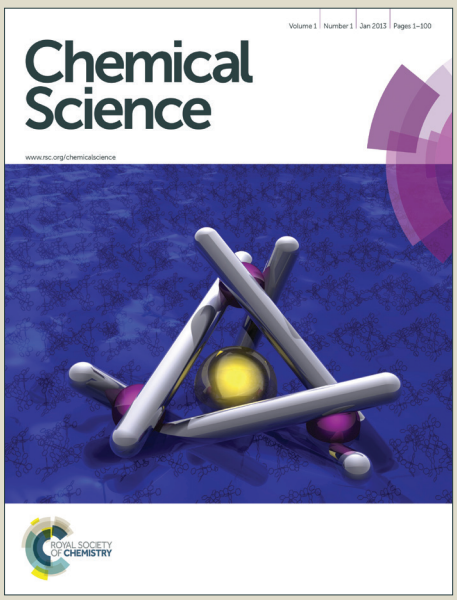
Chemical Science

Accepted Manuscript



ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/chemicalscience

Journal Name

RSCPublishing

ARTICLE

Imine-Based Chiroptical Sensing for Analysis of Chiral Amines: From Method Design to Synthetic Application

L. A. Joyce,* E. C. Sherer and C. J. Welch

Cite this: DOI: 10.1039/xoxxoooooox

Received ooth January 2012,
Accepted ooth January 2012

DOI: 10.1039/xoxxoooooox

www.rsc.org/

Imine-bond formation between a chiral amine analyte and 3-hydroxypyridine-2-carboxaldehyde (**HCA**) was used to create a fast and robust method for enantiopurity analysis. This approach showed good universality, and was applied to a variety of different classes of chiral amines. The sign of the measured CD signal was enantiospecific across the range of amines tested, allowing some confidence in absolute configuration determination. This technique was transitioned to an HPLC-CD detector to allow for rapid and automated sample introduction, while maintaining the level of accuracy noted for the standalone CD spectrophotometer. Finally, the enantiomeric purity of a series of crude reaction mixtures of synthetic amines produced by biocatalytic transamination was accurately determined using this approach.

Inroduction

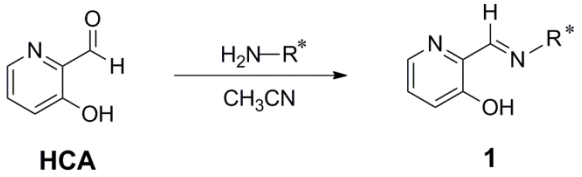
Over the past decade, the development of sensor technologies to provide fast analysis of chemical composition has been a very active area of chemical research.[1-4] Of these techniques, optical sensors offer a number of attractive features including the potential for very rapid analysis and, in some cases, direct visual readout. Despite many successful demonstrations of proof of principle, the use of such sensor-based analytical tools in the chemical industry is still quite rare. Approaches based on readily available and affordable chemosensors that offer generality, ease of use, speed, sensitivity, accuracy, and tolerance for a variety of sample matrices will be required for more widespread implementation.

A variety of functional group-specific sensors for rapid determination of enantiopurity of chiral molecules have been reported, with specialized systems being described for alcohols,[5,6] amines,[7-9] amino acids,[10-12] amino alcohols,[13-15] carboxylic acids,[16-19] diamines,[20,21] and diols.[22,23] Many of these approaches employ specialized chemosensors that, while effective, are synthetically complex and not commercially available. Other approaches rely on dynamic assemblies formed from several species, either through supramolecular interaction or covalent bond formation.

A recent development by Anslyn and coworkers describes a circular dichroism-based sensor for measuring the enantiopurity of chiral amines.[9] This system is based on the detection of a metal-based complex that self assembles from readily available starting materials. Formation of an imine bond between an amine analyte and 3-hydroxypyridine-2-carboxaldehyde (**HCA**), and subsequent complexation of three of these imines around an iron(II) metal center gives rise to a CD-active iron complex. This complex affords strong circular dichroism (CD) signals above 500 nm, where the potential for sample interference from other absorbing species is minimized.

While this approach allows the enantiomeric excess (*ee*) of a variety of chiral amines to be measured within ± 5% of their actual values, there are several challenges limiting its practical application. First, the several hours required for self-assembly of the metal complex limits utilization in high throughput analysis. In addition, since three imine derivatives of the chiral amine are involved in assembly of the chemosensor, diastereoselectivity in complex formation leads to nonlinear response in ee measurement. Finally, the complex formation is sensitive to additional reaction components. Addition of exogenous solvents, additional metals, unreacted starting materials or side products interfere with the output signal.

We now report a related chiroptical system that addresses these limitations, allowing for rapid and accurate measurement of the enantioenrichment of chiral amines. The use of an HPLC-CD detector removes several of the aforementioned limitations of practical application, and allows very rapid (< 1 min) enantiopurity determination. This work represents one of the first implementations of chiroptical sensing systems in crude reaction mixture monitoring.



Scheme 1. Imine bond formation between HCA and a chiral amine leading to imine 1, followed by subsequent iron complexation to yield metal-based CD sensor 2.

Results and Discussion

Initial CD studies

While investigating potential speed improvements for the Ansyln system, we were pleased to discover that imine **1** immediately formed between amine analytes and **HCA** shows the presence of two CD maxima, occurring at 250 and 317 nm. While the CD signals for these imines are not as intense or long wavelength-shifted as those of their iron complexes we recognized the potential for the direct use of this rapidly formed **HCA** imine as an enantioselective chemosensor. Addition of one equivalent of enantiopure (*S*)-α-methylbenzylamine (**MBA)** to **HCA** leads to rapid formation of a strong CD signal (**Figure 1**). Addition of enantiopure (*R*)-**MBA** to **HCA** affords a CD signal with an equal magnitude, but opposite sign. Neither **HCA** nor **MBA** has an observable CD signal at 317 nm, hence, the chirality of the amine is effectively transferred to the imine, which in turn functions as a CD-active reporter.[24] While the magnitude of the signal at 250 nm is larger, this signal occurs at a region in the UV spectrum where there is a significant potential for interference from solvents, catalysts, and ligands that are often present in high throughput process chemistry investigations. As fewer routinely used organic compounds absorb above 300 nm, we decided to focus on the 317 nm signal for the rest of our analysis.

Mixing of amine and aldehyde led to very rapid formation of the CD signal at 317 nm, with maximum signal observed as quickly as it could be measured, indicating very rapid formation of the imine bond. Titration of either enantiomer of **MBA** into a solution of **HCA** afforded a CD signal that increased linearly until one equivalent of the amine had been added. At one equivalent of added amine the signal became saturated (**Figure 2A**), suggesting that the equilibrium for imine formation lies far to the right. The CD signal has no concentration dependence above this threshold.

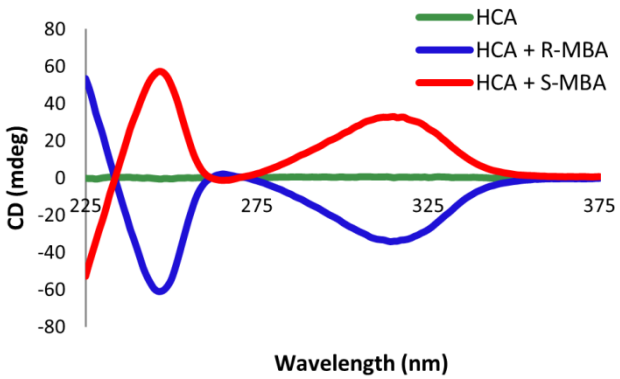


Figure 1. CD spectra for HCA (2 mM) and indicated enantiomer of MBA (2 mM) in acetonitrile. Spectra were recorded at 25°C.

After establishing this relationship for **MBA**, we sought to test the generality of this approach with other amine substrates. CD spectra were recorded after the addition of one equivalent of the (*S*)-enantiomer of the amines **CEA**, **CMA**, **PPA**, **AMH**, and **MPP** to the **HCA** sensor. (**Figure 2B**). In all cases, the observed spectra for the imines formed from the (*S*)-enantiomers of these amines showed a positive CD signal at 317 nm, with some difference in spectral shape and magnitude across the substrates. The opposite trend is observed for enantiopure (*R*)-amines, which give rise to a negative CD signal at 317 nm in presence of the **HCA** sensor.

Conformational modeling and calculation of CD spectra were carried out as previously reported (see Supplemental Information).[25,26] This modeling showed the predominance of a single contributing conformer for imines formed with α-chiral amines, depicted pictorially in **Figure 2C**. The global minimum for each imine was found to adopt a planar conformation through the conjugated system with an intramolecular hydrogen bond between the imine nitrogen and the pyridine hydroxyl substituent. Gaussian simulation of the CD spectra afforded good agreement with the sign of the experimentally measured spectra. On the basis of these observations, measurement of the sign of the CD signal at 317 nm for **HCA** imine complexes of certain α-chiral amines may be a valuable tool for assigning absolute configuration according to the mnemonic displayed in **Figure 2C**.

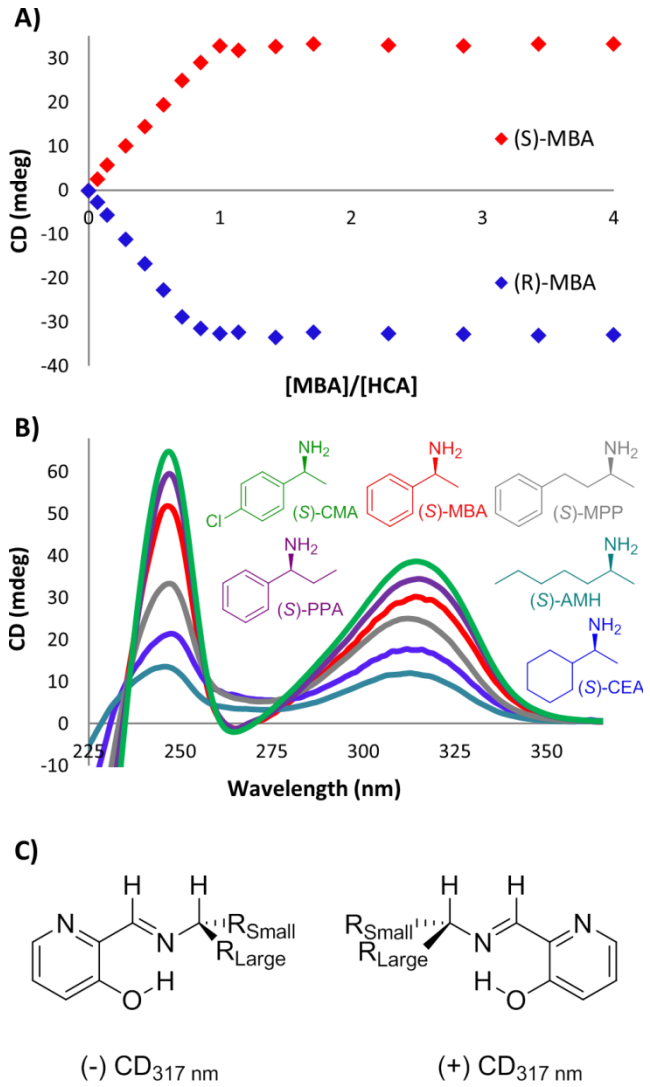


Figure 2. A) CD signal observed at 317 nm for the titration of the indicated enantiomer of **MBA** (0-4 mM) into **HCA** (2 mM) in acetonitrile at 25°C. B) CD signals for **HCA** (2 mM) and the (*S*)-enantiomer of the indicated amine guest (2 mM) in acetonitrile at 25°C. C) Mnemonic showing the sign of the absolute configuration of **HCA** imine derivatives of selected α-chiral amines.

In an effort to explore the scope of the imine-based sensing method, we examined the extension of the technique to amino alcohols,[15,27-30] which have been fairly well studied by other optical sensing techniques. The condensation product formed from (*S*)-2-aminopropanol ((*S*)-**2-AP**) and **HCA** displays a positive CD signal with λ_{max} at 317 nm (**Figure 3**), consistent with the hydroxymethyl group acting as the large group in the model illustrated in **Figure 2C**.

Interestingly, the CD signal obtained when enantiopure (*S*)-2-phenylglycinol ((*S*)-**2-PG**) was added to the **HCA** sensor had a negative sign, suggesting that the phenyl group is now playing the role of the large group, though the hydroxymethyl group gets priority according to Cahn-Ingold-Prelog rules of stereochemical assignment.[31,32] Conformational modeling of the **HCA** derivatives of amino alcohols showed that while two intramolecular hydrogen bonds are possible, the hydrogen bond coming from the hydroxypyridine dominates, as evidenced by a longer hydrogen bond distance of 2.5-2.6 Å versus 1.7 Å (see supplemental information).

We next examined β-chiral amines, a more challenging substrate class that has received minimal attention in the chiroptical sensing literature.[33] Since the stereocenter is now an additional carbon atom further from the imine bond formed between **HCA** and the nitrogen of the amine, an attenuation of the CD signal could be expected. The **HCA** imine of (*R*)-β-methylbenzylamine **(β-MBA)** does show a CD signal, albeit with decreased intensity and opposite sign to that observed for imine formed from **HCA** and (*R*)-**MBA** (**Figure 3B**). This switch in the sign of the CD signal is accurately predicted by conformational modeling and calculation of CD spectra.

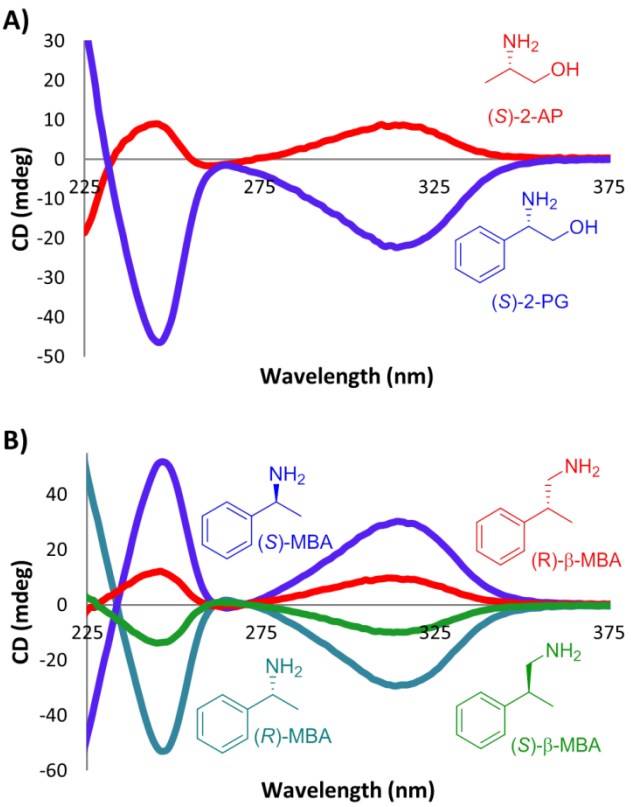


Figure 3. A) Opposite signs for CD spectra of **HCA** (2 mM) and the (*S*)-enantiomers of **2-AP** and **2-PG**, recorded in acetonitrile at 25°C. B) CD spectra for **HCA** (2 mM) and indicated enantiomer of each amine (2 mM) in acetonitrile at 25°C.

Determination of ee

We next investigated the potential for using the CD signal at 317 nm to determine the *ee* for unknown samples of chiral amines. In order to do so, calibration curves were created for **HCA** imine derivatives of three different amines by preparing and analyzing samples that covered the range of *ee* values. For a given concentration of amine, the CD signal is directly proportional to the *ee*. The equation of the best-fit line for this calibration curve can then be used to find the *ee* of unknown

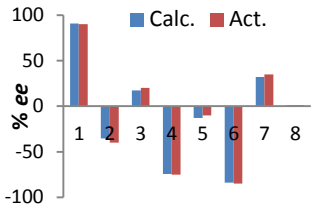
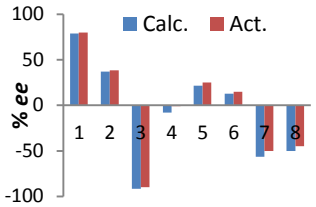
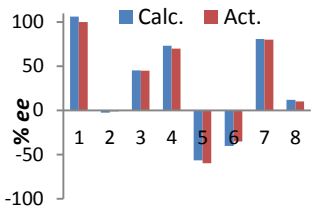
samples. The value that we report for *ee* was calculated using the equation [([*R*]-[*S*])/([*R*]+[*S*])], with values that range from 100% (pure (*R*) enantiomer) to -100% (pure (*S*) enantiomer). The three amines **MBA**, **MPP**, and **AMH** were selected because they constitute a wide range of CD signal intensities. One equivalent of each of the enantiopure amines was added to **HCA**, and these solutions were used to prepare the representative calibration curves.

Eight test solutions of unknown *ee* were then prepared for each of the three amines. These amines were selected as they represent a range of signal intensities, with the difference in magnitude between the pure (*R*)- and (*S*)- enantiomers (ΔCD_{317}) shown in **Table 1**. These solutions were uniquely generated, and were not the same ones used for the calibration curves. The observed CD signal at 317 nm was recorded, and applied to the best-fit line of the calibration curve to determine the *ee* values. The average error for each of the amines was determined, reported as the absolute discrepancy between the calculated and observed values. The results are shown in **Table 1**, with an average error of 2.8%. The error does not increase significantly as the magnitude of the signal decreases, and these errors are in line with those observed for the three component iron complex.[9]

While this approach was suitable for determination of the *ee* of a few samples of commercial substrates, the labor intensive step of manually loading the sample into the CD cuvette was not amenable to a high-throughput screening approach. To mitigate this problem we investigated the use of HPLC-CD, where an injection cycle times of less than 25 seconds can be possible using available autosampler equipment. This has the potential to be significantly faster than the conventional approach of chiral chromatography, where analysis of each sample can require up to 10 minutes. The use of an achiral HPLC column also allows elution of the target imine free from potentially interfering substances.

The first step in application of HPLC-CD detection was to find appropriate HPLC conditions for the elution of the **HCA** imines. The imine species could potentially undergo hydrolysis under acidic conditions, so a mobile phase with pH of 8.5 was used, requiring the use of an HPLC column with extended pH stability. A 2 cm Charged Surface Hybrid (CSH) C18 column afforded sufficient chromatographic retention while still allowing for a fast analysis method. Isocratic elution was necessary, since a gradient method would add unnecessary equilibration time to the process, as well as complicating the zeroing process for the CD detector. The UV and CD signals for the eluted **HCA** imine product were measured at 317 nm (**Figure 4A-B**), with the UV signal providing a measure of the total amount of compound, and the CD signal providing a measure of the amount of optical activity.

Table 1. Calculated and actual ee values for a set of eight test samples prepared for three different amines. The average errors are compared to the difference in magnitude of the signals between enantiomers. These values were obtained from a stand-alone CD spectrophotometer.

Amine	Unknown	Avg Error	ΔCD_{317} (mdeg)
MBA		2.0%	63.1
MPP		3.6%	45.7
AMH		2.9%	23.2

The ratio of the CD signal to the UV signal (g-factor) provides a direct measure of the enantioenrichment, mitigating any inconsistencies in injection volume of the HPLC autosampler, and accounting for variation in the amount of product found in different wells in a typical high-throughput experimentation analysis. A %*ee* calibration curve was created for **MBA** by plotting the g-factor as a function of product enantioenrichment (**Figure 4C**), showing excellent linearity. Using this approach the analysis of the enantiopurity of test samples can be carried out with an injection autosampler and analysis cycle time of considerably less than one minute, allowing for analysis of an entire 96 well microplate in less than one hour.

We next applied the combined **HCA** derivatization/HPLC-CD analysis method to the measurement of the enantioenrichment of unknown samples. The enantiomeric purity of eight unknown samples of amine guests **MBA**, **MPP**, and **AMH** were estimated by measuring the ratio of CD to UV peak area at 317 nm and comparing to a calibration curve created from pure (*R*)- and (*S*)-enantiomers of the respective amines. The average error for each of the amines is reported as the absolute discrepancy between the values that were calculated and observed. The values obtained with the HPLC-CD method were virtually indistinguishable from those obtained with the stand-alone CD spectrophotometer (**Table 2**).

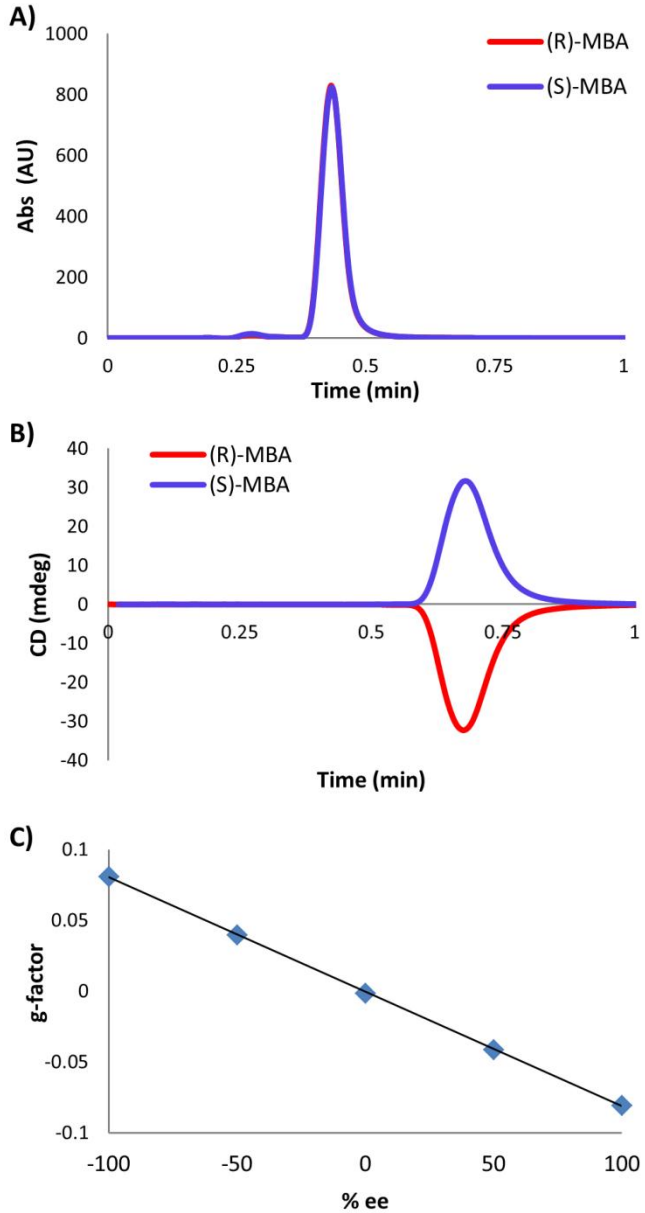
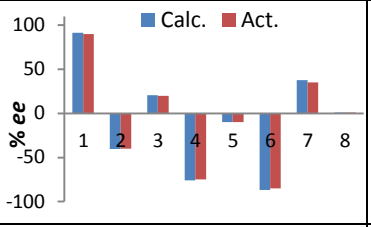
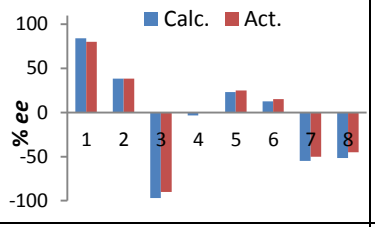
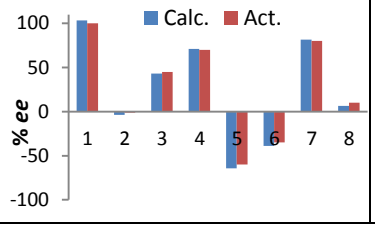
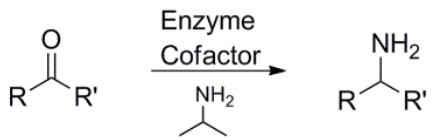


Figure 4. A) UV spectra and B) CD spectra for the HPLC-CD results from the indicated enantiomer of **MBA** (2 mM) and **HCA** (2 mM) in acetonitrile at room temperature, after passing through a Waters CSH column (20x4.6mm, 3.5 µm) with 65% acetonitrile/35% 2 mM ammonium formate at pH 8.5. C) G-factor (CD signal/UV signal) at 317 multiplied by 100 plotted against % *ee* for solutions of **HCA** (2 mM) and **MBA** (2 mM) with indicated *ee* in acetonitrile at room temp.

Table 2. Calculated and actual errors in *ee* for all eight unknown test samples created for three different amine guests, as determined using the HPLC-CD method.

Amine	Unknown	Avg Error
MBA		1.1%
MPP		3.8%
AMH		2.9%

We next investigated the practical use of this technique in high-throughput analysis to support high-throughput screening of enantioselective biocatalytic transamination conditions (**Scheme 2**). In this approach, a prochiral ketone is enzymatically transformed directly into a chiral amine.[34,35] Recent years have seen the development of many different transaminase enzymes that can catalyze this transformation efficiently,[36,37] and with improved tolerance of organic solvents, allowing convenient access to both potential stereoisomeric chiral amine products.[38]



Scheme 2. General scheme for an enzyme-catalyzed transamination, forming a chiral amine product from a prochiral ketone starting material. The nitrogen for the transamination comes from the isopropylamine.

In these laboratories the enzymatic transformation reaction is often carried out using isopropylamine as a nitrogen source in a water/dimethylsulfoxide mixture (80%/20%) buffered to pH 10.5.[34] The reaction also requires the addition of the enzymatic cofactor, pyridoxyl-5'-phosphate (PLP), to enhance reactivity. This protocol was used for three different amines **MBA**, **CMA**, and **MPP**. After the mixtures were shaken for 24 hours at a constant temperature of 45°C, they were worked up according to the extraction procedure outlined in the supporting

information. These samples were concentrated by evaporation of methylene chloride, and re-dissolved in a fresh portion of acetonitrile.

Each sample was then split into two parts: the first part being used for imine complex formation and HPLC-CD analysis, while the remainder was used to determine the *ee* by chiral supercritical fluid chromatography (SFC), one of the established methods of choice for chiral analyses.[39] The HPLC-CD chromatographic conditions were adjusted to separate the desired **HCA** imine from the by-product resulting from the reaction of **HCA** with residual isopropylamine, which can lead to incorrect estimation of the total amount of desired amine. This by-product, as well as any residual amine and aldehyde, are eluted prior to the desired imine (**Figure 5**). The later eluting peak at 0.6 min contains the desired **HCA** imine, which is well resolved from interfering substances. A strong signal for this peak is seen by CD, appearing at a later time owing to a delay in movement of the components from the UV detector through intervening tubing, to the CD detector cell.

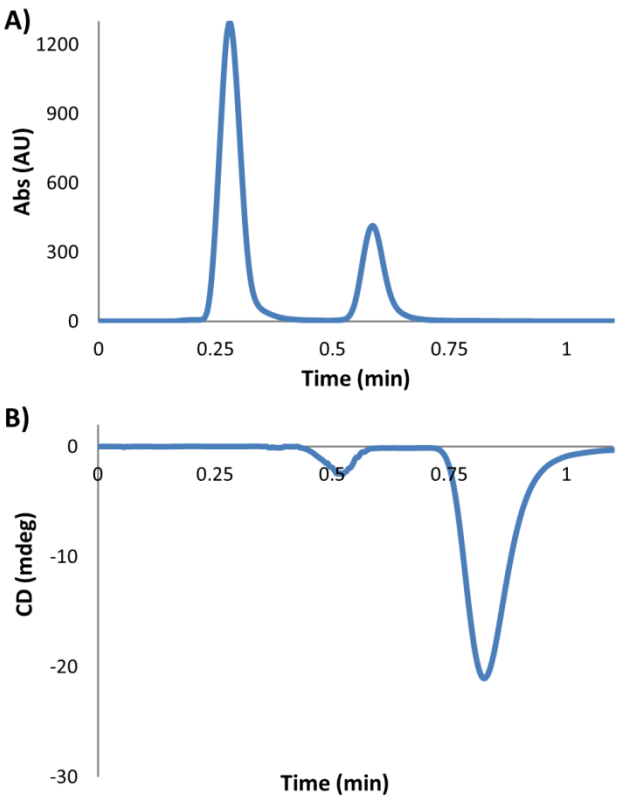
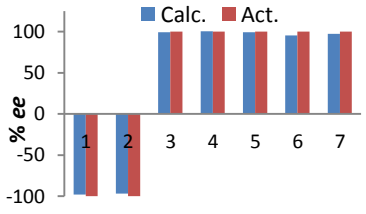
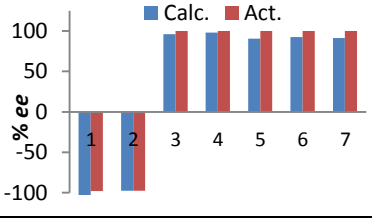
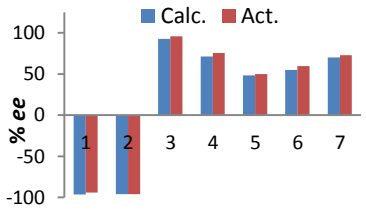


Figure 5. A) UV spectra and B) CD spectra for the HPLC-CD results from the product of transamination catalyzed by CDX-010 enzyme and **HCA** (4 mM) in acetonitrile at room temperature, after passing through a Waters CSH column (20x4.6mm, 3.5 µm) with 60% acetonitrile/40% 2 mM ammonium formate at pH 8.5. Note that the CD peak is slightly delayed from the UV response peak, resulting from the instrumental setup.

The ratio of the CD signal to the UV signal at 317 was calculated for each of the HPLC-CD chromatograms. These values were entered into the equation of the calibration curve line made from pure product enantiomers, and the calculated values of enantioenrichment were obtained. Chiral SFC methods were created separately for the racemic mixture of each of the amines that were synthesized. Since the *ee* values of these synthetic samples are truly unknown and because chiral chromatography is a well-established technique, the value of the chiral SFC analysis was taken as the actual value. Thus, the error that is reported is equivalent to the absolute value of the difference between the *ee* found by the SFC method and the value obtained from the imine sensor. The results compiled in **Table 3** show very good correlation between the two techniques, suggesting a good potential for broad application of the HCA imine HPLC-CD technique to the high-throughput analysis of enantioselective biocatalytic transaminations.

Table 3. Errors in *ee* calculations for the same three amine guests indicated, between the HPLC-CD method and chiral SFC.

Amine	Unknown	Avg Error
MBA		1.8%
CMA		4.7%
MPP		2.3%

Conclusions

Formation of the **HCA** imine derivatives afforded a CD active complex, with a large signal at λ_{max} of 317 nm, where interference from other reaction components is minimal. The sign of the CD signals can be correlated with absolute configuration using a simple model, and conformational modeling and calculation of CD spectra shows good agreement with experimental results, suggesting potential value of the **HCA** imine approach as a method for assigning absolute configuration. In addition, the **HCA** imine approach also shows value for high-throughput analysis of enantiopurity where the *ee* for unknown samples can be measured within ±2.8%. Demonstration of the approach using a series of

biocatalytic transamination reactions allowed accurate analysis of enantiopurity within ±2.9% with an analysis cycle time of less than a minute.

Acknowledgements

The authors would like to thank Johannah Moncecchi and Erika Milczek for assistance with the biocatalytic transamination reactions, and Professor Eric Anslyn for helpful discussion.

Notes and references

Process and Analytical Chemistry, Merck Research Laboratories, Rahway, NJ 07086. Email: leo.joyce@merck.com; Tel: +1 732-594-2447

† Electronic Supplementary Information (ESI) available: details of experiemntal conditions, conformational analysis, CD, and ee calculations. See DOI: 10.1039/b000000x/

1 C. McDonagh, C. S. Burke, B. D. MacCraith, *Chem. Rev.* 2008, **108**, 400.
2 A. Lobnik, M. Turel, S. K. Urek, Optical Chemical Sensors: Design and Application, in Advances in Chemical Sensors, Wang, W. (ed.) 2012, Intech, p 1-28.
3 H. H. Qazi, A. B. bin Mohammad, M. Akram, *Sensors*, 2012, **12**, 16522.
4 D. Leung, S. O. Kang, E. V. Anslyn. *Chem. Soc. Rev.* 2012, **41**, 448.
5 S. Sasaki, Y. Kotegania, H. Tamaki, *Tetrahedron Lett.* 2006, **47**, 4849.
6 L. You, J. S. Berman, E. V. Anslyn, *Nature Chemistry*, 2011, **3**, 943.
7 J. Zhang, A. E. Holmes, S. Zahn, J. W. Canary, *Chirality*, 2003, 15, 180.
8 D. P. Iwaniuk, C. Wolf, *J. Am. Chem. Soc*. 2011, **133**, 2414.
9 J. M. Dragna, G. Pescitelli, L. Tran, V. M. Lynch, E. V. Anslyn, L. Di Bari, *J. Am. Chem. Soc*. 2012, **134**, 4398.
10 Y. Kubo, N. Hirota, S. Tokita, *Anal. Sci*. 1998, **14**, 183.
11 A. E. Holmes, S. Zahn, J. W. Canary, *Chirality*, 2002, **14**, 471.
12 D. Leung, J. F. Folmer-Andersen, V. M. Lynch, E. V. Anslyn, *J. Am. Chem. Soc*. 2008, **130**, 12318.
13 K. Tsubaki, D. Tanima, M. Nuruzzaman, T. Kusumoto, K. Fujii, T. Kawabata, *J. Org. Chem*. 2005, **70**, 4609.
14 S. Liu, J. P. C. Pestano, C. Wolf, *J. Am. Chem. Soc*. 2008, **73**, 4267.
15 K. W. Bentley, K. C. Wolf, *J. Am. Chem. Soc*. 2013, **135**, 12200.
16 X. Mei, C. Wolf, *J. Am. Chem. Soc.* 2004, **126**, 14736.
17 Z. –B. Li, J. Lin, M. Sabat, M. Hyacinth, L. Pu, *J. Org. Chem.* 2007, **72**, 4905.
18 L. A. Joyce, M. S. Maynor, J. M. Dragna, G. M. da Cruz, V. M. Lynch, J. W. Canary, E. V. Anslyn, *J. Am. Chem. Soc.* 2011, **133**, 13746.
19 L. A. Joyce, J. W. Canary, E. V. Anslyn, *Chem. Eur. J.* 2012, **18**, 8064.
20 S. Nieto, V. M. Lynch, E. V. Anslyn, H. Kim, J. Chin, J. *J. Am. Chem. Soc*. 2008, **130**, 9232.
21 S. Yu, W. Plunkett, M. Kim, L. Pu, *J. Am. Chem. Soc.* 2012, **134**, 20282.
22 S. H. Shabbir, C. J. Regan, E. V. Anslyn, *Proc. Natl. Acad. Sci. U.S.A.* 2009, **106**, 10487.
23 S. H. Shabbir, L. A. Joyce, G. M. da Cruz, V. M. Lynch, S. Sorey, E. V. Anslyn, *J. Am. Chem. Soc*. 2009, **131**, 13125.
24 N. Berova, L. Di Bari, G. Pescitelli, *Chem. Soc. Rev*. 2007, **36**, 914.
25 E. C. Sherer, C. H. Lee, J. Shpungin, J. F. Cuff, C. Da, R. Ball, R. Bach, A. Crespo, X. Gong, C. J. Welch, *J. Med. Chem.* 2014, **57**, 477.
26 E. L. Regalado, E. C. Sherer, M. D. Green, D. W. Henderson, R. T. Williamson, L. A. Joyce, C. J. Welch, *Chirality* 2014, **26**, 95.
27 H. Tsukube, M. Hosokubo, M. Wada, S. Shinoda, H. Tamiaki, *Inorg. Chem.* 2001, **40**, 740.
28 D. P. Iwaniuk, K. W. Bentley, C. Wolf, *Chirality* 2012, **24**, 584.
29 M. M. Wanderly, C. Wang, C. –D. Wu, W. Lin, *J. Am. Chem. Soc.* 2012, **134**, 9050.
30 P. Zhang, C. Wolf, *Chem. Commun.* 2013, **49**, 7010.
31 R. S. Cahn, C. Ingold, V. Prelog, *Angew. Chem. Int. Ed. Engl*. 1966, **5**, 385.
32 Signal switch upon addition of a methylene spacer between the binding site and the stereocenter was also observed by Anslyn and coworkers in reference 17.
33 S. –G. Kim, K. –H. Kim, Y. K. Kim, S. K. Shin, K. H. Ahn, *J. Am. Chem. Soc*. 2003, **125**, 13819.
34 N. Turner, R. Carr, In *Biocatalysis in the Pharmaceutical and Biotechnology Industries*; Patel, R., Ed.; CRC Press: Boca Raton, FL, 2007; pp 743-755.
35 M. Truppo, J. Rozzell, N. Turner, *Org. Process Res. Dev.* 2010, **14**, 234.
36 M. Truppo, N. Turner, *Org. Biomol. Chem.* 2010, **8**, 1280.
37 M. Truppo, J. Rozzell, J. Moore, N. Turner, *Org. Biomol. Chem.* 2009, **7**, 395.
38 M. Truppo, H. Strotman, G. Hughes, *Chem. Cat. Chem.* 2012, **4**, 1071.
39 W. Schafer, T. Chandrasekaran, Z. Pirzada, C. Zhang, X. Gong, M. Biba, E. L. Regalado, C. J. Welch, *Cheirality* 2013, **25**, 799.