Tetrahedron 70 (2014) 1357–1362

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Rapid determination of enantiomeric excess of α-chiral aldehydes using circular dichroism spectroscopy

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ARTICLE INFO

Article history:
Received 15 September 2013
Received in revised form 21 November 2013
Accepted 25 November 2013
Available online 7 December 2013

Keywords:
Enantiomeric excess
Exciton coupled circular dichroism
High-throughput screening
Metal to ligand charge transfer

ABSTRACT

A method for enantiodiscrimination of α-chiral aldehydes is reported. The method utilizes circular dichroism (CD) spectroscopy and a sensing ensemble composed of 2-(1-methylhydrazinyl) pyridine (**1**) and Fe(II)$(TfO)_2$. Aldehydes react rapidly with hydrazine (**1**) to form chiral imines, which form complexes with Fe(II). By monitoring the CD bands above 320 nm, one can determine the enantiomeric excess (ee) values of α-chiral aldehydes with an average absolute error of ±5%. The analysis was fast, and thus can have potential applications in high-throughput screening (HTS) of catalytic asymmetric induction.

1. Introduction

Asymmetric synthesis is a well-recognized method for the synthesis of enantiomerically enriched compounds.[1] However, the process of finding the best catalyst for a particular asymmetric reaction can be time consuming and depends heavily on trial and error to find the best catalyst and suitable reaction conditions. Combinatorial chemistry, combined with parallel synthesis, is an alternate tool for finding an optimal catalyst and reaction conditions, as this technique can explore a large number of candidates in a short time span.[2] However, the determination of each reaction's ee value is a slow process. The most popular techniques to determine the ee of an asymmetric reaction are chromatographic techniques, such as chiral HPLC and GC.[3] Although these techniques are very accurate, the time required by serial chromatographic techniques restricts their use in high-throughput screening (HTS). Although NMR has been implemented in HTS, it also suffers from being a serial technique.[4]

For HTS of ee values, optical signaling techniques, such as fluorescence, UV–vis spectroscopy, and colorimetric analysis are well suited due to their speed of analysis compared to chromatographic techniques.[5–7] Due to this advantage, many research groups are exploring optical techniques for the determination of ee in HTS.[8] Moreover, to speed up the analysis time during screening, optical techniques can be carried out in a microwell plate format. In recent years, our group and others have focused on developing assays for determining the ee of chiral molecules containing carboxylic acids, ketones, amines, and alcohols by various optical techniques.[9–12]

2. Results and discussions

Here, we describe the determination of ee for the α-chiral aldehydes using CD spectroscopy. No optical methods are reported in the literature for the determination of the ee of α-chiral aldehydes, in part due to their propensity to racemize. However, α-chiral aldehydes are building blocks for many pharmaceuticals, hence creating an assay to determine their handedness could be generally useful.[13] An analyte binding event that would induce CD signals in wavelengths longer than 320 nm was sought as most organic functional groups are CD silent in this region.[10] This would allow determination of the ee values of crude reaction mixtures, and hence, can make this technique rapid and useful for HTS.

To create an assay for chiral aldehydes, we have combined the best aspects of two protocols we have previously reported for chiral amines and ketones.[10,11] Both protocols used CD active bands created upon metal complexation of imines. For example, with chiral ketones a condensation with 2-(1-methylhydrazine) pyridine (**1**) gave bidentate imines (**2**), which were then mixed with a chiral Cu(I) complex giving rise to structures, such as **3** (Scheme 1). These

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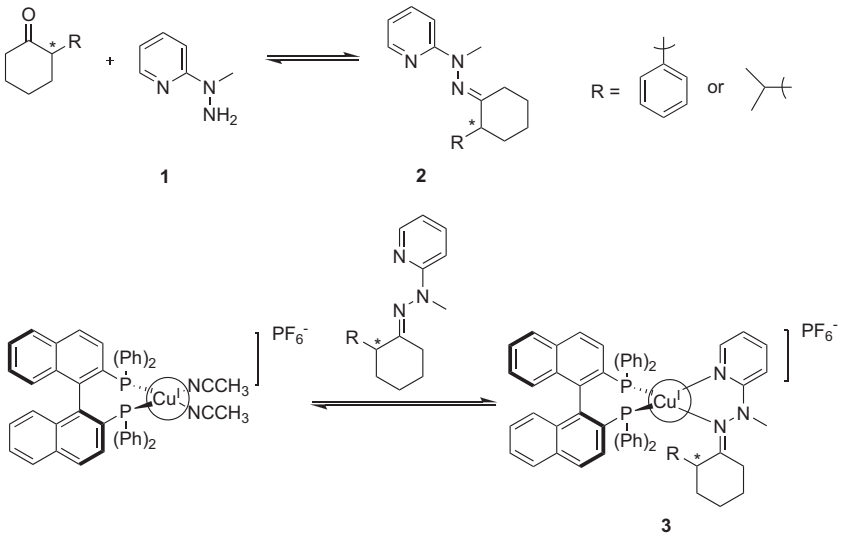
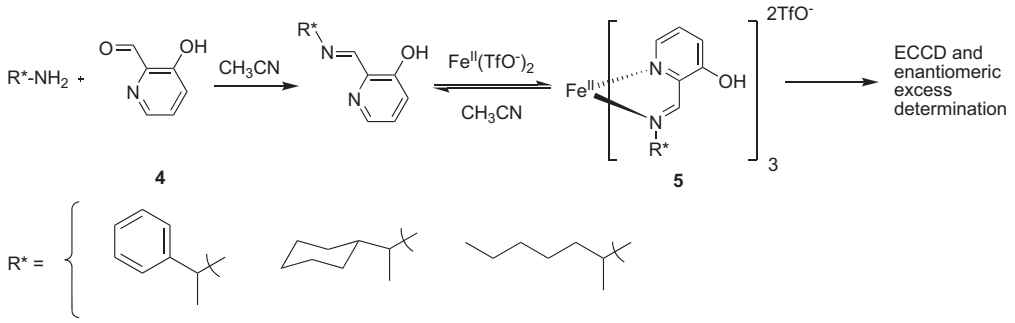
http://dx.doi.org/10.1016/j.tet.2013.11.086



Scheme 1. Our previously reported system for chiral ketones: CD active charge-transfer band is present in the receptor and modulated upon binding of the imine.[10]

structures possess CD active metal to ligand charge transfer (MLCT) bands, whose intensities can be used to determine the ee of the chiral ketones. While this method was successful, the detriment was weak CD signals that were only slightly different for the enantiomers of **2**. In contrast, a different strategy for chiral amines gave large CD signals with equal and opposite spectra. This assay also relies on a condensation to make bidentate imines, but the electrophilic and nucleophilic partners are exchanged (Scheme 2). Condensation of chiral amines with aldehyde **4**, followed by mixing the resulting imine with Fe(II) triflate gives the octahedral complexes represented by **5**. Both MLCT and exciton coupled circular dichroism (ECCD) bands could be used to determine the ee of the chiral amines.



Scheme 2. Our previously reported system for chiral amines: exciton coupled circular dichroism (ECCD) spectrum was generated when chiral imine analyte bind to the Fe(II) center, thereby facilitating the determination of ee of chiral amines.[11]

Herein, we show that by using compound **1** with chiral aldehydes, followed by the addition of Fe(II) triflate, we can create relatively large CD signals for the determination of the ee values of the chiral aldehydes. The preparatory work for our current approach is faster than the previous two cases because we demonstrate that making a very quick and simple derived calibration curve, consisting of just three points, gives the same ultimate error in ee values as our previous approaches.[10]

2.1. Choice of chiral aldehydes

Because no α-chiral aldehydes are commercially available, we synthesized a handful from commercially available chiral alcohols. The chiral aldehydes 2-phenylpropanal, 2-methoxy-2-phenylacetaldehyde, and 2-methyl butanal were chosen to span a range of chemical space representing both aromatic and aliphatic moieties (Fig. 1). All these chiral aldehydes were synthesized from their alcohol precursors. After perusal of the literature (SciFinder) search, we found that 2-phenyl propanol, 2-methoxy-2-phenyl ethanol, and 2-methyl butanol, are the only chiral alcohols commercially available for oxidation to α-chiral aldehydes and for which both the enantiomers are sold. The synthesis scheme involves oxidation to the aldehyde with the mild oxidizing agent DesMartin Periodinane (Scheme 3).[14] Imine bond formations with pyridine 2-(1-methylhydrazinyl, **1**) was completed in 30 min after

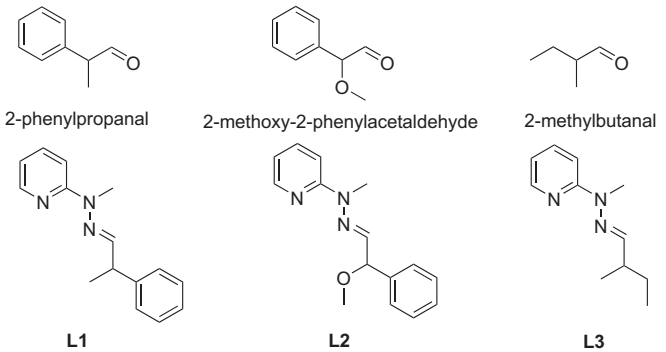
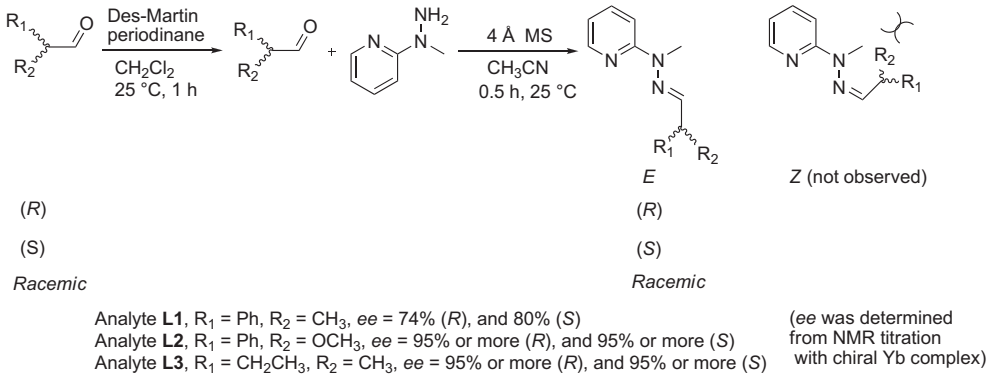
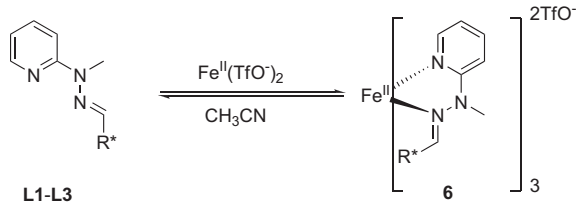


Fig. 1. Structures of (top) aldehydes studied, and (bottom) **L1**, **L2**, and **L3** created by reaction with 2-(1-methylhydrazinyl) pyridine (**1**).



Scheme 3. Synthesis of the imine derivatives of α-chiral aldehydes (no *Z* isomer was observed in the ^{1}H NMR spectrum).

the addition of 4 Å molecular sieves. The ^{1}H NMR spectra for the derivatized analytes (**L1**, **L2**, and **L3**) showed essentially only one diastereomer, with the hydrazone linkage in a *Z*-form, and the imine being the *E* isomer. These conformational preferences likely result due to the minimization of steric interactions. Complexation of the bidentate imines (**L1**–**L3**) with Fe(II) was performed in acetonitrile, resulting in complexes represented by **6** (Scheme 4).



Scheme 4. Complexation of the imine derivative with $Fe^{II}(TfO^{-})_2$ in acetonitrile.

2.2. Determining saturation via UV–vis titrations

UV–vis titrations were performed to determine the equivalents of analytes **L1**, **L2**, and **L3** to Fe(II) required to reach signal saturation (Fig. 2). The determination of the equivalents to reach saturation is important as it allows one to create concentration independent calibration curves for enantiomeric excess at concentrations beyond saturation.[10] As long as the assays are performed above saturation, the ee calibration curve developed at a single concentration can be used to determine the unknown's ee at any concentration. Saturation also generates the maximum signal-to-noise ratio and minimizes the contributions of 1:1 and 1:2 metal:analyte species, thereby simplifying the stereochemical interpretation of the CD data. As previously reported from our group for the determination of the ee of chiral amines (Scheme 2), we find saturation at 3 equiv analyte (**L1**, **L2** or **L3**) to 1 equiv of Fe(II) (Fig. 2).[11] Analyte **L2** does not show as clear an end point as that for **L1** and **L3**. This can be attributed to a lower affinity of **L2** for Fe(II), which is possibly due to increased strain in the 1:3 (metal:analyte) complex as a result of the larger methoxy group compared to methyl in **L1** and **L3**, respectively. As previously observed,[11] the binding curves have sigmoidal shapes, reflecting the 1:3 stoichiometry of the system.

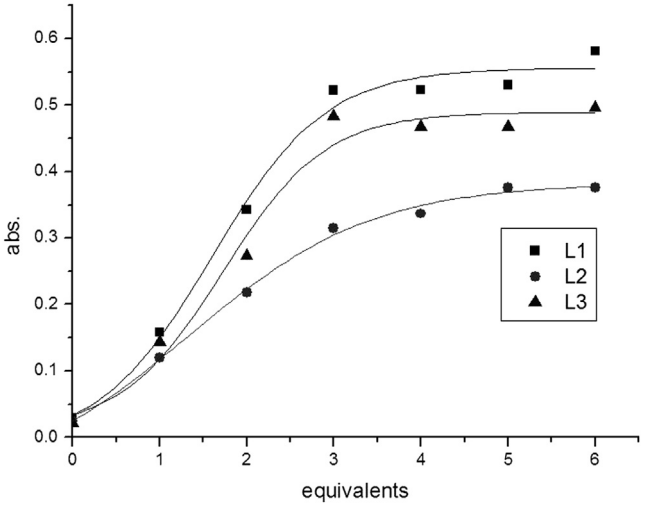


Fig. 2. Changes in absorption as a function of the number of equivalents of imine titrated into an acetonitrile solution of 1 mM Fe(II) at 334, 330, and 345 nm for **L1**, **L2**, and **L3**, respectively. The number of equivalents is defined as the concentration of imine divided by the concentration of Fe(II).

2.3. Stereoisomerism

The dominant species in solution with an Fe(II) to imine stoichiometry of 1:3 is an octahedral complex, which can exist in two helical isomers (Δ and Λ) and two configurational isomers (*fac* and *mer*) (Fig. 3). Hence for an enantiomerically pure aldehyde sample,

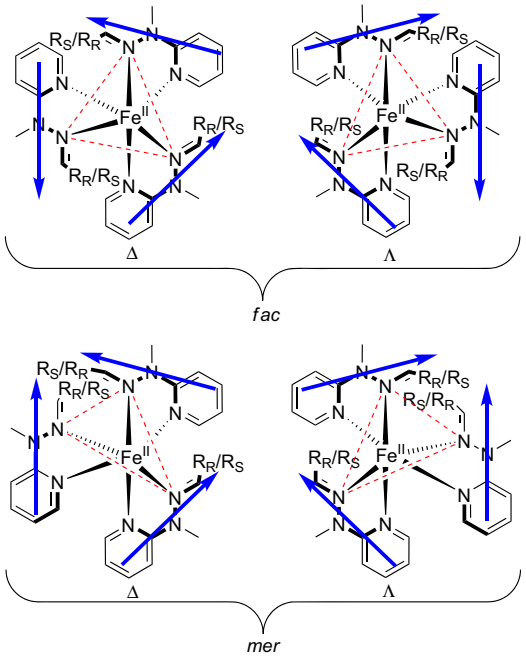


Fig. 3. Δ and Λ stereoisomers of the *fac* and the *mer* configurational isomers with enantiomerically pure imines.

four possible stereoisomers exist in solution. For aldehydes that are not enantiomerically pure, there are eight possible stereoisomers for the *fac* isomer and 16 possible isomers for the *mer* isomer, giving a total of 24 possible stereoisomers (see Supplementary data for all the isomeric forms). Complexity may arise while determining the ee of chiral aldehydes when a mixture of *R* and *S* isomers were added to a solution of Fe(II) due to the formation of this large number of stereoisomers. However, as long as all the isomers are in equilibria and rapidly exchanging, the CD spectra will be consistent and indicative of the ee value of the aldehydes.

2.4. Ee determination of the imines with chiral ytterbium tris [3-(trifluoromethylhydroxymethylene)-(+) camphorate] complex

As chiral aldehydes are prone to racemize, and the formation of the imines may lead to racemization, we measured the ee of the imines with the chiral shift reagent Ytterbium tris[3-(trifluoromethylhydroxymethylene)-(+) camphorate] via ^{1}H NMR.[15] We performed NMR titrations by adding progressively increasing equivalents of the chiral shift reagent to the chiral imines in $CDCl_3$ and monitored the methyl or the methoxy resonances in analytes **L1**, **L2**, and **L3** (Fig. 1). For the *racemic* imines, we observed two resonances with equal intensity for the methyl or the methoxy groups for all three analytes. Whereas for enantio-enriched *R* and *S* isomers, the intensity of the same peaks either varied from 1:1, or we could only observe one peak for the methyl or the methoxy group, suggesting that the enantiomeric excess to be more than 95%. For analyte **L1**, the ee of the *R* and the *S* isomers were 74 and 80%, respectively, whereas for analytes **L2** and **L3**; the ee were found to be $\geq$95% for both the *R* and the *S* isomers.

2.5. CD analysis stereoisomerism

All the Fe(II) octahedral complexes showed CD spectra, with the *R* and the *S* isomers of the original aldehydes giving mirror image spectra (Fig. 4). We postulated that the appearance of the CD signal in the imine-Fe(II) complex is due to the helical twist imparted by the three imine ligands in the octahedral geometry. No CD signals are observed at wavelengths longer than 290 nm for the enantio enriched alcohols or aldehydes, nor any signal at wavelengths longer than 300 nm were observed for the imines alone. Hence, any signal observed above 300 nm is produced by the formation of the complexes between chiral imines and Fe(II). The CD spectra were recorded above saturation after reaching equilibria, and hence are concentration independent.

For analytes **L1** and **L3**, the first Cotton effect observed at 334 and 345 nm, respectively, are positive for the *R* isomer and negative for the *S* isomer. However, for analyte **L2**, the sign of the first Cotton effect at 330 nm is reversed for the *R* and the *S* isomers, and the intensity of the CD signal is much higher than analytes **L1** and **L3**. The difference of sign of the CD signals for analyte **L2** as a function of *R*/*S* nomenclature is attributed simply to the priority of the groups around the stereocenter. Looking at the chiral center, **L2** contains methoxy, phenyl, and hydrogen whereas **L1** and **L3** contain methyl, phenyl, and hydrogen. Clearly methoxy has higher priority than phenyl in **L2** whereas phenyl and ethyl have higher priority in **L1** and **L3**, respectively. Hence this phenomenon explains the difference in sign of the CD signals for the three analytes. The larger intensity CD signal for analyte **L2** compared to **L3** can be attributed to the larger steric interactions from the bulky phenyl rings of the aldehyde compared to small alkyl groups in analyte **L3**, forcing a larger twist and thereby the higher CD signal. However, the larger intensity CD signal for analyte **L2** compared to **L1** can be attributed simply to the higher enantiomeric excess of **L2**. The peaks from 330 to 345 nm for all three analytes are attributed to a single strong electric-dipole-allowed $\pi-\pi^*$ transition, localized on the 2-iminopyridine chromophore and directed approximately along the bond between the imine and 2-pyridine carbon atoms after complexation (Fig. 3).[11]

2.6. Building a calibration curve for the ee determination of unknown α-chiral aldehydes

To demonstrate the assay's ability to determine the ee values of unknown samples, a calibration curve was generated by plotting the molar ellipticities at 334, 330, and 345 nm for analytes **L1**, **L2**, and **L3**, respectively, versus the ee for each of these analytes. Obviously, the racemic sample showed zero molar ellipticity and ee. Using only three values for each analyte found by the NMR chiral shift analysis and CD analysis, we generated calibration curves for each of the aldehydes (Fig. 5). Unknown samples were prepared for the three aldehydes by varying the enantiomeric excess at concentrations above saturation. Errors were calculated for each sample by taking the absolute difference between the actual and the experimentally determined ee. The average absolute error for the assay was calculated and determined to be ±5% for all the aldehydes. In the present

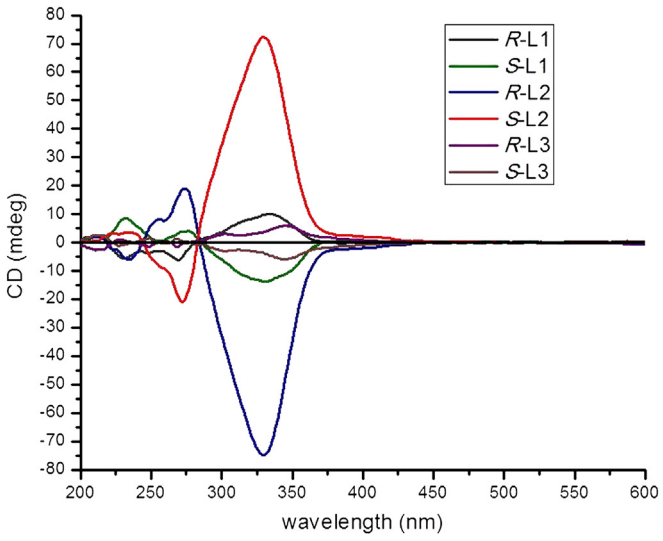


Fig. 4. CD spectra for analytes **L1**, **L2**, and **L3** (each 0.6 mM) in acetonitrile with 0.2 mM Fe(II) in a 0.1 cm quartz cell from 200 to 600 nm.

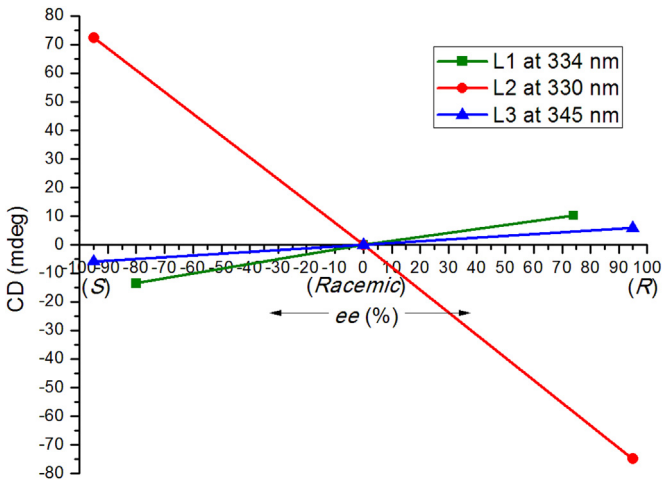


Fig. 5. Calibration curve for analytes **L1**, **L2**, and **L3**. Molar ellipticities for **L1**, **L2**, and **L3** at 334, 330 and 345 nm, respectively, from Fig. 4, versus enantiomeric excess values as determined from ^{1}H NMR titrations.

scenario, the total time required to analyze the ee of 96 samples of a particular aldehyde is not more than 1 h considering the derivatization, then complexation, followed by CD analysis. However, one might argue that the present system needs the calibration curve for each aldehyde takes another 2–3 h. Considering these factors, we still could analyze nearly 2400 samples of a particular aldehyde sample in 24 h, and hence this fits the definition of high-throughput analysis. Unknown samples containing both very high as well as very low chiral purity generated an absolute error within limit (±5%) as well. Hence, although only three points are used in the calibration curve, this study shows no loss of accuracy relative to previous studies. Because the calibration curves are linear, and three points defines a line, this is not necessarily surprising, but it is gratifying for the ultimate desire of minimizing the amount of preparatory work before measuring samples with unknown ee values.

In summary, using commercially available $Fe(II)(TfO)_2$, pyridine 2-(1-methylhydrazinyl), and a fast straight forward condensation reactions with the α-chiral aldehydes, we created an assay for the determination of the enantioselectivity of some α-chiral aldehydes using circular dichroism spectroscopy. The speed at which CD operates is advantageous for high-throughput screening of asymmetric catalysts/auxiliaries. The calibration curve based upon only three points was linear, and allowed for determination of the enantiomeric excesses of a series of chiral aldehydes. We have demonstrated this system's ability to differentiate the enantiomers of three derivatized α-chiral aldehydes, determining the enantiomeric excess of unknown samples with approximately ±5% absolute error.

3. Experimental section

3.1. General experimental procedure

All commercially obtained reagents were used as received. A Varian Mercury 400 MHz, and a Varian Inova 400 MHz spectrometer were used to obtain ^1H and ^{13}C NMR spectra, which were referenced using the solvent residual peak. Chemical shifts are given in parts per million (ppm). Signals are reported as m (multiplet), s (singlet), d (doublet), t (triplet), q (quartet), br s (broad singlet), br m (broad multiplet). LC–MS data was recorded on an Agilent 6130 Quadrupole instrument. High resolution mass spectrometry was performed with a Varian 9.4T QFT-ESI ICR system. Circular dichroism spectra were obtained on a CD-Jasco-815 CD spectrophotometer using a temperature controller at 25 °C in a Starna 1 mm quartz cuvette. Syntheses of aldehydes from alcohols were carried out by published procedure. All solvents were removed by rotary evaporation under vacuum using a standard rotavapor equipped with a dry ice condenser. All filtrations were performed with a vacuum. Flash chromatography was performed using Sorbtech 60 Å 230X400 mesh silica gel.

3.2. General procedure for the synthesis of the aldehydes

To a 50 mL round bottom flask, chiral alcohol (1 mmol) was dissolved in 10 mL of dry dichloromethane under nitrogen atmosphere and was cooled to 0 °C. Sodium bicarbonate (1.2 equiv) and Des-Martin Periodinane (1.2 equiv) were added and the reaction mixture was allowed to warm to room temperature. The reaction mixture was stirred for 1 h and was hydrolyzed by the addition of a 1:1 mixture of $Na_2S_2O_3$ (satd aqueous) and $NaHCO_3$ (satd aqueous). The aqueous phase was extracted with dichloromethane and the organic phase was subsequently washed with $NaHCO_3$ (satd aqueous) then dried over anhydrous sodium sulfate. After removal of the organic solvent under reduced pressure, a colorless oily pure product was obtained as the product (yield 75–85%).

3.3. General procedure for the synthesis of imines

To a 50 mL round bottom flask, charged with 4 Å molecular sieves, pyridine 2(1-methyl hydrazinyl) (**1**) (1 mmol), *R*/*S*/*Racemic* aldehyde (1 mmol) and dry acetonitrile (5.0 mL) were added and stirred under nitrogen for 30 min at room temperature. The reaction mixture was filtered through Celite and the solvent was removed in vacuo to afford the analytes **L1**, **L2**, and **L3** as oil with 70–80% yield.

*3.3.1. (E)-1-Methyl-2-(2-phenylpropylidene)-1-(pyridine-2-yl)hydrazine (**L1**).* ^1H NMR ($CDCl_3$, 400 MHz) δ ppm: 1.56 (d, *J*=4.8 Hz, 3H), 3.42 (s, 3H), 3.79 (m, 1H), 6.71 (t, *J*=4.2 Hz, 1H), 7.02 (d, *J*=4.6 Hz, 1H), 7.20–7.40 (m, 5H), 7.56–7.60 (m, 2H), 8.18 (d, *J*=3.8 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm: 19.9, 29.1, 44.0, 109.9, 114.8, 126.6, 128.0, 128.8, 137.8, 140.4, 142.0, 146.2, 158.0. HR-MS $(M+H)^{+1}$: 240.14952 (calcd), 240.14933 (obsd) (error −0.8 ppm).

*3.3.2. (E)-2-(2-Methoxy-2-phenylethylidene)-1-methyl-1-(pyridine-2-yl)hydrazine (**L2**).* ^1H NMR ($CDCl_3$, 400 MHz) δ ppm: 3.39 (s, 3H), 3.41 (s, 3H), 4.84 (d, *J*=4.2 Hz, 1H), 6.68 (t, *J*=4.0 Hz, 1H), 6.82 (d, *J*=4.6 Hz, 1H), 7.24 (m, 1H), 7.32 (m, 5H), 7.49 (m, 3H), 8.10 (d, *J*=3.8 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm: 29.8, 57.0, 83.9, 110.0, 115.8, 127.0, 128.0, 129.1, 136.2, 138.0, 140.0, 146.4, 157.9. HR-MS $(M+H)^{+1}$: 256.14444 (calcd), 256.14424 (obsd) (error −0.76 ppm).

*3.3.3. (E)-1-Methyl-2-(2-methylbutylidene)-1-(pyridin-2-yl)hydrazine (**L3**).* ^1H NMR ($CDCl_3$, 400 MHz) δ ppm: 0.93 (t, *J*=4.6 Hz, 3H), 1.14 (d, *J*=4.2 Hz, 3H), 1.40–1.55 (m, 1H), 1.55–1.62 (m, 1H), 2.30–2.44 (m, 1H), 3.42 (s, 3H), 6.62 (t, *J*=3.6 Hz, 1H), 6.81 (d, *J*=3.4 Hz, 1H), 7.42–7.52 (m, 2H), 8.16 (d, *J*=1.8 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm: 11.9, 18.2, 28.0, 29.4, 38.6, 109.9, 114.8, 137.9, 142.8, 146.5, 158.0. HR-MS $(M+H)^+$: 192.14952 (calcd), 192.14920 (obsd) (error −1.67 ppm).

3.4. General experimental details on ee determination of imines

In an NMR tube around 10 mg of analyte (**L1**, **L2**, and **L3**) was dissolved in $CDCl_3$. Then progressively with an increment of 5%, Ytterbium tris[3-(trifluoromethylhydroxymethylene)-(+) camphorate] complex was added starting from 5% (wt/wt) up to 150%. After each addition, the entire solution was sonicated and allowed to stand for 30 min prior to obtaining 1 H NMR spectra. At 30% (wt/wt) addition, the ^1H NMR peak of the methyl, methoxy and methyl at the chiral center for analytes **L1**, **L2**, and **L3**, respectively, showed clear characteristic splitting pattern with 1:1 intensity for *racemic* and with various ratios for the *R* and the *S* isomers for all the analytes. The ee for each isomer was determined from the integration of the methyl peak.

Acknowledgements

We gratefully acknowledge the financial support from the National Institute of Health (R01 GM077437) and Welch Foundation (F-1151).

Supplementary data

Experimental procedures, ^1H, ^{13}C NMR, HR-MS, UV–vis, and CD spectral data are available. Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2013.11.086. These data include MOL files and InChiKeys of the most important compounds described in this article.

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