Enantioselective Sensing of Chiral Amino Alcohols with a Stereodynamic Arylacetylene-based Probe

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ABSTRACT Enantioselective induced circular dichroism analysis of amino alcohols has been accomplished using a conformationally flexible arylacetylene-based probe exhibiting two terminal aldehyde groups. The chirality of the amino alcohol substrates is imprinted on the stereodynamic receptor upon [1 + 2] condensation, which ultimately generates a strong chiroptical response. The distinct induced circular dichroism effects of the diimines obtained can be used for enantioselective sensing and enantiomeric excess determination of a wide range of substrates. *Chirality 24:584–589, 2012.* © 2012 Wiley Periodicals, Inc.

KEY WORDS: enantiodifferentiation; stereoselective analysis; induced circular dichroism; molecular recognition

INTRODUCTION

Chiroptical spectroscopy, in particular circular dichroism (CD), has received significant attention in recent years, and an increasing number of efficient and broadly useful assays for the stereochemical analysis of chiral compounds have appeared in the literature.[1] Induced circular dichroism (ICD) is observed when covalent or noncovalent association between a chiral substrate and a UV active, stereodynamic probe favors population of a chiral conformation or configuration of the latter, thus causing a distinct CD output.[2–4] The development of conformationally flexible receptors capable of reporting a molecular recognition event upon binding to a substrate provides new avenues for chiroptical analysis.[5–10] For example, Rosini and Toniolo demonstrated that the absolute configuration of chiral amino acids, carboxylic acids, and alcohols can be correlated to the ICD output of a covalently linked stereodynamic biphenyl reporter unit.[11–16] The same principles have been exploited with molecular bevel gears,[17] propellers,[18] and other well-defined arrangements.[9,19,20] Berova, Nakanishi, Anslyn, Canary, and others have introduced elegant probes showing distinct chiral amplification and ICD signals that can be used for both reliable structural analysis and enantiomeric excess (ee) determination of chiral substrates.[7,19,21–37]

Because of the ever-increasing demand for enantiopure pharmaceuticals, the development of fast, accurate, and practical methods for the stereochemical analysis of amino alcohols, which serve as chiral building blocks of many bioactive compounds, has become very important.[38,39] To date, few probes that exploit the practicality of CD spectroscopy for enantioselective recognition of amino alcohols have been identified, and examples of quantitative analysis of the enantiomeric excess of scalemic mixtures are rare.[40–44] Our group has previously developed 1,8-diheteroarylnaphthalene-derived sensors[45–50] and stereodynamic triaryl-derived probes[43,44] for enantioselective recognition and UV, fluorescence, or CD analysis of amines, carboxylic acids, amino acids, and amino alcohols. Recently, we introduced 1,4-bis(2(2-formylphenylethynyl) phenylethynyl)benzene (**1**, Fig. 1). This dialdehyde was designed to undergo central-to-axial chirality induction upon cyclocondensation with diamines.[51,52] The macrocyclic diimines obtained proved to be highly CD active, which allowed quantitative ee analysis of the substrates used. In addition, **1** was found to give strong Cotton effects suitable for CD analysis when monoamines were employed. We therefore decided to investigate if the substrate scope of **1** can be extended to aromatic and aliphatic amino alcohols.

MATERIALS AND METHODS

General

All reagents and solvents were commercially available and used without further purification. Reactions were carried out under inert atmosphere and anhydrous conditions. Electrospray ionization mass spectra (ESI-MS) were collected with samples dissolved in methanolic chloroform (0.1:10, 0.5 mg/ml).

Enantioselective Sensing Experiments

A stock solution of **1** (0.00375 M) in anhydrous $CDCl_3$ was prepared, and 350-μl aliquots of this solution were placed in 4-ml vials. Then, solutions of the substrates (0.2828 M) in $CDCl_3$ were prepared. For each diimine formation, 10 μl of a substrate stock solution was placed in a vial containing the sensor solution (350 μl) over molecular sieves (4 Å, 8–12 mesh). The reactions were stirred at room temperature for 90 min. Prior to each use, the CD instrument was purged with nitrogen for 20 min at room temperature. CD spectra were collected with a standard sensitivity of 100 mdeg, a data pitch of 0.5 nm, a band width of 1 nm, a scanning speed of 500 nm s^{-1}, and a response of 0.5 s using a quartz cuvette (1 cm path length). The data were baseline corrected and smoothed using a binomial equation. The CD analysis was conducted with sample concentrations of 9.38×10^{-5} M, generally showing acceptable optical density. Control experiments with **5–14** at the same concentration range showed that the free substrates are CD silent in the region of interest.

Calibration Curve and ee Determination

A calibration curve was constructed using samples of **5** with varying ee. A stock solution of **1** (0.00375 M) in anhydrous $CDCl_3$ was prepared, and 350-μl aliquots of this solution were placed in 4-ml vials. Stock solutions of

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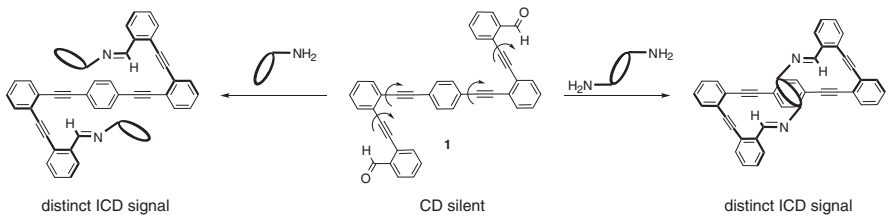


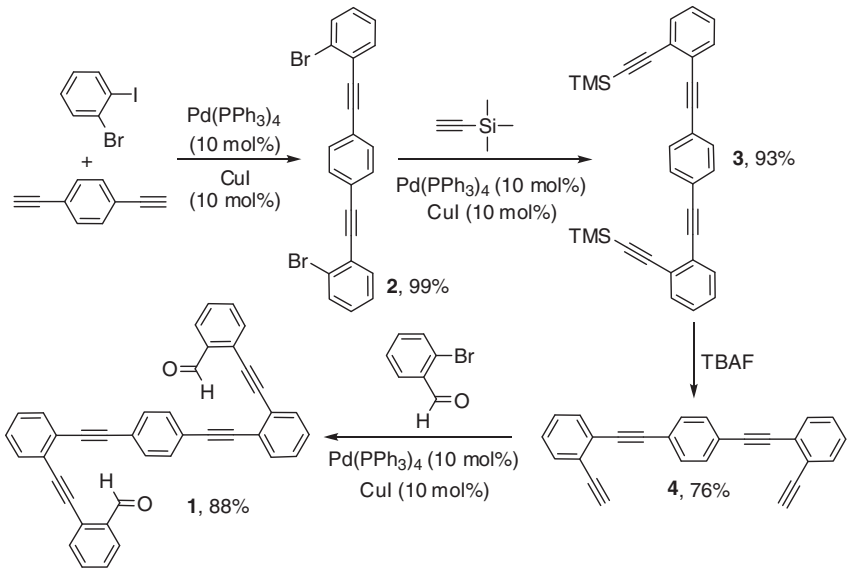
Fig. 1. Schematic illustration of the reaction between **1** and diamines or monoamines towards [1 + 1] or [1 + 2] diimine condensation products, respectively.

5 (0.1313 M) with varying ee composition (+100.0, +80.0, +60.0, +20.0, 0.0, −20.0, −40.0, −60.0, −80.0, −100.0) were prepared in anhydrous $CDCl_3$. For each diimine formation, 10 μl of a substrate stock solution was placed in a vial containing the sensor solution, and molecular sieves (4 Å, 8–12 mesh) were added. The reactions were stirred at room temperature for 90 min. Upon completion, the reaction solution was diluted to 9.38×10^{-5} M for CD analysis. The data were baseline corrected and smoothed using a binomial equation. The CD amplitudes (mdeg) at 290 nm were plotted versus % ee. The calibration curve shows a linear relationship (mdeg = 0.0813 [% ee] + 0.5762) with $R^2 = 0.992$.

RESULTS AND DISCUSSION

Stereodynamic probe **1** was prepared in four steps and 62% overall yield as described previously (Scheme 1).[51,52] Treatment of **1** with all the aromatic and aliphatic amino alcohols **5–14** shown in Figure 2 gave the expected [1 + 2] condensation products. The reaction was monitored by ESI-MS, IR, and NMR spectroscopic analysis, which showed the disappearance of the formyl protons of **1** (Fig. 3 and Supplementary Information). Comparison between the IR spectra of the diimine product and **1** clearly shows that the carbonyl stretching of the aldehyde moiety in **1** (1695 cm^{-1}) disappeared, whereas the relatively weak imine stretching absorption (1637 cm^{-1}) emerged (Fig. 3).

The chiroptical properties of the diimines were then determined by CD spectroscopy without further purification. We were pleased to find that the diimines of aromatic substrates **5–11** provided strong Cotton effects even at



Scheme 1. Synthesis of sensor **1**.

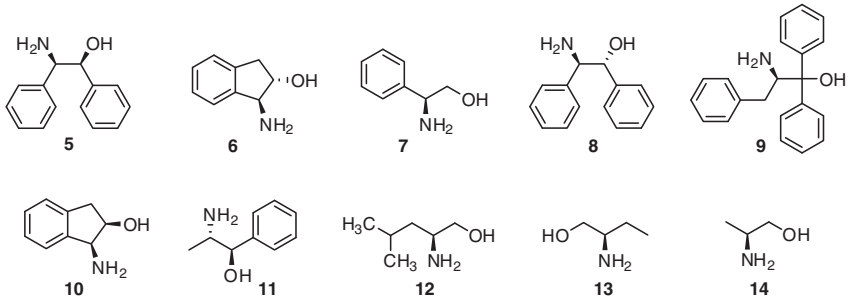


Fig. 2. Structures of amino alcohols tested (only one enantiomer is shown for simplicity).

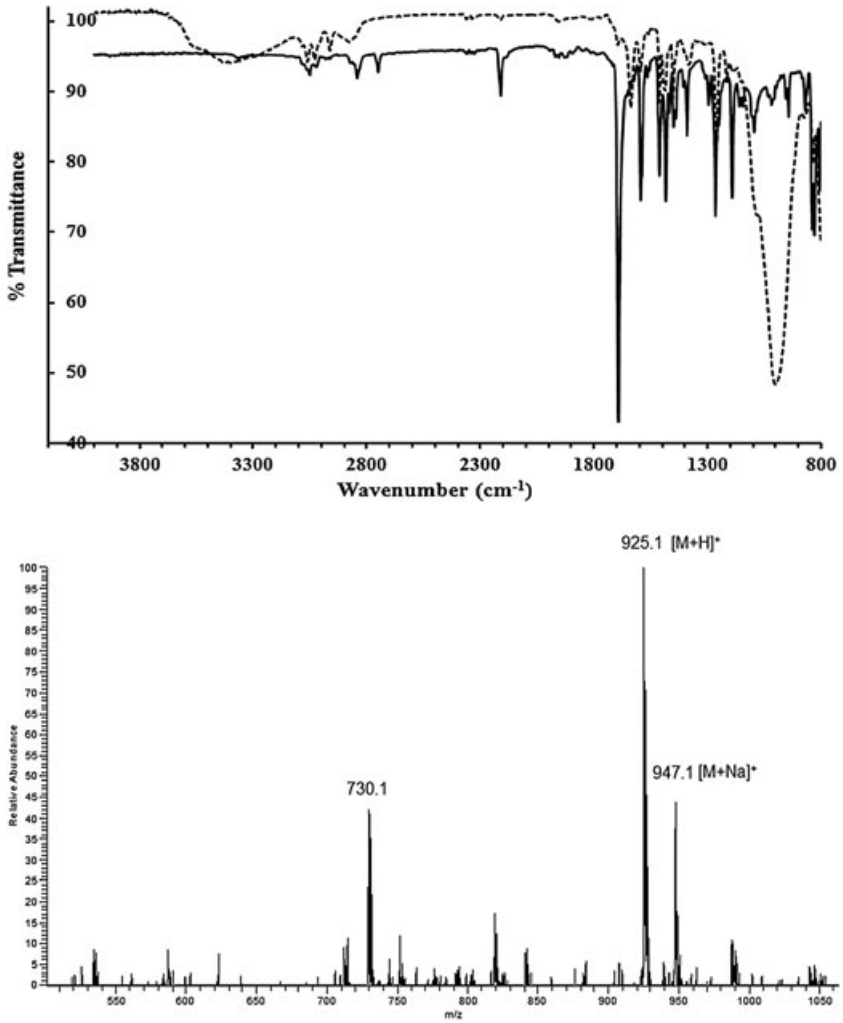


Fig. 3. Top: Stacked IR spectra of **1** (solid line) and the diimine (dashed line) obtained with (1*R*,2*S*)-**5**. Bottom: ESI-MS spectrum of the diimine obtained from **1** and (1*R*,2*S*)-**5** (m/z = 924).

micromolar concentrations albeit with less intensity than previously reported for the condensation products obtained with amines and diamines.[51,52] The CD spectra of the diimines observed for the enantiomers of 2-amino-1,2-diphenylethanol, **5**, show ICD signals that originate from substrate-controlled induction of axial chirality across the arylacetylene framework of the probe (Fig. 4). Similarly, the condensation products obtained with aliphatic substrates **12–14** exhibit distinct Cotton effects suitable for CD analysis. A representative example of the ICD effects obtained by condensation of **1** with the enantiomers of 2-amino-4-methyl-1-pentanol, 12, is shown in Figure 4.

We believe that the diimines formed exist as a complex mixture of rapidly interconverting isomers, each having different thermodynamic stability and chiroptical properties. Therefore, both solvent and temperature effects on the CD amplitude of the **1**-derived condensation product obtained with (1*R*,2*S*)-**5** were investigated. First, the Cotton effects in several solvents (methanol, acetonitrile, diethyl ether, ethyl acetate, hexanes, tetrahydrofuran, and chloroform) were studied. In all cases, a negative Cotton effect was observed. However, the ICD amplitude of the diimine increased about twofold when methanol was used as solvent (Fig. 5). In addition, we found that the ICD signal can be further increased by ~15% when the temperature is reduced from 25 to 5 °C. Both effects are attributed to selective stabilization of a highly CD active conformation of the **1**-derived diimine.

To demonstrate the practical use of sensor **1** in quantitative enantioselective sensing applications, a calibration curve was constructed using amino alcohol **5** in varying ee. The corresponding **1**-derived diimines were prepared in chloroform at 3.75 mM, and the samples were diluted to 9.38×10^{-5} M for CD analysis. Plotting of the CD amplitudes at 290 nm versus % ee showed a linear relationship ($R^2 = 0.992$) (Fig. 6). Four scalemic samples of **5** were then prepared and treated with sensor **1** as described previously. Using the linear regression equation calculated from the calibration curve and the measured CD amplitudes at 290 nm, the enantiomeric excess of these samples was determined. Experimentally obtained data were within 4.4% of the actual values, which is perfectly acceptable for high throughput screening purposes (Table 1). We like to point out that the diimine preparation under the unoptimized conditions used requires 90 min for completion. However, the time for the condensation reaction can

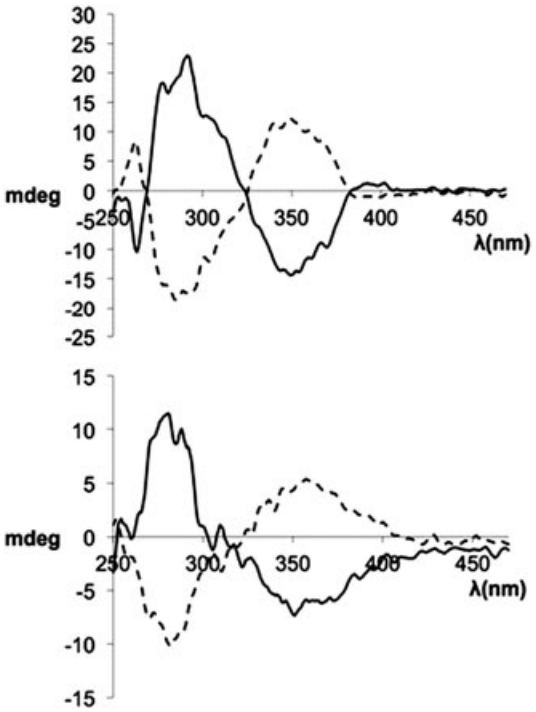


Fig. 4. Top: ICD spectra of the diimines formed from **1** (9.38×10^{-5} M in chloroform) and (1*R*,2*S*)-**5** (solid line) and (1*S*,2*R*)-**5** (dashed line). Bottom: ICD spectra of the diimines formed from **1** and (*R*)-**12** (solid line) and (*S*)-**12** (dashed line) at the same concentration.

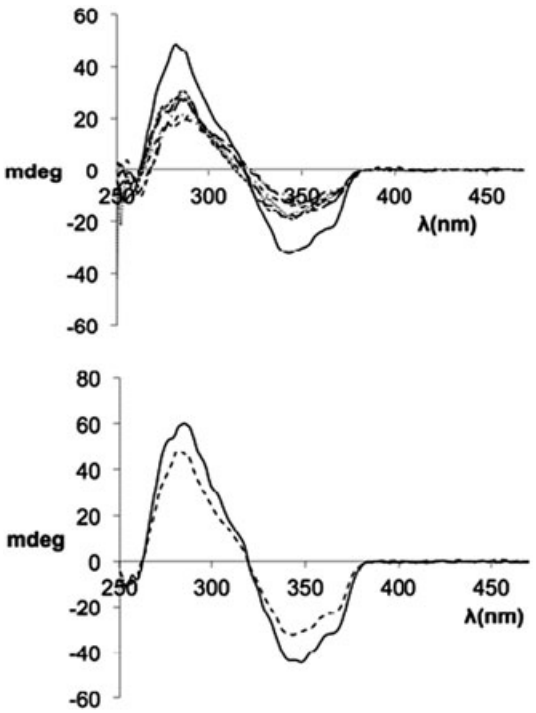


Fig. 5. Top: ICD spectra of the diimine formed from **1** (9.38×10^{-5} M in chloroform) and (1*R*,2*S*)-**5** in methanol (—), acetonitrile (— — —), diethyl ether (– –), ethyl acetate (• •), hexanes (— • —), tetrahydrofuran (– – • – –), and chloroform (— —). Bottom: ICD spectra of the diimine formed from **1** (9.38×10^{-5} M in chloroform) and (1*R*,2*S*)-**5** in methanol at 25 °C (dashed line) and at 5 °C (solid line).

probably be significantly shortened by adding catalytic amounts of acid if a faster readout of the sensing results is desirable.[53]

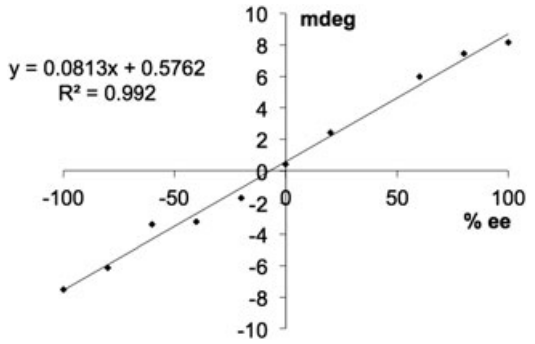


Fig. 6. Calibration curve of the diimines generated from amino alcohol **5** (in varying % ee) and **1**.

TABLE 1. Experimentally determined ee's of four scalemic samples of 5

Actual % ee (1*R*,2*S*)-**5**	Calculated % ee (1*R*,2*S*)-**5**
70.0	74.4
26.0	24.9
−36.0	−31.6
−69.0	−68.2

CONCLUSIONS

In summary, the stereodynamic sensor **1** was prepared with high overall yield in four steps and used for enantioselective sensing of aromatic and aliphatic amino alcohols. Upon diimine formation, this CD silent probe undergoes substrate-controlled chiral induction resulting in bisignate ICD signals that can be used for quantitative ee determination. The Cotton effects obtained with the diimines derived from **1** are both temperature and solvent dependent and generally occur at high wavelengths, which eliminates potential interference from chiral impurities. This probe can be used for enantioselective metal-free in situ CD analysis of chiral amino alcohols and avoids cumbersome isolation and purification of reaction products.

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LITERATURE CITED

1. Nieto S, Lynch VM, Anslyn EV, Kim H, Chin J. High-throughput screening of identity, enantiomeric excess, and concentration using MLCT transitions in CD spectroscopy. J Am Chem 2008;130:9232–9233.
2. Gawroski J, Grajewski J. The significance of induced circular dichroism. Org Lett 2003;5:3301–3303.
3. Allenmark S. Induced circular dichroism by chiral molecular interaction. Chirality 2003;15:409–422.
4. Berova N, Di Bari L, Pescitelli G. Application of electronic circular dichroism in configurational and conformational analysis of organic compounds. Chem Soc Rev 2007;36:914–931.
5. Tumambac GE, Mei X, Wolf C. Stereoselective sensing by substrate-controlled syn/anti interconversion of a stereodynamic fluorosensor. Eur J Org Chem 2004:3850–3856.
6. Kawai H, Katoono R, Fujiwara K, Tsuji T, Suzuki T. Multipoint recognition of catecholamines by hydrindacene-based receptors accompanied by the complexation-induced conformational switching. Chem Eur J 2005; 11:815–824.
7. Katoono R, Kawai H, Fujiwara K, Suzuki T. Change in conformation upon complexation of double-armed terephthalamide hosts: dynamic molecular

recognition of ditopic guests with strong CD signaling. Tetrahedron Lett 2006;47:1513–1518.

8. Kohmoto S, Takeichi H, Kishikawa K, Masu H, Azumaya I. Conformation of S-shaped aromatic imide foldamers and their induced circular dichroism. Tetrahedron Lett 2008;49:1223–1227.
9. Tartaglia S, Pace F, Scafato P, Rosini C. A new case of induced helical chirality in a bichromophoric system: absolute configuration of transparent and flexible diols from the analysis of the electronic circular dichroism spectra of the corresponding di(1-naphthyl)ketals. Org Lett 2008; 10:3421–3424.
10. Kim H, So SM, Yen CPH, Vinhato E, Lough AJ, Hong JI, Kim HJ, Chin J. Highly stereospecific generation of helical chirality by imprinting with amino acids: a universal sensor for amino acid enantiopurity. Angew Chem Int Ed 2008;47:8657–8660. For a review of supramolecular sensors: Hembury GA, Borovkov VV, Inoue Y. Chirality-sensing supramolecular systems. Chem Rev 2008;108:1–73.
11. Superchi S, Casarini D, Laurita A, Bavoso A, Rosini C. Induction of a preferred twist in a biphenyl core by stereogenic centers: a novel approach to the absolute configuration of 1,2- and 1,3-diols. Angew Chem Int Ed 2001;40:451–454.
12. Hosoi S, Kamiya M, Kiuchi F, Ohta T. Chirality transmission in flexible 5,5-dinitrodiphenic esters connected with chiral secondary alcohols. Tetrahedron Lett 2001;42:6315–6317.
13. Mazaleyrat JP, Wright K, Gaucher A, Toulemonde N, Wakselman M, Oancea S, Peggion C, Formaggio F, Setnicka V, Keiderling TA, Toniolo C. Induced axial chirality in the biphenyl core of the C^{α}-tetrasubstituted α-amino acid residue Bip and subsequent propagation of chirality in $(Bip)_n$/Val oligopeptides. J Am Chem Soc 2004;126: 12874–12879.
14. Mazaleyrat JP, Wright K, Gaucher A, Toulemonde N, Dutot L, Wakselman M, Broxterman QB, Kaptein B, Oancea S, Peggion C, Crisma M, Formaggio F, Toniolo C. Induced axial chirality in the biphenyl core of the proatropoisomeric, C^{α}-tetrasubstituted α-amino acid residue Bip in peptides. Chem Eur J 2005;11:6921–6929.
15. Superchi S, Bisaccia R, Casarini D, Laurita A, Rosini C. Flexible biphenyl chromophore as a circular dichroism probe for assignment of the absolute configuration of carboxylic acids. J Am Chem Soc 2006;128: 6893–6902.
16. Dutot L, Wright K, Gaucher Wakselman M, Mazaleyrat JP, De Zotti M, Peggion C, Formaggio F, Toniolo C. The Bip method, based on the induced circular dichroism of a flexible biphenyl probe in terminally protected -Bip-Xaa*- dipeptides, for assignment of the absolute configuration of β-amino acids. J Am Chem Soc 2008;130:5986–5992.
17. Sciebura J, Skowronek P, Gawronski J. Trityl ethers: molecular bevel gears reporting chirality through circular dichroism spectra. Angew Chem Int Ed 2009;48:7069–7072.
18. Katoono R, Kawai H, Fujiwara K, Suzuki T. Dynamic molecular propeller: supramolecular chirality sensing by enhanced chiroptical response through the transmission of point chirality to mobile helicity. J Am Chem Soc 2009;131:16896–16904.
19. Waki M, Abe H, Inouye M. Translation of mutarotation into induced circular dichroism signals through helix inversion of host polymers. Angew Chem Int Ed 2007;46:3059–3061.
20. Kim H, So SM, Yen CPH, Vinhato E, Lough AJ, Hong JI, Kim HJ, Chin J. Highly stereospecific generation of helical chirality by imprinting with amino acids: a universal sensor for amino acid enantiopurity. Angew Chem Int Ed 2008;47:8657–8660.
21. Kikuchi Y, Kobayashi K, Aoyama Y. Complexation of chiral glycols, steroidal polyols, and sugars with a multibenzenoid, achiral host as studied by induced circular dichroism spectroscopy: exciton chirality induction in resorcinol-aldehyde cyclotetramer and its use as a supramolecular probe for the assignments of stereochemistry of chiral guests. J Am Chem Soc 1992;114:1351–1358.
22. Tsukube H, Hosokubo M, Wada M, Shinoda S, Tamiaki H. Chirality probing of amino alcohols with lanthanide complexes via induced circular dichroism spectroscopy. J Chem Soc Dalton Trans 1999: 11–12.
23. Borovkov VV, Lintuluoto JM, Inoue Y. Supramolecular chirogenesis in zinc porphyrins: mechanism, role of guest structure, and application for the absolute configuration determination. J Am Chem Soc 2001;123: 2979–2989.
24. Kurtan T, Nesnas N, Li YQ, Huang X, Nakanishi K, Berova N. Chiral recognition by CD-sensitive dimeric zinc porphyrin host. 1. Chiroptical protocol for absolute configurational assignments of monoalcohols and primary monoamines. J Am Chem Soc 2001;123: 5962–5973.
25. Kurtan T, Nesnas N, Koehn FE, Li YQ, Nakanishi K, Berova N. Chiral recognition by CD-sensitive dimeric zinc porphyrin host. 2. Structural studies of host guest complexes with chiral alcohol and monoamine conjugates. J Am Chem Soc 2001;123:5974–5982.
26. Zhang J, Holmes AE, Sharma A, Brooks NR, Rarig RS, Zubieta J, Canary JW. Derivatization, complexation, and absolute configurational assignment of chiral primary amines: application of exciton-coupled circular dichroism. Chirality 2003;15:180–189.
27. Proni G, Pescitelli G, Huang X, Nakanishi K, Berova N. Magnesium tetraarylporphyrin tweezer: a CD-sensitive host for absolute configurational assignments of α-chiral carboxylic acids. J Am Chem Soc 2003; 125:12914–12927.
28. Yang Q, Olmsted C, Borhan B. Absolute stereochemical determination of chiral carboxylic acids. Org Lett 2002;4:3423–3426.
29. Proni G, Pescitelli G, Huang X, Quaraishi NQ, Nakanishi K, Berova N. Configurational assignment of α-chiral carboxylic acids by complexation to dimeric Zn–porphyrin: host–guest structure, chiral recognition and circular dichroism. Chem Commun 2002:1590–1591.
30. Huang X, Fujioka N, Pescitelli G, Koehn FE, Williamson RT, Nakanishi K, Berova N. Absolute configurational assignments of secondary amines by CD-sensitive dimeric zinc porphyrin host. J Am Chem Soc 2002;124: 10320–10335.
31. Tamiaki H, Unno S, Takeuchi E, Tameshige N, Shinoda S, Tsukube H. Induced circular dichroism by complexation of gadolinium(III) porphyrinates with chiral amino acids and dipeptides: effects of axial β-diketonate ligands on chirality sensing and recognition. Tetrahedron 2003;59: 10477–10483.
32. Ishii H, Chen Y, Miller RA, Karady S, Nakanishi K, Berova N. Chiral recognition of cyclic α-hydroxyketones by CD-sensitive zinc tetraphenylporphyrin tweezer. Chirality 2005;17:305–315.
33. Balaz M, De Napoli M, Holmes AE, Mammana A, Nakanishi K, Berova N, Purrello R. A cationic zinc porphyrin as a chiroptical probe for Z-DNA. Angew Chem Int Ed 2005;44:4006–4009.
34. Holmes AE, Das D, Canary JW. Chelation-enhanced circular dichroism of tripodal bisporphyrin ligands. J Am Chem Soc 2007;129:1506–1507.
35. Berova N, Pescitelli G, Petrovic AG, Proni G. Probing molecular chirality by CD-sensitive dimeric metalloporphyrin hosts. Chem Commun 2009:5958–5980.
36. Canary JW, Mortezaei S, Liang J. Redox-reconfigurable tripodal coordination complexes: stereodynamic molecular switches. Chem Commun 2010; 46:5850–5860.
37. Joyce LA, Maynor MS, Dragna JM, Da Cruz GM, Lynch VM, Canary JW, Anslyn EV. A simple method for the determination of enantiomeric excess and identity of chiral carboxylic acids. J Am Chem 2011;133:13746–13752.
38. Wolf C. Dynamic Stereochemistry of Chiral Compounds. Cambridge: The Royal Society of Chemistry; 2008.
39. He X, Zhang Q, Liu X, Lin L, Feng X. Determination of concentration and enantiomeric excess of amines and amino alcohols with a chiral nickel(II) complex. Chem Commun 2011;47:11641–11643.
40. Tsukube H, Hosokubo M, Wada M, Shinoda S, Tamiaki H. Specific recognition of chiral amino alcohols via lanthanide coordination chemistry: structural optimization of lanthanide tris(β-diketonates) toward effective circular dichroism/fluorescence probing. Inorg Chem 2001; 40:740–745.
41. Frelek J, Grecki M, Jawiski J, Masnyk M, Rukowska P, Szmigielski R. Configurational assignment of *vic*-amino alcohols from their circular dichroism spectra with dirhodium tetracetate as an auxiliary chromophore. Tetrahedron- Asymmetr 2005;16:3188–3197.
42. Li X, Tanasova M, Vasileiou C, Borhan B. Fluorinated porphyrin tweezer: a powerful reporter of absolute configuration for *erythro* and *threo* diols, amino alcohols, and diamines. J Am Chem Soc 2008;130: 1885–1893.
43. Ghosn M, Wolf C. Chiral amplification with a stereodynamic triaryl probe: assignment of the absolute configuration and enantiomeric excess of amino alcohols. J Am Chem Soc 2009;131:16360–16361.
44. Ghosn M, Wolf C. Enantioselective CD analysis of amino acids based on chiral amplification with a stereodynamic probe. Tetrahedron 2010;66: 3989–3994.

45. Mei X, Wolf C. A highly congested *N,N*-dioxide fluorosensor for enantioselective recognition of chiral hydrogen bond donors. Chem Commun 2004:2078–2079.
46. Mei X, Wolf C. Enantioselective sensing of chiral carboxylic acids. J Am Chem Soc 2004;126:14736–14737.
47. Tumambac GE, Wolf C. Enantioselective analysis of an asymmetric reaction using a chiral fluorosensor. Org Lett 2005;7:4045–4048.
48. Mei X, Martin RM, Wolf C. Synthesis of a sterically crowded atropisomeric 1,8-diacridylnaphthalene for dual-mode enantioselective fluorosensing. J Org Chem 2006;71:2854–2861.
49. Liu S, Pestano JPC, Wolf C. Enantioselective fluorescence sensing of chiral α-amino alcohols. J Org Chem 2008;73:4267–4270.
50. Mei X, Wolf C. Determination of enantiomeric excess and concentration of unprotected amino acids, amines, amino alcohols, and carboxylic acids by competitive binding assays with a chiral scandium complex. J Am Chem Soc 2006;128:13326–13327.
51. Iwaniuk DP, Wolf C. A stereodynamic probe providing a chiroptical response to substrate-controlled induction of an axially chiral arylacetylene framework. J Am Chem Soc 2011;133:2414–2417.
52. Iwaniuk DP, Wolf C. Enantioselective sensing of amines based on [1 + 1]-, [2 + 2]-, and [1 + 2]-condensation with fluxional arylacetylene-derived dialdehydes. Org Lett 2011;13:2602–2605.
53. Hine J, Chou Y. Rates of imine formation from acetone and some *N,N*-dimethyl vicinal diamines. J Org Chem 1981;46:649–652.