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Research paper

Chiral sensor for enantiomeric purity of amines, amino alcohols and amino esters based on bis-cyclometalated Ir(III) complex using ^{1}H NMR spectroscopy

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ABSTRACT

A new chiral sensor assembly with enantiomeric Ir(III) complex Δ-[Ir(ppy)$_2$(MeCN)$_2$](PF$_6$) (ppy is 2-phenylpyridine) and 3-hydroxypyridine-2-carboxaldehyde as anxiliaries for chiral amines and amino derivatives, including α-amines, α-amino alcohols, α-amino esters, β-amines and β-amino alcohols as well as amino ether, was developed on the basis of ^{1}H NMR spectroscopy. The assembly reaction is rapid and quantitative in equivalent under mild conditions, generating the corresponding diastereomers that are applied to discriminate the absolute configuration and quantitatively determine the enantiomeric excess (*ee*) directly without physical separation. The chelating coordination to Ir(III) ion much enhances the stability of the formed Schiff base ligand. Furthermore, more than one pair of diastereotopic resonances in wide detection regions ensures a convenient and high degree of accuracy in quantifying the *ee* value of chiral amines and amino derivatives. The absolute errors of the *ee* determinations by ^{1}H NMR spectroscopy in different detection windows are within 1.9%. The linear relationship between the experimentally measured *ee* values and the gravimetrically prepared samples is found to be excellent.

1. Introduction

Chiral amines and amino derivatives are fundamental organic chemicals that have been widely applied in organic synthesis and pharmaceutical chemistry [1,2], many considerable efforts have been made into their asymmetric synthesis. In the meantime, the determination of the absolute configuration and enantiomeric excess (*ee*) of chiral molecules remain time-consuming and costly in high-throughput synthesis, therefore, rapid and convenient methods for the determination of chiral compounds are high desirable. Although many analytical techniques, such as HPLC [3,4], GC [5,6], UV-vis [7–10], circular dichroism (CD) [11–15] and fluorescence spectroscopy [16–24] have been used to determine chiral molecules, NMR spectroscopy, especially ^{1}H NMR, is one of the most efficient and widely used analytical techniques for the determination of *ee* value of chiral molecules due to several advantages such as accuracy, convenience and no calibration curve [25–35]. To actualize in situ direct chiral analysis of chiral amines by NMR spectroscopy, a suitable chiral auxiliary, such as a chiral derivatizing agent (CDA) [27–29,36–38], chiral solvating agent [30–32,39,40], or chiral lanthanide shift reagent [33], can be introduced to produce diastereomeric adducts and generate distinguishable chemical shifts. In spite of great advances, the drawbacks such as line-broadening, narrow substrate scope, poor solubility, and poor resolution still limit its application. Thus, NMR technique is infrequently used for direct chiral analysis. Generally, chiral aldehydes are usually used to react with chiral amines or amino derivatives as auxiliaries to generate Schiff base diastereomers rapidly, due to involving covalent bond formation and resulting in better discrimination for a large chemical shift difference [29,37]. However, the imine bond in Schiff base is reversible and sensitive to water. To overcome this, Bull and James used a three-component protocol to afford a mixture of diastereomers whose ratio can be determined by ^{1}H NMR spectra [27,28]. All these techniques rely on the different chemical shifts of the analytical analytes arising from the formation of diastereomers, thus, the analysis requires formation of a stable adduct and is complicated when the NMR signals overlap.

In light of these challenge, we pay our attention to octahedral Ir(III) complexes with chirality at the metal as a highly efficient and practical chiral discriminating agent [41,42]. In fact, the discrimination of enantiomers has been achieved with chiral metal complexes [43–45], in which the enantiopuric complexes with a chiral environment that can be used to discriminate or selectively bind with a chiral substrate. Our previous works on asymmetric synthesis of chiral sulfoxides on the basis of Ru(II) chiral-at-metal complexes [46–49] and resolution of chiral

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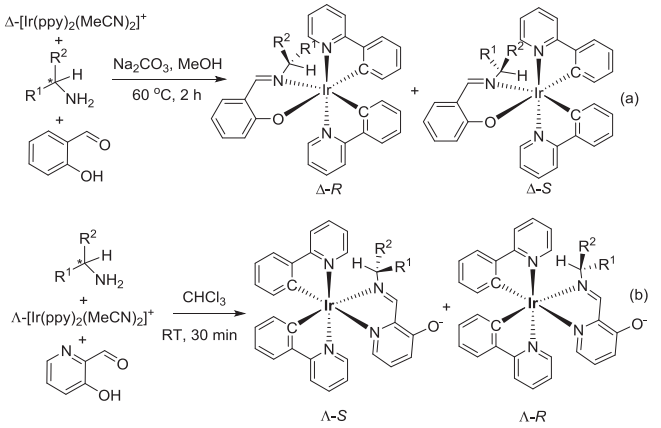

Scheme 1. Diagrammatic presentation of a three-component protocol for determination *ee* of chiral amines and amino derivatives based on salicylaldehyde or 3-hydroxypyridine-2-carboxaldehyde with enantiopuric $[Ir(ppy)_2(MeCN)_2](PF_6)$.

sulfoxides with Ir(III) chiral-at-metal complexes [50] showed that the diastereomers not only have distinct ^{1}H NMR chemical shifts for the enantiomeric sulfoxides but also display distinguishable signals at low-field with good resolution for the α-H of the auxiliary ligand bpy or ppy (bpy is 2,2′-bipyridine and ppy is 2-phenylpyridine) in the chiral complexes. This may offer a new detection window at low-field to overcome the limitation of signals overlap in the narrow detection area of the analytes in ^{1}H NMR spectroscopy. Following this strategy, a three-component protocol in combination of chiral primary amine, salicylaldehyde and enantiomerically pure Ir(III) complex Δ-[Ir(ppy)$_2$(MeCN)$_2$](PF$_6$) was successfully developed to discriminate and determine *ee* value of chiral primary amines [51]. However, in that protocol, the imine formation is slow, requiring 2 h to go to completion in the presence of Na_2CO_3 as a base at 60 °C (Scheme 1a), which may limit its application to the thermally and base sensitive substrates, such as low boiling point amines and amino esters. In the present paper, a new chiral sensor in combination of enantiomeric Λ-[Ir(ppy)$_2$(MeCN)$_2$](PF$_6$) and 3-hydroxypyridine-2-carboxaldehyde was developed to discriminate and determine *ee* value of various chiral amines and amino derivatives, including α-amines, α-amino alcohols, α-amino esters, β-amines and β-amino alcohols as well as amino ether (Scheme 1b). The introduction of 3-hydroxypyridine-2-carboxaldehyde much increases the imine formation and the assembly with Λ-[Ir(ppy)$_2$(MeCN)$_2$](PF$_6$); thus, there is no need to add a base. This also shortens the preparation time for the assay to 30 min and decreases the reaction temperature to room temperature. Therefore, the protocol overcomes the aforementioned limitations of our previously reported method for *ee* value determination of chiral amine and amino derivatives.

2. Experimental

2.1. Materials and methods

All chemicals were commercially available and used as purchased unless otherwise noted. The enantiopure Λ-[Ir(ppy)$_2$(MeCN)$_2$](PF$_6$) (ee ≥ 98%) was synthesized according to the literature [52]. Elemental (C, H and N) analyses were carried out on an Elementar Vario EL analyzer. Electrospray ionization mass spectra (ESI-MS) were obtained on a Thermo LCQ DECA XP mass spectrometer. CD spectra were measured on a JASCO J-810CD spectropolarimeter. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ or CD_3OD on a Bruker AV-400 spectrometer and chemical shifts (in ppm) were referenced to a residual solvent proton peak. The racemic and scalemic samples were prepared by mixing the enantiopure compounds in the appropriate ratios.

2.2. General procedure for discrimination and ee determination of chiral amines and amino derivatives

Λ-[Ir(ppy)$_2$(MeCN)$_2$](PF$_6$) (0.0072 g, 0.01 mmol), 3-hydroxypyridine-2-carboxaldehyde (0.0012 g, 0.01 mmol) and amine or amino derivative (0.01 mmol) was added to a $CHCl_3$ (3 mL) solution sequentially. The solution was stirred at room temperature for 30 min. Then the solvent was removed and the mixture was transferred to a NMR tube with 0.5 mL $CDCl_3$ for ^{1}H NMR determination. For 3-aminopropane-1,2-diol experiment, CH_3OH and CD_3OD solvents were used.

2.3. Synthesis of Λ-Ir(III)-Schiff base complexes with S-1-phenylpropan-1-amine (Λ-PPAS) and R-1-phenylpropan-1-amine (Λ-PPAR)

The enantiopure complexes Λ-**PPA*S*** and Λ-**PPA*R*** were prepared via the above procedure, enantiopure *S*-1-phenylpropan-1-amine (**PPA*S***) and *R*-1-phenylpropan-1-amine (**PPA*R***) were used, respectively. Yield, 95%; Anal. Calcd for $C_{37}H_{31}IrN_4O$: C, 60.06; H, 4.22; N, 7.57. Found: C 60.00, H 4.00, N 7.60; ESI-MS: m/z = 741.07 $[M-H]^+$. For Λ-**PPA*S***: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.61 (s, 1H), 7.95 (d, J = 5.6 Hz, 1H), 7.86 (t, 1H), 7.79 (d, J = 8.1 Hz, 1H), 7.74 (d, J = 7.6 Hz, 1H), 7.67 (d, J = 8.3 Hz, 1H), 7.61 (dd, J = 14.9, 7.6 Hz, 2H), 7.50 (d, J = 5.4 Hz, 1H), 7.36–7.29 (m, 3H), 7.22 (d, J = 5.6 Hz, 1H), 7.18 (t, 1H), 7.06 (dd, J = 10.4, 6.2 Hz, 2H), 6.99 (dd, J = 7.4, 4.9 Hz, 3H), 6.90 (t, 1H), 6.85 (t, 1H), 6.54 (t, 1H), 6.20 (d, J = 7.4 Hz, 1H), 6.15 (d, J = 7.5 Hz, 1H), 4.41 (t, 1H), 2.98 (s, 1H), 1.75–1.56 (m, 2H), 0.23 (t, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.10, 167.52, 163.23, 162.25, 159.54, 150.90, 150.72, 150.01, 149.16, 143.64, 143.61, 142.58, 141.70, 138.58, 138.39, 137.75, 133.07, 131.74, 131.36, 130.74, 130.29, 129.38, 129.38, 129.02, 128.56, 128.41, 128.41, 124.82, 124.67, 123.78, 122.79, 122.79, 123.67, 119.34, 72.60, 28.38, 10.54. CD (Δε, M^{-1} cm^{-1}, DCM): 323 (+89), 362 (+54), 412 nm (−27) (see Fig. S1). For Λ-**PPA*R***: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.51 (s, 1H), 8.05 (d, J = 5.5 Hz, 1H), 7.86 (d, J = 8.0 Hz, 1H), 7.79 (t, 1H), 7.67 (d, J = 8.4 Hz, 1H), 7.57 (t, 2H), 7.44 (d, J = 8.1 Hz, 1H), 7.33 (d, J = 7.6 Hz, 1H), 7.29–7.25 (m, 2H), 7.23–7.17 (m, 2H), 6.99 (d, J = 7.7 Hz, 2H), 6.94 (t, 2H), 6.88 (q, 3H), 6.80 (t, 1H), 6.29 (dd, J = 7.4, 2.8 Hz, 3H), 5.98 (d, J = 7.6 Hz, 1H), 4.73 (dd, J = 9.6, 4.9 Hz, 1H), 2.21–2.07 (m, 1H), 1.97–1.80 (m, 1H), 0.71 (t, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.90, 167.72, 162.19, 158.53, 149.96, 149.75, 149.36, 148.56, 144.33, 143.53, 143.41, 142.35, 138.19, 137.56, 136.53, 131.78, 131.30, 131.13, 130.78, 130.28, 128.33, 128.17, 127.93, 127.33, 124.72, 124.59, 123.60, 123.00, 122.77, 123.26, 119.74, 119.44, 123.67, 119.34, 74.96, 28.96, 11.28. CD (Δε, M^{-1} cm^{-1}, DCM): 324 (+87), 364 (+52), 390(+41), 412 nm (−31) (see Fig. S1).

2.4. Synthesis of Λ-Ir(III)-Schiff base complexes with S-2-amino-2-phenylethanol (Λ-PEOS) and R-2-Amino-2-phenylethanol (Λ-PEOR)

The enantiopure complexes Λ-**PEO*S*** and Λ-**PEO*R*** were prepared via the above procedure, enantiopure *S*-2-amino-2-phenylethanol (**PEO*S***) and *R*-2-amino-2-phenylethanol (**PEO*R***) were used, respectively. The reaction mixture was concentrated to dryness and crystallized from acetonitrile solution, affording orange crystals. Yield, 93%; Anal. Calcd for $C_{36}H_{29}IrN_4O_2$:C, 58.28; H, 3.94; N, 7.55. Found: C 58.20, H 4.00, N 7.57; ESI-MS: m/z = 743.10 $[M-H]^+$. For Λ-**PEO*S***: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.77 (s, 1H), 8.77 (d, J = 5.5 Hz, 1H), 7.79 (d, J = 8.0 Hz, 1H), 7.66 (t, 1H), 7.59 (d, J = 5.5 Hz, 1H), 7.54 (d, J = 7.6 Hz, 1H), 7.36 (t, 1H), 7.15 (d, J = 8.1 Hz, 1H), 7.12–7.06 (m, 2H), 7.02 (d, J = 8.9 Hz, 1H), 6.89 (ddd, J = 14.7, 9.6, 3.5 Hz, 3H), 6.85–6.80 (m, 3H), 6.75 (dd, J = 14.9, 7.4 Hz, 2H), 6.71 –6.67 (m, 2H), 6.29 (d, J = 6.6 Hz, 1H), 6.21 (d, J = 7.6 Hz, 2H), 6.08 (d, J = 7.5 Hz, 1H), 5.12 (d, J = 7.5 Hz, 1H), 4.26 (t, 1H), 3.56 (dd, J = 12.9, 3.9 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ172.00, 168.30, 165.33, 153.87, 152.11, 150.98, 148.57, 144.59, 144.46, 143.98, 136.93, 136.31, 136.31, 134.65, 133.30, 131.78, 131.36, 130.60, 130.08, 130.08,