids, Amino Alcohols, and α-Hydroxy Acids with a Single Probe

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Supporting Information

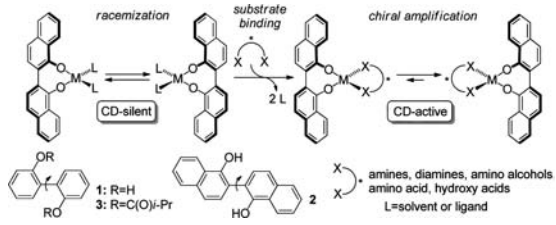
ABSTRACT: A stereodynamic probe for determination of the absolute configuration and enantiomeric composition of chiral amines, diamines, amino alcohols, amino acids, and α-hydroxy carboxylic acids is described. The chirality sensing is based on spontaneous asymmetric transformation of the first kind with stereolabile binaphtholate boron and zinc complexes. The substrate binding and chiral amplification processes yield a distinctive chiroptical sensor output at high wavelength that can be used for rapid and accurate ee detection of minute sample amounts.

Chirality plays an essential role in nature and throughout the chemical sciences. Enantioselective synthesis and analysis of chiral compounds have become central aspects of drug discovery, material sciences, and other rapidly expanding research areas. The advance of combinatorial methods and automated synthesis allows the production of large numbers of chiral samples literally overnight. The steadily increasing efficiency in asymmetric synthesis has shifted focus toward the development of time efficient optical techniques with potential for high-throughput screening.[1] In this regard, chiroptical methods are particularly promising. Following Nakanishi's and Berova's seminal work with porphyrin receptors,[2] many examples of chirality sensing with CD probes have been reported by Rosini,[3] Anslyn,[4] Canary,[5] Borhan,[6] Toniolo,[7] Gawronski,[8] our group,[9] and others.[10]

We initiated a search for a universal CD probe that is capable of fast and sensitive detection of the chirality and ee of a large variety of important targets. We envisioned that this can be accomplished with a chromophoric tropos ligand that (a) reacts with Et_2Zn and $B(OMe)_3$ toward stable complexes capable of binding stoichiometric amounts of a wide variety of *N*- and *O*-donating compounds, (b) is prone to an instantaneous and distinctive chiral amplification process upon coordination of a chiral substrate to such a complex, and (c) provides a strong CD response to the binding event at high wavelengths and low concentration. These considerations pointed us to biphenol **1** and binaphthol **2**, and we decided to first use commercially available **1** to assess the stereodynamic properties and suitability for chiroptical sensing applications (Scheme 1).

Biphenol and its derivatives have found widespread applications as amplifiers of molecular chirality in liquid crystals[11] and as a practical means to improve the efficiency of catalytic enantioselective reactions.[12] Mikami, Kwit, and others have reported that the addition of biphenols to metal-catalyzed

Scheme 1. CD Sensing with a Binaphtholate Probe



reactions can increase the yield and ee.[13] The dynamic stereochemistry of biphenol and its analogues is critical in any of the applications mentioned above. Surprisingly, experimental racemization data for these compounds have not been reported and little is known about other tropos ligands. Maier and Trapp recently determined the enantioconversion barrier of a series of biphep (2,2′-bis(diphenylphosphino)-1,1′-biphenyl) ligands by dynamic HPLC.[14] These ligands racemize at rt but may become conformationally stable upon formation of a metal complex.[15] Gagné observed that coordination of biphep to Pt increases its rotational energy barrier by ∼30% from 90 kJ/mol (398 K) to 123 kJ/mol (382 K).[16]

We first attempted to determine the racemization kinetics of **1** by dynamic HPLC at low temperatures. The screening of several chiral stationary phases even at −60 °C did not show a sign of enantioseparation, and we therefore decided to resort to variable-temperature NMR analysis of 1,1′-biphenyl-2,2′-diol diisobutyrate **3** (Supporting Information (SI)). Analysis of the coalescence of the diastereotopic methyl protons at low temperature allowed us to determine the rotational barrier, $\Delta G^{\ddagger}$, as 52.6 kJ/mol. This value is in good agreement with Fujimura's DFT calculation suggesting a racemization barrier of 48.1 kJ/mol for **1**.[17] Based on Gagné's study with biphep and because the buttressing effect of the fused benzene rings on the ortho-substituents in **1** is expected to increase the rotational energy barrier by no more than 10%,[18] we concluded that both **1** and **2** undergo instantaneous enantioconversion at rt even in a metal complex.

To corroborate the chirality sensing strategy depicted in Scheme 1, we added a stoichiometric amount of enantiopure 1,2-diphenyl-1,2-diaminoethane to a complex formed from biphenol **1** and diethyl zinc at 3.0×10^{-4} M in diethyl ether. A weak CD response above 300 nm was indeed observed, but the complex proved unstable and quickly decomposed upon exposure to air. In an effort to improve the stability and to enhance the chiral amplification, tropos ligand **2** was synthesized with the

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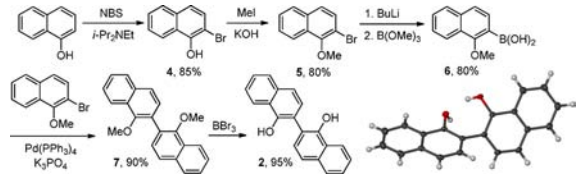
Scheme 2. Synthesis and Crystal Structure of Binaphthol 2



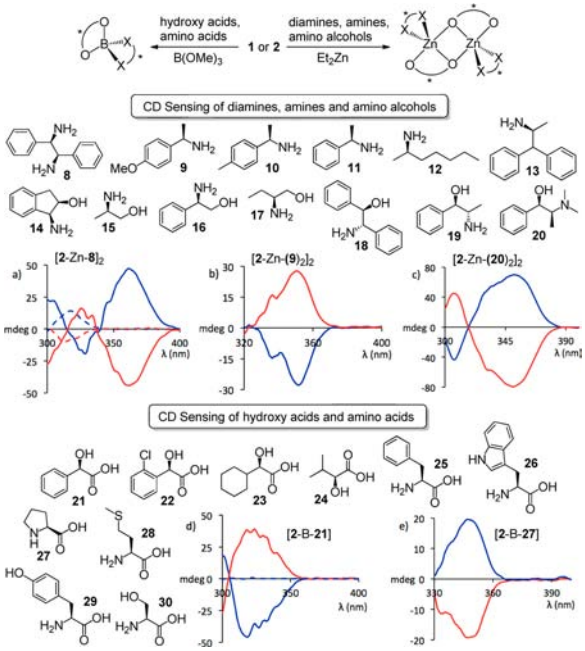


Figure 1. Top: General CD sensing scheme. Bottom: (a) CD spectra of the Zn complex derived from **2** and (1*R*,2*R*)-**8** (solid blue) or (1*S*,2*S*)-**8** (solid red) and from **1** and (1*R*,2*R*)-**8** (dashed blue) or (1*S*,2*S*)-**8** (dashed red). (b) CD spectra of the Zn complex derived from **2** and (*R*)-**9** (blue) or (*S*)-**9** (red). (c) CD spectra of the Zn complex derived from **2** and (1*R*,2*S*)-**20** (blue) or (1*S*,2*R*)-**20** (red). (d) CD spectra of the B complex derived from **2** and (*R*)-**21** (solid blue) or (*S*)-**21** (solid red) and from **1** and (*R*)-**21** (dashed blue). (e) CD spectra of the B complex derived from **2** and (*R*)-**27** (blue) or (*S*)-**27** (red). Concentrations of samples were 3.0×10^{-4} M in Et_2O. Only one enantiomer of the substrates tested is shown.

expectation that this probe would give a stronger chiroptical readout and shift the CD signal to higher wavelengths (Scheme 2).[19]

We were pleased to find that enantioselective recognition of diamine **8** with **2** gives a red-shifted and much stronger CD signal than **1** under identical conditions (Figure 1a). The substrate scope was then expanded to include monoamines **9**−**13** and primary and tertiary amino alcohols **14**−**20**. The CD sensing of all aliphatic and aromatic compounds tested with the zinc binaphtholate gave strong Cotton effects showing a maximum at ~350 nm (Figure 1a−c and SI). The CD signals appear immediately after the samples are mixed, and all measurements were taken within 5 min. We found that the binaphtholates prepared from $Mg(Ot\text{-}Bu)_2$, $Zn(OTf)_2$, and $Al(Oi\text{-}Pr)_3$ are also suitable for CD sensing but superior results were generally obtained with Et_2Zn. A closer look at the sign of the maximum CD amplitudes reveals trends that allow prediction of the absolute configuration (Table 1). A positive CD maximum is observed for amines with an *S* configuration while the opposite is true for *R* amines (entries 2−6). Amino alcohols having a single

Table 1. Chiroptical Sensing of 8−30

Entry	Substrate Class	Substrate	Δ_{max} (mdeg)[a]	λ_{max}	Predicted CD Signal[b]
1	DA	(1*R*,2*R*)-**8**	+47	362	+
		(1*S*,2*S*)-**8**	-44		-
2	MA	(*R*)-**9**	-28	351	-
		(*S*)-**9**	+28		+
3	MA	(*R*)-**10**	-16	352	-
		(*S*)-**10**	+21		+
4	MA	(*R*)-**11**	-12	351	-
		(*S*)-**11**	+12		+
5	MA	(*R*)-**12**	-11	314[c]	-
		(*S*)-**12**	+12		+
6	MA	(*R*)-**13**	-10	346	-
		(*S*)-**13**	+9		+
7	AA	(1*R*,2*S*)-**14**	-23	311[c]	-
		(1*S*,2*R*)-**14**	+22		+
8	AA	(*R*)-**15**	+13	348	+
		(*S*)-**15**	-13		-
9	AA	(*R*)-**16**	+20	345	+
		(*S*)-**16**	-17		-
10	AA	(*R*)-**17**	+16	348	+
		(*S*)-**17**	-18		-
11	AA	(1*R*,2*S*)-**18**	+59	345	+
		(1*S*,2*R*)-**18**	-58		-
12	AA	(1*R*,2*S*)-**19**	+62	345	+
		(1*S*,2*R*)-**19**	-56		-
13	AA	(1*R*,2*S*)-**20**	+70	350	+
		(1*S*,2*R*)-**20**	-79		-
14	HA	(*R*)-**21**	-44	319	-
		(*S*)-**21**	+41		+
15	HA	(*R*)-**22**	-30	318	-
		(*S*)-**22**	+32		+
16	HA	(*R*)-**23**	-21	321	-
		(*S*)-**23**	+19		+
17	HA	(*R*)-**24**	-23	315	-
		(*S*)-**24**	+23		+
18	AC	(*R*)-**25**	+28	351	+
		(*S*)-**25**	-25		-
19	AC	(*R*)-**26**	+19	352	+
		(*S*)-**26**	-16		-
20	AC	(*R*)-**27**	+19	348	+
		(*S*)-**27**	-19		-
21	AC	(*R*)-**28**	+14	349	+
		(*S*)-**28**	-13		-
22	AC	(*R*)-**29**	+11	350	+
		(*S*)-**29**	-11		-
23	AC	(*R*)-**30**	+9	354	+
		(*S*)-**30**	-10		-

[a]All CD measurements were conducted within 5 min after mixing the probe, Et_2Zn, or $B(OMe)_3$ and the substrate at 3.0×10^{-4} M in Et_2O or $CHCl_3$. [b]Predicted sign at 350 nm for monoamines: *R* is negative, *S* is positive; amino alcohols: *R* is positive, *S* is negative; amino alcohols with two chiral centers (the absolute configuration at the amino group is determined): *R* is negative, *S* is positive. Note that due to nomenclature rules the amino moiety in aminoindanol is at C-1 but at C-2 in the other amino alcohols; α-hydroxy acids: *R* is negative, *S* is positive; amino acids: *R* is positive, *S* is negative. [c]The CD sensing of **12** and **14** also yields a signal at 350 nm. DA = diamine, MA = monoamine, AA = amino alcohol, HA = hydroxy acid, AC = amino acid.

chiral center yield a positive couplet for the *R* enantiomer and a negative CD response at 350 nm for the *S* antipodes (entries 8−10). The opposite rule applies to amino alcohols with two chiral centers (entries 7 and 11−13).

Interestingly, mass spectrometric analysis of solutions containing **8** and **9**, respectively, showed a bimetallic species with a stoichiometry of 2:2:2 (**2**:Zn:**8**) and 2:2:4 in the case of monodentate **9** (SI). Despite the important role in asymmetric

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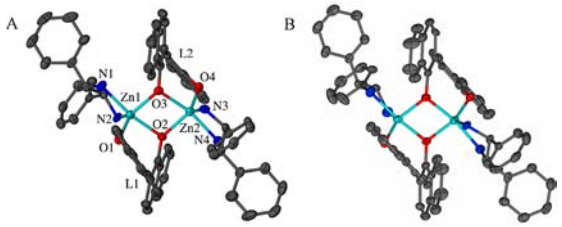

Figure 2. Crystal structure of the Zn complexes obtained with **2** and (1*S*,2*S*)-**8** (H's are omitted for clarity). Selected distances [Å] and angles [deg] for complex A: Zn1−O1 1.926, Zn1−O2 2.087, Zn1−N1 2.144, Zn1−N2 2.095, L1 aryl−aryl torsion angle 46.7, L2 aryl−aryl torsion 41.8. Complex B: L1 aryl−aryl torsion 50.7, L2 aryl−aryl torsion 51.1.

catalysis, very little about the structure of (biphenolate)- and (binaphtholate)Zn(diamine) complexes is known. Walsh et al. reported the X-ray structure of a monometallic zinc complex carrying 3,3′-diphenyl-BINOLate and a bulky secondary diamine having the generally accepted 1:1:1 stoichiometry with a tetrahedral Zn center.[20] Slow diffusion of diethyl ether into a chloroform solution of **2**, Et_2Zn, and **8** gave blue single crystals. X-ray analysis showed two complexes in the asymmetric unit, both having a bimetallic structure with a 2:2:2 stoichiometry which is in agreement with our MS analysis (Figure 2 and SI). One oxygen of each binaphtholate bridges the two metal centers forming a four-membered μ-oxo ring, while each Zn carries one molecule of bidentate **8** to give a pentacoordinate bimetallic Zn complex. Both metal centers thus afford a slightly distorted bipyramidal geometry. Apparently, the formation of pentacoordinate bimetallic (binaphtholate)Zn(diamine) complexes is favored in the absence of steric hindrance, and we assumed that this finding may prove invaluable for the interpretation of chiral induction and amplification effects in asymmetric catalysis and ee sensing, vide infra. The two binaphtholate ligands have opposite stereochemical bias in the crystal and give an overall (1*S*,2*S*,*P*,*M*) configuration. This was unexpected due to the strong CD output observed in solution and may be attributed to packing forces in the solid state.

For CD sensing of α-hydroxy acids **21**−**24** and amino acids **25**−**30** we chose to replace Et_2Zn with $B(OMe)_3$, following reports from Shan and Riguera on structurally related (BINOLate)borate complexes.[21,22] The employment of biphenol **1** as a probe for CD analysis of **21** was ineffective, and no CD response above 300 nm even at elevated concentrations was observed (Figure 1d). In contrast, the borate complexes obtained with binaphthol **2** and substrates **21**−**24** produced strong CD amplitudes at ∼320 nm, and the expected formation of a negatively charged (binaphtholate)boron(α-alkoxy carboxylate) complex with 1:1:1 stoichiometry was confirmed by MS analysis (SI). Again, the complex formation and subsequent chiroptical response of our probe were instantaneous and CD measurements were performed within 5 min. Inspection of the trend in Table 1 shows that substrates with an *R* configuration display a negative CD couplet at 320 nm, while the opposite applies to the *S* enantiomers (entries 14−17). Finally, we applied several amino acids in our CD assay and found that the instantaneous CD readout can be correlated to the absolute configuration of both aliphatic and aromatic substrates (Figure 1e). All *R* amino acids yielded a positive CD maximum at 350 nm while opposite CD responses were observed for the *S* enantiomers (entries 18−23).

Recently, Anslyn, James, and Bull introduced an attractive assay for the detection and ee analysis of primary amines that is based on a three-component assembly with enantiopure atropos

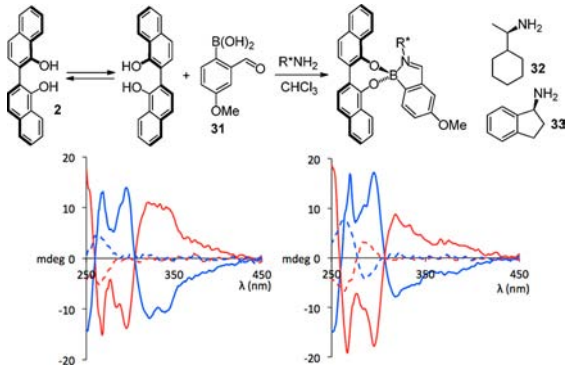

Figure 3. Three-component assembly with **2** and **31**. Left: CD spectra of the reaction products obtained using **2**, **31**, and (*R*)-**32** (solid blue) or (*S*)-**32** (solid red). The spectra shown with dashed lines correspond to the condensation products of **31** with (*R*)-**32** (dashed blue) or (*S*)-**32** (dashed red) in the absence of **2**. Right: The same comparison was performed with amine **33**. Concentrations were 3.75×10^{-5} M in $CHCl_3$.

BINOL and 2-formylphenylboronic acid.[23] We assumed that the covalent binding of monoamines via condensation with a 2-formyl-4-methoxyphenylborate complex carrying binaphtholate **2** would yield a strong CD output originating from asymmetric amplification in our probe. Indeed, weak CD signals below 300 nm were obtained from the condensation product of 2-formyl-4-methoxyphenylboronic acid **31** and amines **11**, **32**, and **33**, respectively. This largely changed when the same reaction was performed in the presence of 1 equiv of **2**, and we observed significantly enhanced Cotton effects at higher wavelengths (Figure 3 and SI). This approach eliminates the use of enantiopure BINOL and solely relies on chiral amplification based on central-to-axial chirality induction with stereolabile binaphthol **2** serving as the CD reporter unit. Compared to the general chirality sensing method with $B(OMe)_3$ and **2** described above, the three-component assembly with **31** is limited to substrates having a primary amino group. But it is not applicable to *N*-methyl ephedrine, **20**, and other amines or amino alcohols with secondary or tertiary amino functions.

In order to prove the efficiency of **2** for fast ee analysis, we measured the CD readout of the Zn complex obtained with **2** and nonracemic samples of **8** and **18**. We found that the chiroptical response of **2** to the enantiomeric substrate composition does not follow a linear trend which is indicative of formation of homo- and heterochiral aggregates (SI).[24] The nonlinear effect in ee sensing is in agreement with our MS and crystallographic detection of bimetallic Zn species.[24a] Nonlinear regression plots provided the basis for accurate analysis of 10 unknown samples (Table 2). The experimentally obtained values were all within 3.4% of the actual ee compositions which is generally considered

Table 2. Quantitative Sensing Results[a]

(1*R*,2*R*)-**8**			(1*S*,2*R*)-**18**		
actual ee (%)	calcd ee (%)	absolute error (%)	actual ee (%)	calcd ee (%)	absolute error (%)
87.0	84.1	2.9	87.0	84.4	2.6
12.0	15.4	3.4	76.0	76.7	0.7
−26.0	−23.5	2.5	12.0	14.9	2.9
−68.0	−65.4	2.6	−26.0	−27.3	1.3
−89.0	−87.0	2.0	−89.0	−87.2	1.8

[a]CD Measurements were performed at 3.0×10^{-5} M in Et_2O.

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sufficient for HTS applications. We also observed that a red shift in the UV spectrum occurs upon substrate recognition which has potential for analysis of the total analyte concentration.

In conclusion, we have introduced a universal probe **2** that can be used for chirality sensing of many monoamines, diamines, amino alcohols, amino acids, and α-hydroxy acids. The enantioselective chemosensing is based on asymmetric transformation of the first kind of stereolabile zinc and boron binaphtholates that undergo prompt chiral amplification upon coordination of a chiral substrate. The central-to-axial chirality induction process can easily be measured by CD spectroscopy, and the sign and the amplitude of the Cotton effect can be correlated to the absolute configuration and ee of the samples tested.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Synthetic details, analytical procedures, MS, UV, CD, fluorescence and NMR spectra, and X-ray analysis. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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