

ARTICLE

Rapid Organocatalytic Chirality Analysis of Amines, Amino Acids, Alcohols, Amino Alcohols and Diols with Achiral Iso(thio)cyanate Probes†

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

Eryn Nelson,^a Jeffrey S. S. K. Formen^a and C. Wolf^{*a}

The widespread occurrence and significance of chiral compounds does not only require new methods for their enantioselective synthesis but also efficient tools that allow rapid determination of the absolute configuration, enantiomeric composition and overall concentration of nonracemic mixtures. Although chiral analysis is a frequently encountered challenge in the chemical, environmental, materials and health sciences it is typically addressed with slow and laborious chromatographic or NMR spectroscopic techniques. We now show with almost 40 analytes representing 5 different compound classes, including mono-alcohols which are particularly challenging sensing targets, that this task can be solved very quickly by chiroptical sensing with a single, readily available arylisocyanate probe. The probe reacts smoothly and irreversibly with amino and alcohol groups when an organocatalyst is used at room temperature toward urea or carbamate products exhibiting characteristic UV and CD signals above 300 nm. The UV signal induction is not enantioselective and correlated to the total concentration of both enantiomers, the concomitant generation of a CD band allows determination of the enantiomeric composition from the same sample, and the sense of the induced Cotton effect reveals the absolute configuration by comparison with a reference. This approach eliminates complications that can arise when enantiomerically impure NMR derivatizing agents are used and it outperforms time-consuming HPLC protocols. The generation of distinct UV and CD signals at high wavelengths overcomes issues with insufficient resolution of overlapping signals often encountered with chiral NMR solvating agents that rely on weak binding forces. The broad solvent compatibility is another noteworthy and important characteristic of this assay. It addresses frequently encountered problems with insufficient solubility of polar analytes, for example pharmaceuticals, in standard mobile phase mixtures required for chiral HPLC analysis. We anticipate that the broad application spectrum, ruggedness and practicality of organocatalytic chiroptical sensing with aryliso(thio)cyanate probes together with the availability of automated CD multi-well plate readers carry exceptional promise to accelerate chiral compound development projects at reduced cost and with less waste production.

Introduction

Many important natural compounds and synthetic drugs are chiral and their enantiomers typically have individual biological functions or display different pharmacological properties. The determination of the enantiomeric composition of chiral compounds has become a fundamental task in the pharmaceutical business and in many other fields whenever chirality is encountered. This is particularly important in asymmetric synthesis when nonracemic products can be formed or when chiral building blocks of unknown enantiopurity need to be examined prior to use. The differentiation between enantiomers and the quantification of their ratio are, however, often very elaborate and daunting tasks.

Traditionally, enantioselective analysis is accomplished by NMR spectroscopy with the help of either a chiral solvating agent (CSA) or a chiral derivatizing agent (CDA).¹ Alternatively, enantiomers are resolved by chromatography on a chiral stationary phase (CSP) or indirectly after derivatization with a CDA on an achiral stationary phase.² While these methods are well-established and often provide sufficient enantiomeric resolution, they do not satisfy the increasing demand for parallel data acquisition and high-throughput screening capacities. The time usually required for chromatographic enantioseparations is not acceptable when large numbers of samples need to be examined. Both NMR and chromatography are inherently serial techniques which means only one sample can be analyzed at a time. The necessary use of an enantiopure chiral reagent, additive or CSP can increase costs and preparation time. Furthermore, false results are obtained with CDAs that are not perfectly enantiomerically pure.³

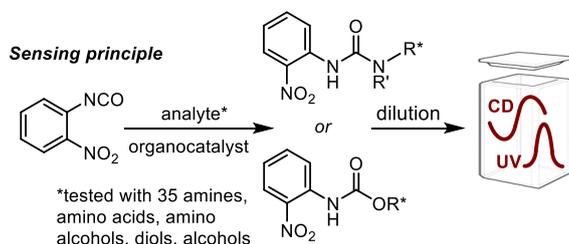
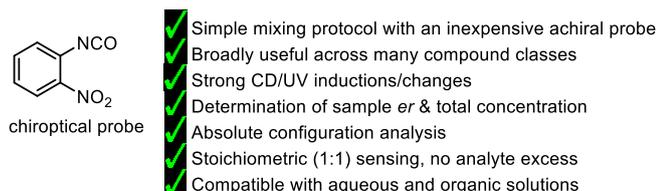
To address these shortcomings in enantioselective analysis, other techniques for example mass spectrometry,⁴ IR thermography,⁵ capillary electrophoresis,⁶ and biochemical assays⁷ have received increasing interest. In particular, optical

^a Department of Chemistry, Georgetown University, Washington, DC, 20057, USA.
E-mail: cw27@georgetown.edu

† Electronic Supplementary Information (ESI) available: Details of experimental conditions and reaction optimization, sensing scope, quantitative concentration and ee determination, and crystallographic data. See DOI: 10.1039/x0xx00000x

methods such as fluorescence,⁸ UV⁹ and circular dichroism (CD) spectroscopy have become popular and cost-effective alternatives for accelerated enantiomeric ratio (*er*) determination, and the potential of cyclic chemiluminescence with luminol immobilized in a flow reactor was recently reported.^{10,11} The simplicity of CD analysis combined with the possibility of fast and parallel data collection at minimal solvent usage can reduce the workload and increase sample throughput. Several examples demonstrating the efficacy of chiroptical *er* determination have been reported.¹²

Optical assay features



Scheme 1 Use of an achiral arylisocyanate probe for quantitative concentration and *er* determination of chiral compounds.

Because CD spectroscopy is inherently primed to distinguish between enantiomers it eliminates the need for CSAs and CDAs, and it allows combined determination of the enantiomeric composition *and* total concentration of a chiral sample if used in conjunction with UV spectroscopy, a task that is easily accomplished with modern spectrophotometers. Herein, we present an inexpensive, commercially available achiral arylisocyanate probe that smoothly reacts with amino and alcohol groups under mild organocatalytic conditions toward urea or carbamate products exhibiting characteristic UV and CD signals above 300 nm which we use for quantitative *er* and concentration analysis, Scheme 1. Our optical sensing assay is easily performed and broadly applicable to amines, amino alcohols, amino acids, diols and the notoriously challenging class of alcohols, which is demonstrated with 35 examples. Cumbersome work-up procedures and the risk of producing false results due to enantiomeric impurities or kinetic resolution effects when CDAs need to be used are avoided. At the same time, the *in situ* generation of distinct UV and CD signals at high wavelengths overcomes issues with insufficient resolution of overlapping signals often encountered with chiral NMR solvating agents that rely on weak binding forces rather than covalent bond formation. The analytes are CD-silent above 300 nm and show none or very weak CD signals in the 200–300 nm region that are not suitable for accurate *er* and concentration determination. In contrast to inherently serial, traditional NMR and chromatographic methods that may consume large

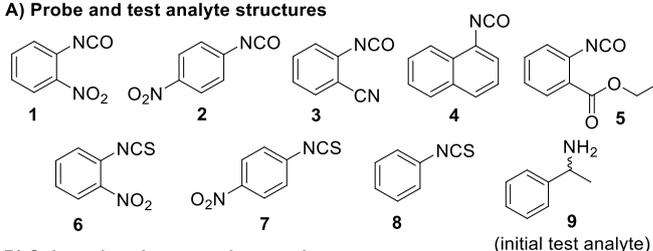
amounts of solvents, our optical sensing assay is operationally simple, cost-effective and amenable to high-throughput experimentation where many samples can be screened in parallel. This has far-reaching implications and potential to streamline chiral compound development projects in numerous laboratories.

Results and Discussion

Chiroptical assay development

At the beginning of this study we screened the ability of the arylis(thio)cyanates **1–8** to react with the enantiomers of 1-phenylethylamine, **9**, toward a CD-active (thio)urea product. All probes carry a chromophore in close proximity of the analyte binding unit which was deemed essential to generate a distinct CD signal suitable for quantitative analysis, Figure 1. The urea formation occurs quantitatively and without by-product formation within 15 minutes which was verified by NMR analysis, see ESI. The reaction mixtures were diluted and directly subjected to CD analysis with a standard CD spectrophotometer and without any work-up or further treatment. We were pleased to observe CD signals with high amplitudes above 350 nm using 2-nitrophenylisocyanate, **1**. Strong CD signal induction at long wavelengths is generally advantageous to eliminate possible interferences from chiral impurities that may produce CD signals typically occurring below 300 nm. The other probes produced blue-shifted CD signals with the exception of the isothiocyanate analogue **6** which, however, showed a relatively weak maximum at 400 nm. As expected, the free (*R*)-enantiomer of amine **9** showed no CD signal in the same region.

A) Probe and test analyte structures



B) Selected probe screening results

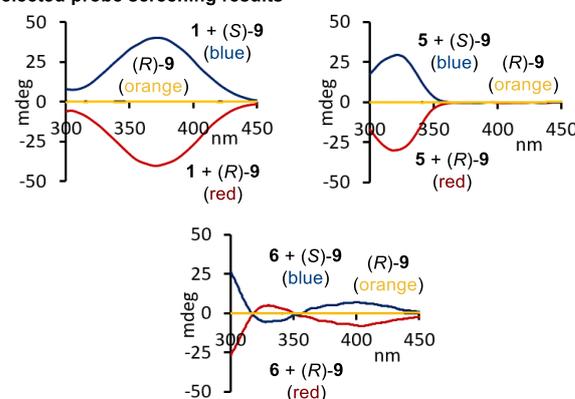


Figure 1 Structures of arylisocyanate and arylisothiocyanates **1–8** and comparison of the chiroptical responses of **1**, **5**, and **6** to the enantiomers of 1-phenylethylamine. The CD spectrum obtained with free (*R*)-**9** under the same conditions but in the absence of an iso(thio)cyanate probe is shown in orange. Conditions: 1-Phenylethylamine (82.5 mM)

and an iso(thio)cyanate probe (99.0 mM) were mixed in 1.0 mL of CHCl_3 and the reaction was stirred overnight followed by dilution with acetonitrile to 0.37–0.50 mM prior to CD analysis, see ESI for details.

Chiroptical sensing of amines and amino acids

Additional screening studies showed that the urea formation from **1** and **9** can be conducted in a variety of organic solvents ranging from hexane to ethanol – or even aqueous mixtures when necessary – and the sensing experiments do not require any precautions. The urea products are stable and the sensing mixtures are easy to handle. We obtained the best results when the reactions were performed in chloroform and then diluted with acetonitrile for CD analysis which we could conduct without delay. This simple mix-dilute-measure protocol was essentially used for all applications with only minor modifications that were necessary to dissolve amino acids or to extend the sensing scope to alcohols and amino alcohols, see below. We decided to first investigate the CD sensing utility of **1** with a structurally diverse group of aromatic and aliphatic amines and applied **9–18** in our straightforward protocol. All analytes gave quantifiable CD signals as shown exemplarily for **11** and **17**, a secondary amine that cannot be analyzed with optical Schiff base probes. We found that aqueous solutions are also tolerated which enabled us to use **1** for chiroptical sensing of amino acids including phenylalanine, **18**, and glutamic acid, **25**, Figure 2. The ease of optical enantiomer differentiation with aromatic substrates and also with compounds such as **15–18** and **22–25** devoid of an aryl moiety is noteworthy because it proves that this optical sensing method is generally useful and does not require the presence of a chromophoric or auxochromic group in the targeted structures.

Mechanistic studies

The success with amine and amino acid chirality sensing via irreversible urea formation and direct CD analysis encouraged us to explore if this can also be achieved with alcohols and amino alcohols. In particular alcohols remain among the most challenging sensing targets to date. This can be attributed to their low nucleophilicity which greatly complicates the development of optical chirality sensing assays based on well-defined stoichiometric molecular recognition processes or the formation of supramolecular assemblies that should preferentially occur under mild conditions and within a few hours. We envisioned that the daunting task of alcohol chirality sensing might become feasible through covalent trapping as carbamate derivatives of **1**. Initial tests with phenylethanol showed that the carbamate formation with **1** is slow at room temperature and impractical. We therefore screened several catalysts that were expected to be compatible with the optical measurements with the goals to accelerate the conversion and to avoid any need to work-up the reaction mixtures prior to the CD analysis, Scheme 2. We found that quantitative carbamate conversion is accomplished in the presence of 20 mol% of DMAP. Monitoring of the reaction between **1** and alcohols by NMR spectroscopy showed that it does not generate by-

products and is complete within 1.5 hours at room temperature, see ESI. This is sufficiently time-efficient even for

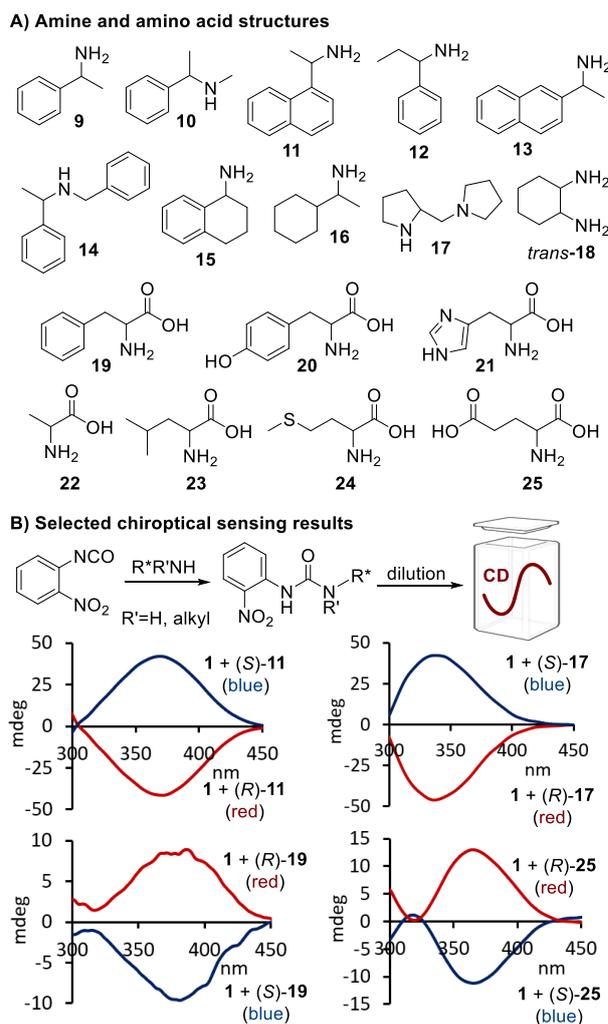
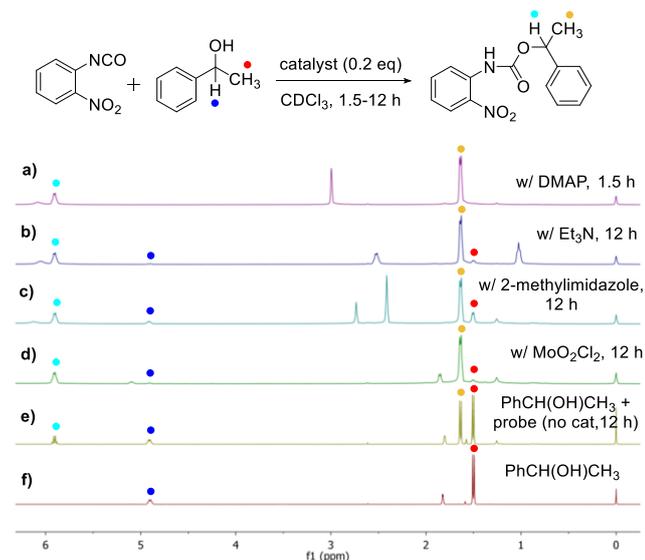


Figure 2 Structures of chiral amines and amino acids tested, and selected CD spectra observed upon binding of **11**, **17**, **19** and **25**, respectively, to **1**. The CD analyses of the reactions with the amines were conducted at 0.58–0.65 mM in acetonitrile and for the amino acid derived ureas at 0.41 mM in aqueous acetonitrile, see ESI for details.

high-throughput purposes because one could run and analyze hundreds of samples in parallel using multiwell-plate UV/CD readers. We note, however, that one could further accelerate the carbamate formation by gentle heating if desired. As expected, amines react faster and we found that the urea formation is complete within 15 minutes, see ESI. During the course of this study we were able to grow single crystals by slow evaporation of dichloromethane:hexanes solutions of the urea and carbamate formed in the reaction of **1** with an amine and an alcohol, respectively. The crystallographic structure elucidation further corroborates the results and conclusions of our NMR reaction analysis, Figure 3. The click chemistry nature of our optical sensing approach is important.¹³ The analyte conversion is quantitative, occurs at room temperature and generates a single carbamate or urea product with a practical mixing procedure. The well-defined chemistry, operational simplicity, ruggedness and the broad application spectrum

render chirality analysis with aryl(thio)isocyanates particularly attractive, see below.



Scheme 2 Catalyst screening to achieve quantitative alcohol conversion with the isocyanate probe **1** at room temperature. Spectra a) to d): (*R*)-Phenylethanol (81.9 mM), probe **1** (98.2 mM) and catalyst (0.2 equivalents, 16.4 mM) were mixed in 1.0 mL of CDCl₃. e) Reference reaction without catalyst. f) NMR spectrum of 1-phenylethanol.

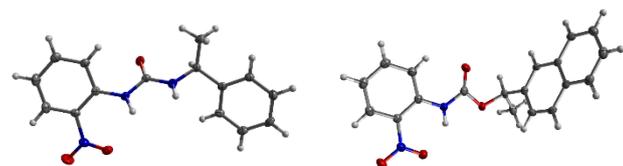
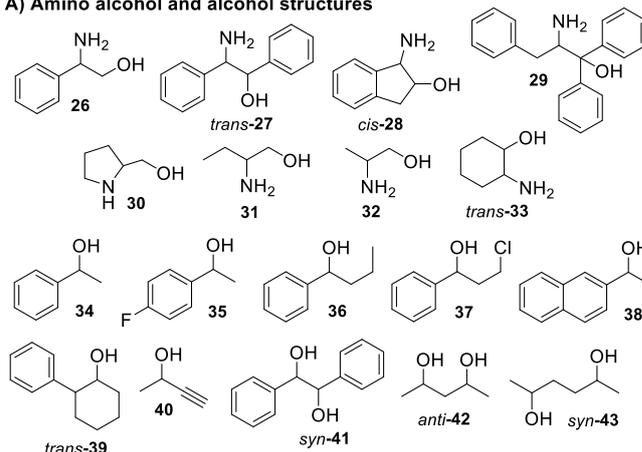


Figure 3 X-ray structures of (*S*)-1-(2-nitrophenyl)-3-(1-phenylethyl)urea and (*R*)-1-(naphthalen-2-yl)ethyl (2-nitrophenyl)carbamate.

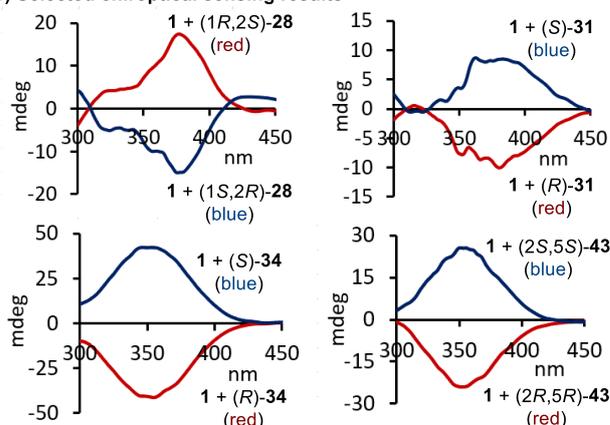
Chiroptical sensing of alcohols, diols, and amino alcohols

With a slightly revised sensing protocol in hand, we then continued to examine the application spectrum of **1** by testing a broad variety of amino alcohols, alcohols, which are particularly challenging sensing targets, and diols **26-43**. The compounds and a few selected CD spectra are shown in Figure 4A and B. Some of these target structures carry phenyl rings that might be beneficial for the generation of strong, red-shifted CD signals once the carbamate is formed but we also included purely aliphatic compounds such **30-33**, **40**, **42** and **43** in our study. Again, we observed distinct CD signals in all cases which underscores the practicality – we just mix the probe with the target compound and take chiroptical measurements upon dilution without any purification and chromatographic separation – and the broad utility of this chirality sensing assay. As expected based on the well-defined sensing stoichiometry, we observed a linear correlation between the CD response measured at 350 nm and the chiral composition of the alcohol **38** which is in perfect agreement with the proposed carbamate formation, see Figure 4C.

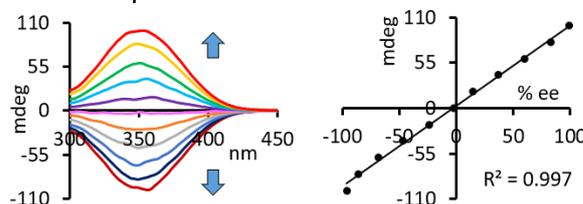
A) Amino alcohol and alcohol structures



B) Selected chiroptical sensing results



C) Linear CD response of **1** at 350 nm to the %ee of alcohol **38**



D) UV response of **1** at 350 nm to the concentration of alcohol **38**

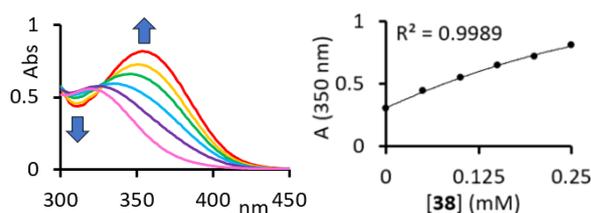


Figure 4 A) Structures of alcohols and amino alcohols tested. B) Selected CD spectra observed upon binding of **28**, **31**, **34** and **43**, respectively, to **1**. Two equivalents of **1** were used for the amino alcohol sensing. C) Linear chiroptical response of probe **1** to nonracemic samples of 1-(2-naphthyl)ethanol. D) UV response to alcohol **38**. The CD analyses of the reactions with the amino alcohols were conducted at 0.17–0.28 mM and for the alcohol derived carbamates at 0.13–0.82 mM in acetonitrile, see ESI for details.

Combined concentration, absolute configuration and *er* analysis

Our results demonstrate that this chiroptical assay works with, but is not limited to, 35 amines, amino alcohols, amino acids, diols and alcohols, which stands out among previously reported sensing methods. The generality of its usefulness encouraged us to go one step further and evaluate the possibility of combined

er and concentration analysis. As shown above, the CD response generated by our chromophoric probe **1** upon binding of a chiral compound changes linearly with the enantiomeric composition of the sample, and this simplifies the quantitative analysis tasks, *vide infra*. We suspected that the formation of a carbamate or urea product derived from **1** and either an alcohol or amine would also yield a characteristic UV change. Because we use an achiral probe in contrast to a chiral derivatizing agent typically employed in NMR or HPLC analysis of chiral compounds, enantiomeric rather than diastereomeric products are formed. The corresponding UV signals can therefore be directly correlated to the total concentration of the chiral analyte, irrespective of the sample *er*. We were able to verify this by CD and UV studies of samples containing either the alcohol **38** as shown in Figure 4D or our initial test analyte 1-phenylethylamine, **9**, see Figure 5A and B. The urea and carbamate formations generate a strong CD signal with a maximum at 375 nm and 350 nm, respectively, as well as a large UV change at the same wavelength. This sets the stage for comprehensive UV/CD sensing of the concentration and enantiomeric ratio of chiral compounds. It is important to note that CD spectrophotometers typically produce UV and CD spectra simultaneously which makes this approach even more attractive.

(entry 4). The UV/CD analysis of a solution of **9** at 25.0 mM with an *S/R* ratio of 10.0 : 90.0 gave 21.0 mM and an enantiomeric composition of 8.1 : 91.9 (entry 9).

Table 1 Results of comprehensive chiroptical concentration and enantiomeric ratio sensing of 1-phenylethylamine samples using **1**.

Entry	Sample compositions			Optical sensing results		
	Abs. Config.	Conc. (mM)	<i>S/R</i>	Abs. Config.	Conc. (mM)	<i>S/R</i>
1	<i>R</i>	100.0	40.0:60.0	<i>R</i>	94.5	41.6:58.4
2	<i>S</i>	100.0	75.0:25.0	<i>S</i>	96.9	78.7:21.3
3	<i>S</i>	75.0	82.0:18.0	<i>S</i>	68.2	88.7:11.3
4	<i>R</i>	60.0	2.0:98.0	<i>R</i>	62.1	1.1:98.9
5	<i>S</i>	50.0	95.0:5.0	<i>S</i>	50.1	96.9:3.1
6	<i>R</i>	50.0	35.0:65.0	<i>R</i>	54.4	33.9:66.1
7	<i>S</i>	40.0	70.0:30.0	<i>S</i>	35.5	68.8:31.2
8	<i>R</i>	80.0	22.0:78.0	<i>R</i>	70.3	23.8:76.2
9	<i>R</i>	25.0	10.0:90.0	<i>R</i>	21.0	8.1:91.9
10	<i>S</i>	25.0	80.0:20.0	<i>S</i>	22.3	78.7:21.3

The concentrations and enantiomeric ratios were determined using the UV and CD responses of the probe at 375 nm. The absolute configuration was assigned by comparison of the observed Cotton effects to a reference sample.

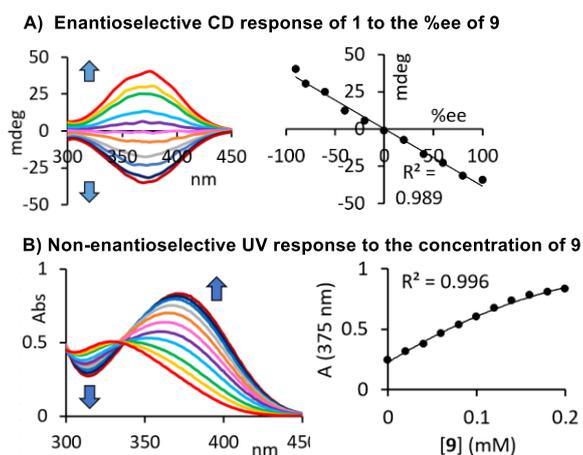


Figure 5 Correlation of the UV and CD probe responses to the concentration and enantiomeric composition of 1-phenylethylamine. The UV and CD measurements were performed after dilution with acetonitrile as described above, see ESI for details.

Having established these chiroptical correlations we set out to apply our assay to ten amine samples containing **9** in widely varying concentrations and enantiomeric ratios, Table 1. The samples were treated as described above and directly subjected to UV and CD analysis for quantification while the sign of the observed CD signal was used to determine the absolute configuration of the major enantiomer simply by comparison with our reference CD spectrum obtained previously during analyte screening. The results show relatively small error margins that are generally considered acceptable for chiroptical sensing applications.^{4a} For example, we determined an *er* of 1.1 (*S*) : 98.9 (*R*) and a total concentration of 62.1 mM for a 60.0 mM sample with 2.0% of the *S*-enantiomer and 98.0% of (*R*)-**9**

Conclusions

In conclusion, we have shown for the first time that organocatalysis with a simple arylisocyanate enables optical concentration and *er* determination of chiral compounds based on fast mixing followed by straightforward UV/CD analysis. The general scope and ease of operation are unprecedented to date and demonstrated with almost 40 analytes representing 5 different compound classes including mono-alcohols which are particularly challenging sensing targets. The probe reacts smoothly and irreversibly with amino and alcohol groups at room temperature toward urea or carbamate products exhibiting characteristic UV and CD signals above 300 nm that are correlated to the total concentration as well as the enantiomeric composition of the target compound. The unprecedented use of such a broadly useful achiral chiroptical agent employed in an organocatalytic assay is very attractive and it combines several features and advantages that outperform current laboratory practice: (1) It eliminates complications that can arise when traditional methods are used, such as kinetic resolution effects and interferences from enantiomeric contamination of chiral derivatizing agents, as well as cumbersome work-up procedures and time-consuming chromatographic protocols that impede fast and accurate enantiomer analysis. (2) The *in situ* generation of distinct UV and CD signals at high wavelengths overcomes issues with insufficient resolution of overlapping signals often encountered with chiral NMR solvating agents that rely on weak binding forces rather than covalent bond formation. (3) The compatibility with a variety of solvents is another noteworthy and important characteristic of this assay. It addresses problems with insufficient solubility of very polar analytes, for

example pharmaceuticals, in standard mobile phase mixtures required for chiral HPLC analysis, which regularly causes major roadblocks in analytical laboratories. (4) Finally, the elimination of any work-up and chromatographic separation steps saves time and solvent consumption. We therefore believe that the broad application spectrum, ruggedness and practicality of chiroptical sensing with aryliso(thio)cyanate probes together with the availability of automated CD multi-well plate readers carry exceptional promise to accelerate chiral compound development projects at reduced cost and with less waste production.

Conflicts of interest

The authors declare no competing financial interest.

Acknowledgements

We are grateful for financial support from the U.S. National Science Foundation (CHE-1764135).

Notes and references

- 1 a) Pirkle, W. H.; Simmons, K. A.; Boeder, C.W. *J. Org. Chem.* **1979**, *44*, 4891–4896. b) Nabeya, A.; Endo, T. *J. Org. Chem.* **1988**, *53*, 3358–3361. c) Sonnet, P. E.; Dudley, R. L.; Osman, S.; Pfeffer, P. E.; Schwartz, D. *J. Chromatogr. A* **1991**, *586*, 255–258. d) Kim, K. H.; Kim, H. J.; Kim, J.-H.; Lee, J. H.; Lee, S. C. *J. Pharm. Biomed. Anal.* **2001**, *947*–956. e) Vodička, P.; Streinz, L.; Koutek, B.; Buděšínský, M.; Ondráček, J.; Císařová, I. *Chirality* **2003**, *15*, 472–478. f) Vodička, P.; Streinz, L.; Vávra, J.; Koutek, B.; Buděšínský, M.; Ondráček, J.; Císařová, I. *Chirality* **2005**, *17*, 378–387. g) Kaik, M.; Gajewy, J.; Grajewski, J.; Gawronski, J. *Chirality* **2008**, *20*, 301–306. h) Sabot, C.; Mosser, M.; Antheaume, C.; Mioskowski, C.; Baati, R.; Wagner, A. *Chem. Commun.* **2009**, *23*, 3410–3412. i) Wenzel, T. J.; Chisholm, C. D. *Chirality* **2011**, *23*, 190–214.
- 2 a) Pirkle, W. H.; Hoekstra, M. S. *J. Org. Chem.* **1974**, *39*, 3904–3906. b) Gal, J. *J. Chromatogr.* **1984**, *314*, 275–281. c) Dunlop, D. S.; Neidle, A. *Analytical Biochemistry* **1987**, *165*, 38–44. d) Martin, E.; Quinke, K.; Spahn, H.; Mutschler, E. *Chirality* **1989**, *1*, 223–234. e) Hsu, C. L.; Walters, R. R. *J. Chromatogr. A* **1991**, *550*, 621–628. f) Sonnet, P. E.; Dudley, R. L.; Osman, S.; Pfeffer, P. E.; Schwartz, D. *J. Chromatogr.* **1991**, *586*, 255–258. g) Ito, S.; Ota, A.; Yamamoto, K.; Kawashima, Y. *J. Chromatogr.* **1992**, *626*, 187–196. h) Bourque, A. J.; Krull, I. S. *Journal of Pharmaceutical and Biomedical Analysis* **1993**, *11*, 495–503. i) Lobell, M.; Schneider, M. P. *J. Chromatogr.* **1993**, *633*, 287–294. j) Olsen, L.; Brønnum-Hansen, K.; Helboe, P.; Jørgensen, G. H.; Kryger, S. *J. Chromatogr.* **1993**, *636*, 231–241. k) Zhou, Y.; Luan, P.; Liu, L.; Sun, Z. P. *J. Chromatogr. B* **1994**, *659*, 109–126. l) Kleidernigg, O. P.; Posch, K.; Lindner, W. *J. Chromatogr. A* **1996**, *729*, 33–42. m) Péter, M.; Péter, A.; Fülöp, F. *Chromatographia* **1999**, *50*, 373–375. n) Kim, K. H.; Heo, S. Y.; Hong, S.-P.; Le, B.-C. *Arch. Pharm. Res.* **2000**, *23*, 568–573. o) Péter, A.; Péter, M.; Fülöp, F.; Török, G.; Tóth, G.; Tourwé, D.; Sági, J. *Chromatographia Supplement* **2000**, *51*, 148–154. p) Péter, M.; Gyéresi, Á.; Fülöp, F. *J. Chromatogr. A* **2001**, *910*, 247–253. q) Sun, X. X.; Sun, L. Z.; Aboul-Enein, H. Y. *Biomed. Chromatogr.* **2001**, *15*, 116–132. r) Ullrich, T.; Menge, S.; Schmid, M.; Gübitz, G.; Krauss, G.-J. *Biomed. Chromatogr.* **2001**, *15*, 212–216. s) Matoga, M.; Forfar, I.; Chaibault, C.; Guillon, J.; Péhourcq, F.; Bosc, J.-J.; Rettori, M.-C.; Jarry, C. *Journal of Enzyme Inhibition and Medicinal Chemistry* **2002**, *17*, 375–379. t) Péter, M.; Fülöp, F. *Chromatographia* **2002**, *56*, 631–636. u) Ko, M. Y.; Shin, D. H.; Oh, J. W.; Asegahegn, W. S.; Kim, K. H. *Arch. Pharm. Res.* **2006**, *29*, 1061–1065. v) Ilisz, I.; Berkecz, R.; Péter, A. *J. Pharmaceut. Biomed.* **2008**, *47*, 1–15. w) Bhushan, R.; Batra, S. *Biomed. Chromatogr.* **2013**, *27*, 956–959. x) Escrig-Doménech, A.; Simó-Alfonso, E. F.; Herrero-Martínez, J. M.; Ramis-Ramos, G. *J. Chromatogr. A* **2013**, *1296*, 140–156.
- 3 Wolf, C.; *Dynamic Stereochemistry of Chiral Compounds - Principles and Applications*. RSC, Cambridge, UK, 2008, 136–179.
- 4 a) Guo, J.; Wu, J.; Siuzdak, G.; Finn, M. G. *Angew. Chem., Int. Ed.* **1999**, *38*, 1755–1758. (b) Reetz, M. T.; Becker, M. H.; Klein, H.-W.; Stockigt, D. *Angew. Chem., Int. Ed.* **1999**, *38*, 1758–1761. (c) Markert, C.; Pfaltz, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 2498–2500. (d) Mueller, C. A.; Markert, C.; Teichert, A. M.; Pfaltz, A. *Chem. Commun.* **2009**, 1607–1618. (e) Ebner, C.; Muller, C. A.; Markert, C.; Pfaltz, A. *J. Am. Chem. Soc.* **2011**, *133*, 4710–4713. (f) Piovesana, S.; Samperi, R.; Laganà, A.; Bella, M. *Chem. Eur. J.* **2013**, *19*, 11478–11494.
- 5 (a) Reetz, M. T.; Becker, M. H.; Kuhling, K. M.; Holzwarth, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 2647–2650. (b) Tielmann, P.; Boese, M.; Luft, M.; Reetz, M. T. *Chem. Eur. J.* **2003**, *9*, 3882–3887.
- 6 Reetz, M. T.; Kuhling, Deege, A.; Hinrichs, H.; Belder, D. *Super-Angew. Chem., Int. Ed.* **2000**, *39*, 3891–3893.
- 7 (a) Abato, P.; Seto, C. T. *J. Am. Chem. Soc.* **2001**, *123*, 9206–9207. (b) Taran, F.; Gauchet, C.; Mohar, B.; Meunier, S.; Valleix, A.; Renard, P. Y.; Creminon, C.; Grassi, J.; Wagner, A.; Mioskowski, C. *Angew. Chem., Int. Ed.* **2002**, *41*, 124–127. (c) Matsushita, M.; Yoshida, K.; Yamamoto, N.; Wirsching, P.; Lerner, R. A.; Janda, K. D. *Angew. Chem., Int. Ed.* **2003**, *42*, 5984–5987. d) Dey, S.; Powell, D. R.; Hu, C.; Berkowitz, D. B. *Angew. Chem., Int. Ed.* **2007**, *46*, 7010–7014. e) Friest, J. A.; Broussy, S.; Chung, W. J.; Berkowitz, D. B. *Angew. Chem., Int. Ed.* **2011**, *50*, 8895–8899. (f) Biedermann, F.; Nau, W. M. *Angew. Chem., Int. Ed.* **2014**, *53*, 5694–5699. (g) Feagin, T. A.; Olsen, D. P. V.; Headman, Z. C.; Heemstra, J. M. *J. Am. Chem. Soc.* **2015**, *137*, 4198–4206.
- 8 (a) James, T. D.; Sandanayake, K. R. A. S.; Shinkai, S. *Nature* **1995**, *374*, 345–347. b) Mei, X.; W., C. *J. Am. Chem. Soc.* **2004**, *126*, 14736–14737. c) Wolf, C.; Liu, S. L.; Reinhardt, B. C.; *Chem. Commun.* **2006**, *40*, 4242–4244. d) Mei, X.; Wolf, C. *J. Am. Chem. Soc.* **2006**, *128*, 13326–13327. e) He, X.; Zhang, Q.; Liu, X.; Lin, L.; Feng, X. *Chem. Commun.* **2011**, *47*, 11641–11643. f) Yu, S.; Pu, L. *J. Am. Chem. Soc.* **2010**, *132*, 17698–17700. g) Yu, S.; Plunkett, W.; Kim, M.; Pu, L. *J. Am. Chem. Soc.* **2012**, *134*, 20282–20285. h) Wen, K.; Yu, S.; Huang, Z.; Chen, L.; Xiao, M.; Yu, X.; Pu, L. *J. Am. Chem. Soc.* **2015**, *137*, 4517–4524. i) Akdeniz, A.; Mosca, L.; Minami, T.; Anzenbacher Jr., P. *Chem. Commun.* **2015**, *51*, 5770–5773. j) Shcherbakova, E. G.; Minami, T.; Brega, V.; James, T. D.; Anzenbacher, Jr., P. *Angew. Chem. Int. Ed.* **2015**, *54*, 7130–7133. k) Akdeniz, A.; Minami, T.; Watanabe, S.; Yokoyama, M.; Ema, T.; Anzenbacher Jr., P. *Chem. Sci.* **2016**, *7*, 2016–2022. l) Pu, L. *Acc. Chem. Res.* **2017**, *50*, 1032–1040. m) Pushina, M.; Farshbaf, S.; Shcherbakova, E. G.; Anzenbacher, P. *Chem. Commun.* **2019**, *55*, 4495–4498. n) Sheykhi, S.; Mosca, L.; Durgala, J. M.; Anzenbacher, P. *Chem. Commun.* **2019**, *55*, 7183–7186. o) Zhu, Y.-Y.; Wu, X.-D.; Gu, X.-D.; Pu, L. *J. Am. Chem. Soc.* **2019**, *141*, 175–181. p) Sasaki, Y.; Kojima, S.; Hamedpour, V.; Kubota, R.; Takizawa, S.-y.; Yoshikawa, I.; Houjou, H.; Kubo, Y.; Minami, T. *Chem. Sci.* **2020**, *11*, 3790–3796.
- 9 a) Zhu, L.; Anslyn, E. V. *J. Am. Chem. Soc.* **2004**, *126*, 3676–3677. b) Eelkema, R.; van Delden, R. A.; Feringa, B. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5013–5016.

- 10 a) Leung, D.; Kang, S. O.; Anslyn, E. V. *Chem. Soc. Rev.* **2012**, *41*, 448-479. b) Wolf, C.; Bentley, K. W. *Chem. Soc. Rev.* **2013**, *42*, 5408-5424. c) Herrera, B. T.; Pilicer, S. L.; Anslyn, E. V.; Joyce, L. A.; Wolf, C. *J. Am. Chem. Soc.* **2018**, *140*, 10385-10401. d) Pilicer, S. L.; Dragna, J. M.; Garland, A. Welch, C. J.; Anslyn, E. V.; Wolf, C. *J. Org. Chem.* **2020**, *85*, 10858-10864.
- 11 Zhang, R.; Zhon, Y.; Lu, Z.; Chen, Y.; Li, G. *Chem. Sci.* **2021**, *12*, 660-668.
- 12 a) Nieto, S.; Lynch, V. M.; Anslyn, E. V.; Kim, H.; Chin, J. *J. Am. Chem. Soc.* **2008**, *130*, 9232-9233. b) Nieto, S.; Lynch, V. M.; Anslyn, E. V.; Kim, H.; Chin, J. *Org. Lett.* **2008**, *10*, 5167-5170. c) Ghosn, M. W.; Wolf, C. *J. Am. Chem. Soc.* **2009**, *131*, 16360-16361. d) Nieto, S.; Dragna, J. M.; Anslyn, E. V. *Chem. Eur. J.* **2010**, *16*, 227-232. e) Joyce, L. A.; Maynor, M. S.; Dragna, J. M.; da Cruz, G. M.; Lynch, V. M.; Canary, J. W.; Anslyn, E. V. *J. Am. Chem. Soc.* **2011**, *133*, 13746-13752. f) Leung, D.; Anslyn, E. V. *Org. Lett.* **2011**, *13*, 2298-2301. g) Dragna, J. M.; Pescitelli, G.; Tran, L.; Lynch, V. M.; Anslyn, E. V.; Di Bari, L. *J. Am. Chem. Soc.* **2012**, *134*, 4398-4407. h) You, L.; Pescitelli, G.; Anslyn, E. V.; Di Bari, L. *J. Am. Chem. Soc.* **2012**, *134*, 7117-7125. i) Bentley, K. W.; Nam, Y. G.; Murphy, J. M.; Wolf, C. *J. Am. Chem. Soc.* **2013**, *135*, 18052-18055. j) Bentley, K. W.; Wolf, C. *J. Am. Chem. Soc.* **2013**, *135*, 12200-12203. k) Bentley, K. W.; Wolf, C. *J. Org. Chem.* **2014**, *79*, 6517-6531. l) Jo, H. H.; Lin, C.-Y.; Anslyn, E. V. *Acc. Chem. Res.* **2014**, *47*, 2212-2221. m) Metola, P.; Nichols, S. M.; Kahr, B.; Anslyn, E. V. *Chem. Sci.* **2014**, *5*, 4278-4282. n) Thanzeel, F. Y.; Sripada, A.; Wolf, C. *J. Am. Chem. Soc.* **2019**, *141*, 16382-16387. o) Thanzeel, F. Y.; Kaluvu, B.; Wolf, C. *Angew. Chem. Int. Ed.* **2020**, *59*, 21382-21386. p) De los Santos, Z. A.; Wolf, C. *J. Am. Chem. Soc.* **2020**, *142*, 4121-4125.
- 13 Kolb, H. C. Finn, M. G. Sharpless, B. K. *Angew. Chem. Int. Ed.* **2001**, *40*, 2004-2021.