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Rohan Ravindranath, Soon Mog So and Jik Chin

EVALUATING BINOL-ALDEHYDE AS A CHIRAL DERIVATIZING AGENT FOR DIAMINES

Department of Chemistry, University of Toronto,
80, St. George str., Toronto, Ontario M5S 3H6, Canada;
jchin@chem.utoronto.ca

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Abstract. We have synthesized and tested a new binol-aldehyde compound **1**, against five diamine compounds. Using ^{1}H NMR (400 MHz) spectroscopy, stable diasteriomeric imine complexes between **1** and five diamines were formed. Chemical shift nonequivalences (up to 0.058 ppm) were obtained for imines. Linear calibration plot was obtained for determining the enantiopurity of diamines.

Keywords: binol, aldehyde, chiral derivatizing agent, diamine, ^{1}H NMR spectroscopy.

1. Introduction

Chiral vicinal diamines have been employed in the development of transition metal based catalysts [1-16], organocatalysts [17-20] and pharmaceuticals [21]. Chiral derivatizing agents (CDA) continue to be an important and convenient tool for determining the enantiopurity of chiral compounds. Over the years, many authors have reported the use of these derivatizing agents on a variety of molecules such as carboxylic acids [22, 23], amino alcohols [24], amines [25-28] and cyanohydrins [29, 30]. Despite the fact that chiral shift reagents (CSA) do not require prior purification of modified substrates, the synthesis of CSAs continues to remain challenging, compared to the synthesis of CDAs. We report the synthesis and use of a novel chiral binol-based aldehyde receptor, **1**, for its use as an effective chiral derivatizing agent for five chiral diamines. This aldehyde receptor relies on formation of reversible covalent bonds with the diamine, to form imine complexes [31-33]. Then this can be used to determine the enantiopurity of the chiral diamine.

2. Experimental

Except for noted, deuterated solvents were used as received from Cambridge Isotopes Laboratories. ^{1}H and ^{13}C NMR spectroscopy was performed at the Department of Chemistry of Toronto University, using a Varian 400 spectrometer. ^{1}H NMR chemical shifts were measured relative to partially deuterated solvent peaks and reported relative to tetramethylsilane (TMS). ^{13}C NMR spectra are ^{1}H-decoupled, and their chemical shifts are referenced relative to solvent peaks. ^{1}H and ^{13}C NMR spectra were processed using MestReNova NMR software. All reagents were obtained commercially and used as received. Gradient column chromatography was performed using Silicycle 230–400 mesh silica gel. EMD Silica gel 60 F_{254} plates were used for thin-layer chromatography (TLC).

2.1. Synthetic Procedure for Chiral Binol-Aldehyde 1

(R)-binol (1.44 g, 5 mM) and 3-(bromomethyl)-5-chloro-2-hydroxybenzaldehyde (0.5 g, 2 mM) were mixed together in a round bottom flask. THF (20 ml) was then added to this mixture, and the reaction flask was placed in an ice bath and stirred using a magnetic stir bar. In small portions, 60 % of NaH (0.28 g, 7.02 mM) was added to the reaction, and the reaction continued to stir for an hour. After one hour, 1 ml of concentrated HCl was added, to neutralize the excess of NaH. Gradient column chromatography was used to purify the chiral binol-aldehyde product, and remove the excess of unreacted (R)-binol. 1:1 mixture of hexane/dichloromethane was initially used as a solvent, to separate the product from the reaction mixture. A higher concentration of dichloromethane was required towards the end, to elute the product from the column. Upon purification by column chromatography, 821 mg of purified product (90.0 % yield) was obtained. Light yellow needles. mp: 370–371 K; ^{1}H NMR (400 MHz, $CDCl_3$): δ: 4.92 (s, 1H), 5.17 (m, J =12.0 Hz, 2H), 9.75 (s, 1H), 11.09 (s, 1H). ^{13}C NMR (400 MHz, CDCl3): δ: 64.47, 115.27, 115.93,

118.82, 120.46, 122.67, 122.80, 123.90, 124.12, 124.39, 125.35, 126.53, 126.76, 128.42, 128.45, 128.47, 129.24, 129.46, 129.61, 129.71, 130.26, 133.74, 133.95, 134.34, 153.27, 153.75, 156.10, 194.99. HRMS (DART, m/z) calcd. for $C_{28}H_{20}ClO_4$ $(M+H)^+$ 455.1050, found 455.1056.

2.2. Preparation of Diastereomeric Imine Complexes 3a-3e

In order to prepare each of the imine complexes **(3a-3e)**, 1 equivalent of corresponding (R,R)/(S,S) diamine (**2a-2e)** was added to 2.5 equivalents of chiral binol-aldehyde **1**, and mixed together in DMSO-d6 respectively. The concentration of diamine in each sample prepared was 15 mM. Formation of the imine complex required one hour at room temperature (298 K).

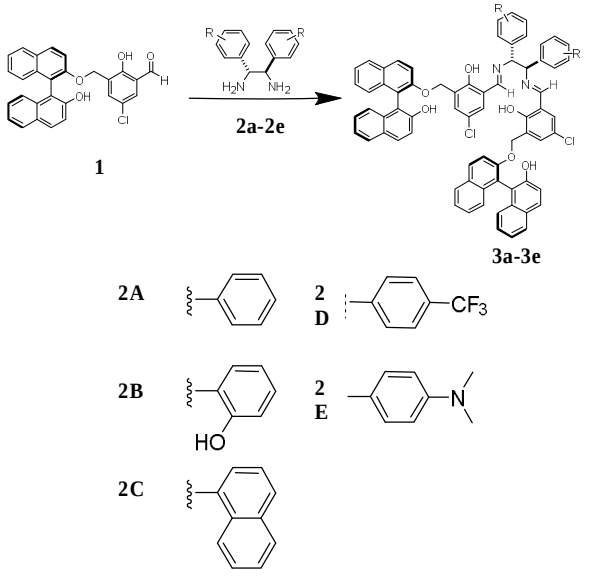
2.3. Determining Enantiomeric Excess (*ee*) for Diamine 2a by ^{1}H NMR spectroscopy

In separate glass vials, 3 ml stock solutions of (R,R) and (S,S) imine complexes **(3a)** were prepared in DMSO-d6. A series of samples with varying (R,R):(S,S) imine ratios were prepared in NMR tubes, to make a total combined volume of 0.8 ml. For example, 75 % *ee* sample of (S,S) imine was prepared by combining 0.1 ml of (R,R) imine stock solution, with 0.7 ml of (S,S) imine stock solution. Using a similar procedure, 50 % and 25 % *ee* of (S,S) imine and 0, 25, 50 and 75 % *ee* of (R,R) imine solutions were also prepared. All samples were equilibrated at room temperature for 1 h, following which ^{1}H NMR spectra of all the samples were obtained, and the resulting imine proton peaks were integrated to determine experimental *ee* values.

3. Results and Discussion

The objective of this study was to determine whether the chiral aldehyde **1** could act as an effective chiral derivatizing agent for diamines **2a-2e**. It was expected that when the chiral aldehyde was dissolved and mixed with the diamines, a diastereomeric imine complex **3** would form. This was indeed observed through ^{1}H NMR spectroscopy.

To ensure a complete reaction, a slight excess of chiral aldehyde was mixed with diamine (2.5:1). This was done because each diamine reacts with two equivalents of the chiral aldehyde. An excess of 0.5 equivalents of diamine was added to **1**, to ensure that all of the diamines reacted with the aldehyde, and that there was no unreacted diamine in the solution. ^{1}H NMR spectroscopy for the resulting imine complexes (**3a-3e**) showed that the pairs of diastereomeric imine peaks were of similar intensity. This was expected that there was 1:1 equivalence of (R,R) and (S,S) diamine in each NMR sample.



Scheme 1. Synthesis of diastereomeric imine complexes **3a-3e** and chemical structures of diamines **2a-2e**

As shown in Scheme 1, diamines **2a-2e** have different substituents on the phenyl rings. These substituents had a profound effect on how well the chiral derivatizing agent **1** could be distinguished between diastereomers of the diamine. Table 1 shows the chemical shifts for the imine protons, as well as their ^{1}H chemical shift nonequivalencies ($\Delta\Delta\delta$). Imine protons typically have a chemical shift between 8.4–8.7 ppm and appear as a singlet.

Table 1

Measurement of ^{1}H NMR chemical shift inequivalencies ($\Delta\Delta\delta$) of imine protons (3a-3e), resulting from reaction of racemic (R,R) and (S,S) diamine 2a-2e with chiral binol-aldehyde receptor 1, by ^{1}H NMR (400 MHz) in DMSO-d_6 at 298 K

Diamine	δ of R,R imine proton	δ of S,S imine proton	$\Delta\Delta\delta$, ppm
2a	8.463	8.407	0.056
2b	8.410	8.362	0.048
2c	8.695	8.671	0.023
2d	8.507	8.449	0.058
2e	8.441	8.393	0.049

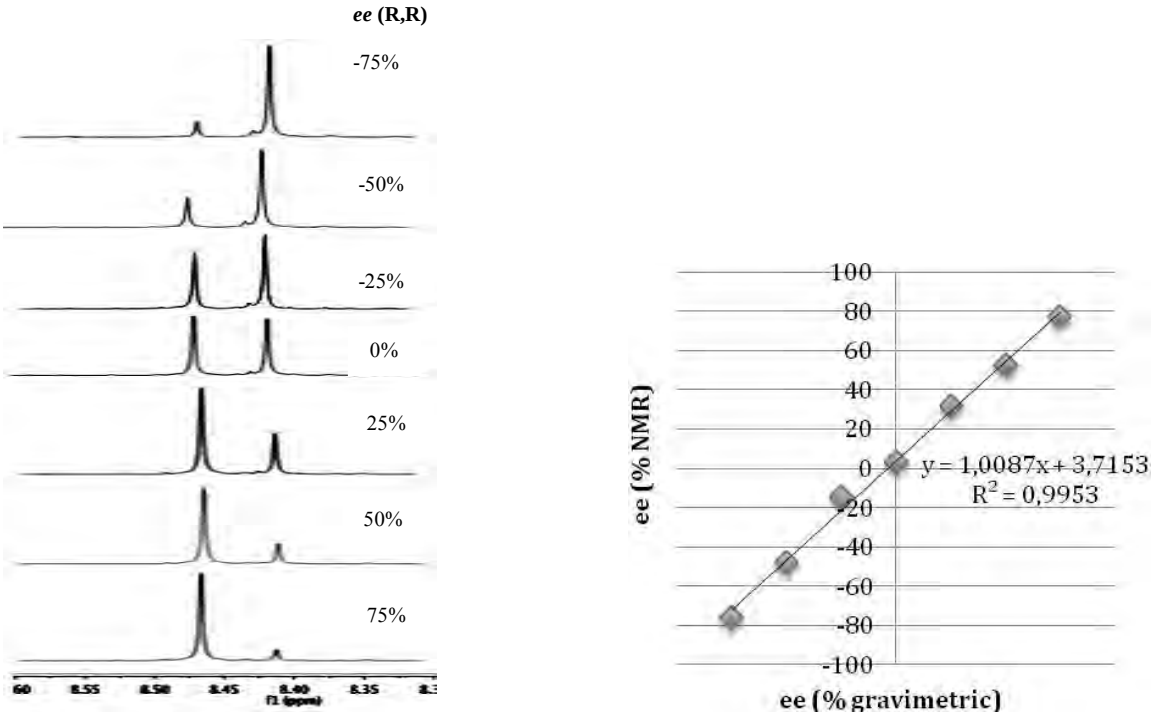


Fig. 1. Partial ^{1}H NMR spectra showing correlation between *ee* values determined gravimetrically and ^{1}H NMR signals. Linear correlation between *ee* values is determined gravimetrically and by integration of ^{1}H NMR signals; *ee* defined in terms of (R,R)-**2a**

The diamine **2d**, with electron-withdrawing groups in the *para*-position, seemed to have the largest separation between (R,R) and (S,S) diastereomeric imine peaks. This is evident from the fact that the ^{1}H chemical shift inequivalence ($\Delta\Delta\delta$) is 0.058 ppm. It is also apparent that the imine peaks for this diamine were shifted downfield relative to the unsubstituted diamine **2a**. The downfield shift corresponded to 0.04 ppm, and can be explained by the fact that electron-withdrawing trifluoromethyl groups on diamine **2d**, deshield the imine proton. Conversely for diamines **2b** and **2e**, they seemed to have a much smaller $\Delta\Delta\delta$ (~ 0.048 ppm). This is possibly due to the electron-donating groups in the *ortho*- and *para*-positions respectively. Diamine **2b** has a hydroxyl group in the ortho-position and diamine **2e** has a dimethylamino group in the para-position. The imine peaks on the ^{1}H NMR spectra of these complexes were shifted upfield relative to diamine **2a**. This is because of the increase in electron density coming from the electron-donating groups on diamines **2b** and **2e**. They allow the imine proton to be shielded. The ^{1}H chemical shift inequivalencies reported in our study were fairly consistent with those reported for other chiral derivatizing agents. D. Yang *et al*. [34] reported $\Delta\Delta\delta$ ranging from 0.03 to 0.11 ppm, for their carboxylate receptor to detect different racemic carboxylic acids.

To demonstrate the utility of the receptor **1** as a chiral derivatizing agent, *ee* values of multiple nonracemic diamine **2a** samples were determined by integration of the diastereomeric imine peaks. Seven samples containing **3a** with 75, 50, 25 % (R,R) *ee*, and 0, 25, 50, 75 % (S,S) *ee* were investigated. The *ee* compositions were determined by ^{1}H NMR spectroscopy (Fig. 1). We also confirmed a linear correlation between the theoretical (x) and observed percent *ee* values (y). The equation $y = 1.00x + 3.75$ (correlation coefficient is 0.9953) demonstrates the high accuracy of this method. In addition, Fig. 1 also shows the partial ^{1}H NMR spectra, for different nonracemic diamine samples.

The fact that such a high correlation coefficient was obtained, suggests that the binol-aldehyde **1** has good chiral recognition abilities amongst different nonracemic mixtures of diamine **2a**. The analytical abilities of **1** were maintained, and allowed us to confidently conclude that this compound is a good chiral derivatizing agent for diamines.

It is clear that the ^{1}H NMR spectra in Fig. 1, supports the calibration curve shown. It is a well-known fact that compounds with a binaphthyl moiety tend to be good chiral shift reagents [22]. These compounds tend not to be flexible, but can form complexes in the solution easily. Assuming that our compound fits this category, this could explain why it behaves as a good chiral derivatizing agent.

4. Conclusions

We have developed a new analytical tool, which can be used to determine the enantiopurity of a given sample of chiral diamines. We were able to confirm the chiral derivatizing agent properties of the compound, by obtaining a good linear correlation on the calibration curve. In addition, there was a good correlation observed between ^{1}H chemical shift inequivalencies, and the nature of the substituent on the aromatic ring of the diamines. Future work includes using computational modeling to evaluate stereospecificity of receptor **1**, with other amine-based compounds (amino amides, amino acids). This will further expand the versatility and scope of our novel chiral receptor.

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ОЦІНКА БІНОЛ-АЛЬДЕГІДУ ЯК ХІРАЛЬНОГО ДЕРИВАТИЗУЮЧОГО АГЕНТУ ДЛЯ ДІАМІНІВ

Анотація. *Синтезовано і досліджено нову бінол-альдегідну сполуку* ***1*** *відносно п'яти діамінів. Використовуючи ^{1}Н ЯМР-спектроскопію (400 МГц), показано утворення стійких діастеріометричних імінних комплексів сполуки* ***1*** *і п'яти діамінів. Визначено нееквівалентність хімічного зсуву для імінів (до 0,058 ppm). Для визначення енантіочистоти діамінів побудовано лінійний калібрований графік.*

Ключові слова: *бінол, альдегід, хіральний диференціюючий агент, діамін, ^{1}Н ЯМР-спектроскопія.*