Inorganic Chemistry

Article

pubs.acs.org/IC

Chiral Recognition and Dynamic Thermodynamic Resolution of Sulfoxides by Chiral Iridium(III) Complexes

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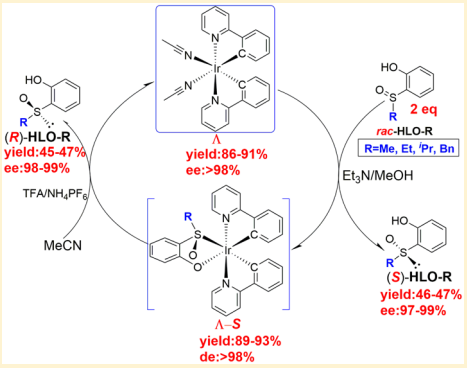
Supporting Information

ABSTRACT: The optically active Ir(III) complex Λ-$[Ir(ppy)_2(MeCN)_2](PF_6)$ (ppy is 2-phenylpyridine) with a chiral-at-metal was first demonstrated to preferentially react with (*R*)-configuration sulfoxides 2-(alkylsulfinyl)phenol (HLO-R, R = Me, Et, ^{i}Pr, and Bn) rather than (*S*)-configuration sulfoxides under thermodynamic equilibrium due to the hydrogen-bonding interaction and the differences in the steric interference, and thus act as a highly efficient enantioreceptor for resolution of sulfoxide enatiomers. Treatment of Λ-$[Ir(ppy)_2(MeCN)_2](PF_6)$ with 2 equiv of *rac*-HLO-R offered (*S*)-HLO-R in yields of 46−47% with 97−99% enantiomeric excess (ee) values and Λ-$[Ir(ppy)_2\{(S)\text{-LO-R}\}]$ complex in yields of 89−93% with 98% diastereomeric excess (de). The (*R*)-HLO-R chiral sulfoxides were obtained by the acidolysis of Λ-$[Ir(ppy)_2\{(S)\text{-LO-R}\}]$ complexes with trifluoroacetic acid (TFA) in the presence of coordinated solvent MeCN in yields of 45−47% with 98−99% ee values. Moreover, the enantioreceptor Λ-$[Ir(ppy)_2(MeCN)_2](PF_6)$ can be recycled in a yield of 86−91% with complete retention of the configuration at metal center and can be reused in a next reaction cycle without loss of reaction activity and enantioselectivity. The absolute configurations at the metal centers and sulfur atoms were determined by X-ray crystallography.



INTRODUCTION

Enantiomeric sulfoxides are an important class of compounds because they are widely employed as chiral auxiliaries in asymmetric synthesis and serve as bioactive ingredients in the pharmaceutical industry.[1,2] A chiral sulfoxide can be obtained by the separation of a racemic mixture, transformation of a reagent from the chemical pool, or enantioselective synthesis in the presence of a chiral catalyst.[3] Asymmetric synthesis providing highly enantioenriched product from racemic substrates offers many advantages, but enantiomeric resolution still provides an alternative and promising methodology to obtain chiral sulfoxides. Although many publications have described the successful resolution of chiral sulfoxides by using chiral stationary phases such as amylose, cellulose, and metal−organic frameworks,[4,5] the development of convenient methods to access enantiomeric sulfoxides remains in high demand because of their extremely similar chemical and physical properties.[6]

Enantioselective recognition is the key step in chiral resolution and transformation processes. Chiral octahedral metal complexes with specially spatial and chemical properties are good candidates as chiral receptors to discriminate between the enantiomers and make separation possible. In fact, the chiral complexes have been used for enantioselective recognition and separation of amino acids and their derivatives.[7−9] In most cases, the chirality of complexes is generated by assembly of metals with chiral ligands. Alternatively, octahedral complexes bearing chelate achiral ligands exhibit intrinsic helical arrangement, resulting in Δ and Λ configurations with chiral-at-metal, which parallel, to a certain extent, the stereogenic carbon atom in organic chemistry.[6a,10] Such asymmetric coordination chemistry has been applied in asymmetric catalysts in recent years.[11] However, their applications on enantioselective recognition and separation are still under development. Coordinatively unsaturated chiral octahedral complexes with different binding sites in a chiral environment have strong capability for recognition of chiral coordinating analytes. Here, we present the chiral recognition and resolution of racemic sulfoxides by using Λ-$[Ir(ppy)_2(MeCN)_2](PF_6)$ or Δ-$[Ir(ppy)_2(MeCN)_2](PF_6)$ (where ppy is 2-phenylpyridine) complex as a chiral receptor, in excellent yields of >45% (50% in theory) and enantioselectivity (>97% ee). In these processes, only the (*R*)-sulfoxide coordinates to the chiral receptor Λ-$[Ir(ppy)_2(MeCN)_2](PF_6)$, forming the stable Λ-$[Ir(ppy)_2\{(S)\text{-sulfoxide}\}]$ complex under dynamic thermodynamic equilibrium.[12] The uncoordinated (*S*)-sulfoxide enantiomer is easily separated from the complex, and the coordinated sulfoxide can then be released in the presence of trifluoroacetic acid (TFA) and coordinated solvent MeCN. The original chiral Ir(III)

Received: October 13, 2016

DOI: 10.1021/acs.inorgchem.6b02494
Inorg. Chem. XXXX, XXX, XXX−XXX

receptor can be regenerated and reused without loss of reactivity and selectivity.

EXPERIMENTAL SECTION

Materials and Methods. All chemicals were commercially available and used as purchased unless otherwise noted. All manipulations were carried out under a N_2 atmosphere unless otherwise noted. Column chromatography was performed with silica gel (300−400 mesh) under reduced light. The enantiopure Λ-$[Ir(ppy)_2(MeCN)_2](PF_6)$ and Δ-$[Ir(ppy)_2(MeCN)_2](PF_6)$,[13] racemic sulfoxides 2-(alkylsulfinyl)phenol (HLO-R, R = Me, Et, ^{i}Pr, Bn),[14] and enantiopure (*R,S*)-HLO-^{i}Pr[15] were synthesized according to the methods described in the literature. Elemental (C, H, N, and S) analyses were performed on an Elementar Vario EL analyzer. Electrospray ionization mass spectra (ESI-MS) were obtained on a Thermo LCQ DECA XP mass spectrometer. ^{1}H NMR spectra were obtained on a Bruker AV-400 spectrometer by using the chemical shift of the solvent as an internal standard. Circular dichroism (CD) spectra were recorded on a JASCO J-810 CD spectropolarimeter (1 s response, 3.41 nm bandwidth, scanning speed of 200 nm/min, accumulation of 3 scans). The enantiomeric excess (ee) values of sulfoxides were measured by chiral high-performance liquid chromatography (HPLC) analyses on a Shimadzu LC 20AT with UV detector SPD-20A (Daicel Chiralpak AD-H or OX-H column, 250 mm × 4.6 mm, flow rate = 1 mL/min, column temperature = 35 °C, 300 nm).

General Procedures for Resolution of Sulfoxide Enantiomers. Λ-$[Ir(ppy)_2(MeCN)_2](PF_6)$ (30.0 mg, 0.0413 mmol), 2 equiv of sulfoxide HLO-R (0.0825 mmol), Et_3N (25 μL, 0.165 mmol), and MeOH (5 mL) were added into a flask, and the mixture was stirred at 45 °C under a N_2 atmosphere for 1−2 h (monitored by thin-layer chromatography (TLC)). After that, the reaction solution was cooled to room temperature and then concentrated to dryness. The residue material was dissolved in EtOH (0.5 mL), and then a mixture of Et_2O (2−5 mL) and hexane (15 mL) was added to the above solution to produce precipitate. The precipitate was filtrated and washed with Et_2O−hexane (1:5) to give a yellow solid. The product was recrystallized from DCM to afford Λ-$[Ir(ppy)_2\{(S)$-LO-R$\}]$. The filtrate was concentrated to dryness and then purified by silica gel chromatography (DCM as an eluent) to give pure (*S*)-sulfoxide product. Δ-$[Ir(ppy)_2\{(R)$-LO-R$\}]$ enantiomers, which were synthesized from Δ-$[Ir(ppy)_2(MeCN)_2](PF_6)$ as starting material, and (*R*)-sulfoxide were isolated.

General Procedures for Release of Chiral Sulfoxide and Recovery of the Chiral Ir(III) Complex. A suspension of sulfoxide complexes Λ-$[Ir(ppy)_2\{(S)$-LO-R$\}]$ (0.03 mmol) and NH_4PF_6 (25.0 mg, 0.15 mmol) in acetonitrile (5 mL) was stirred and degassed by N_2 at 55 °C for 5 min, and then TFA (27 μL, 0.36 mmol) was added to the solution. The reaction continued for 1 h. After that, the reaction solution was cooled to room temperature, and the solvent was concentrated to dryness. The residue material was dissolved in EtOH (0.5 mL), and then a mixture of Et_2O (2−5 mL) and hexane (15 mL) was added to the above solution to produce precipitate. The precipitate was filtrated and washed with Et_2O−hexane (1:5) and then with a KPF_6 solution to afford Λ-$[Ir(ppy)_2(MeCN)_2](PF_6)$. The filtrate was concentrated to dryness and subjected to purification on a silica gel chromatography with DCM as an eluent to afford colorless solid as (*R*)-sulfoxide. When Δ-$[Ir(ppy)_2\{(R)$-LO-R$\}]$ was used instead of Λ-$[Ir(ppy)_2(MeCN)_2](PF_6)$, (*S*)-sulfoxide was obtained.

*Λ-[Ir(ppy)$_2${(S)-(LO-Me)}] (Λ-**1**) and Δ-[Ir(ppy)$_2${(R)-(LO-Me)}] (Δ-**1**).* Anal. Calcd for $C_{29}H_{23}N_2O_2IrS$: C 53.11, H 3.54, N 4.27, S 4.89. Found: C 53.21, H 3.39, N 4.12, S 4.67; ESI-MS: *m/z* = 657.1 $[M+H]^+$, 679.1 $[M+Na]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.85 (d, *J* = 5.5 Hz, 1H), 8.56 (d, *J* = 5.4 Hz, 1H), 7.97 (d, *J* = 8.2 Hz, 1H), 7.90 (t, 1H), 7.86 (t, 1H), 7.79 (t, 1H), 7.64 (d, *J* = 8.0 Hz, 2H), 7.54 (d, *J* = 7.3 Hz, 1H), 7.24−7.14 (m, 3H), 7.01 (d, *J* = 9.0 Hz, 1H), 6.96 (q, 2H), 6.86 (q, 2H), 6.62 (t, 1H), 6.58 (d, *J* = 7.6 Hz, 1H), 6.03 (d, *J* = 7.4 Hz, 1H), 2.25 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.44, 168.67, 168.05, 154.58, 153.37, 148.71, 143.71, 143.46, 142.64, 138.07, 137.41, 134.86, 133.38, 130.93, 130.64, 129.88, 129.70, 125.25, 124.31, 124.18, 123.27, 122.83, 122.53, 122.49, 121.86, 119.23, 119.20, 115.15, 38.56. The diastereomeric excess (de) value is >98% (determined by NMR). For Δ-**1**, yield, 90%; CD ($\Delta\varepsilon/M^{-1}$ cm^{-1}, dichloromethane (DCM)): 280 (+143), 316 (−64), 355 (−169), 406 nm (+43). For Λ-**1**, yield, 86%; CD ($\Delta\varepsilon/M^{-1}$ cm^{-1}, DCM): 280 (−116), 317 (+52), 354 (+141), 406 nm (−33).

*Λ-[Ir(ppy)$_2${(S)-(LO-Et)}] (Λ-**2**) and Δ-[Ir(ppy)$_2${(R)-(LO-Et)}] (Δ-**2**).* Anal. Calcd for $C_{30}H_{25}N_2O_2IrS$: C 53.79, H 3.76, N 4.18, S 4.79. Found: C 53.63, H 3.65, N 4.23, S 4.65; ESI-MS: *m/z* = 671.1 $[M+H]^+$, 693.1 $[M+Na]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.95 (d, *J* = 12.4 Hz, 1H), 8.61 (d, *J* = 5.6 Hz, 1H), 7.97 (d, *J* = 8.1 Hz, 1H), 7.86 (t, 2H), 7.76 (t, 1H), 7.62 (d, *J* = 7.6 Hz, 2H), 7.52 (d, *J* = 8.0 Hz, 1H), 7.26−7.12 (m, 3H), 7.03−6.89 (m, 3H), 6.88−6.80 (m, 2H), 6.60 (t, 2H), 5.93 (d, *J* = 7.6 Hz, 1H), 3.02−2.90 (m, 1H), 2.11−1.99 (m, 1H), 0.79 (t, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.76, 168.88, 168.02, 154.37, 153.44, 148.94, 143.99, 143.72, 143.43, 143.17, 137.97, 137.33, 134.70, 133.43, 130.51, 129.87, 129.37, 126.05, 124.19, 124.07, 123.24, 122.77, 122.37, 121.78, 119.24, 119.14, 114.86, 48.49, 6.62. The de value is >98% (determined by NMR). For Δ-**2**, yield, 92%; CD ($\Delta\varepsilon/M^{-1}$ cm^{-1}, DCM): 283 (+119), 317 (−56), 355 (−130), 416 nm (+32). For Λ-**2**, yield, 90%; CD ($\Delta\varepsilon/M^{-1}$ cm^{-1}, DCM): 280 (−112), 318 (+55), 354 (+118), 411 nm (−28).

*Λ-[Ir(ppy)$_2${(S)-(LO-^{i}Pr)}] (Λ-**3**) and Δ-[Ir(ppy)$_2${(R)-(LO-^{i}Pr)}] (Δ-**3**).* Anal. Calcd for $C_{31}H_{27}N_2O_2IrS$: C 54.45, H 3.98, N 4.10, S 4.69. Found: C 54.28, H 3.74, N 3.87, S 4.43; ESI-MS: *m/z* = 685.1 $[M+H]^+$, 707.1 $[M+Na]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.96 (d, *J* = 5.8 Hz, 1H), 8.83 (d, *J* = 5.7 Hz, 1H), 7.99 (d, *J* = 8.1 Hz, 1H), 7.86 (dd, *J* = 15.8, 7.8 Hz, 2H), 7.74 (t, 1H), 7.63 (d, *J* = 7.8 Hz, 1H), 7.58 (d, *J* = 7.9 Hz, 1H), 7.49 (d, *J* = 8.1 Hz, 1H), 7.24 (t, 1H), 7.19−7.11 (m, 2H), 6.98−6.91 (m, 2H), 6.89 (d, *J* = 8.8 Hz, 1H), 6.84 (dd, *J* = 16.7, 8.0 Hz, 2H), 6.64 (d, *J* = 7.5 Hz, 1H), 6.56 (t, 1H), 5.78 (d, *J* = 7.7 Hz, 1H), 2.80 (m, 1H), 1.09 (d, *J* = 6.7 Hz, 3H), 0.53 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.39, 169.24, 167.93, 153.80, 153.39, 149.78, 144.77, 143.46, 143.31, 137.88, 137.26, 134.37, 133.45, 130.40, 129.88, 129.77, 127.49, 127.38, 124.17, 123.97, 123.21, 122.61, 122.02, 121.97, 121.65, 119.29, 119.00, 114.02, 58.62, 16.45, 15.49. The de value is >98% (determined by NMR). For Δ-**3**, yield, 93%; CD ($\Delta\varepsilon/M^{-1}$ cm^{-1}, DCM): 285 (+100), 319 (−54), 356 (−87), 414 nm (+18). For Λ-**3**, yield, 93%; CD ($\Delta\varepsilon/M^{-1}$ cm^{-1}, DCM): 287 (−109), 323 (+64), 357 (+103), 420 nm (−20). Single crystals were obtained by evaporation of a MeOH solution of the corresponding complex.

*Λ-[Ir(ppy)$_2${(S)-(LO-Bn)}] (Λ-**4**) and Δ-[Ir(ppy)$_2${(R)-(LO-Bn)}] (Δ-**4**).* Anal. Calcd for $C_{35}H_{27}N_2O_2IrS$: C 57.44, H 3.72, N 3.83, S 4.38. Found: C 57.27, H 3.63, N 3.64, S 4.25; ESI-MS: *m/z* = 733.1 $[M+H]^+$, 755.1 $[M+Na]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.87 (d, *J* = 5.7 Hz, 1H), 8.79 (d, *J* = 5.6 Hz, 1H), 7.95−7.85 (m, 3H), 7.75 (t, 1H), 7.62 (d, *J* = 7.7 Hz, 1H), 7.54 (d, *J* = 7.4 Hz, 1H), 7.30 (t, 1H), 7.18 (t, 2H), 7.14−7.08 (m, 2H), 7.01−6.90 (m, 5H), 6.86 (dd, *J* = 14.9, 7.5 Hz, 2H), 6.62 (d, *J* = 7.4 Hz, 1H), 6.57 (d, *J* = 8.0 Hz, 1H), 6.33 (t, 1H), 5.97 (d, *J* = 7.5 Hz, 1H), 3.69 (d, *J* = 13.4 Hz, 1H), 3.26 (d, *J* = 13.3 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.61, 169.11, 167.98, 154.69, 153.38, 148.94, 144.10, 143.51, 142.73, 138.05, 137.36, 134.69, 133.29, 131.42, 130.63, 130.58, 129.88, 128.46, 128.45, 127.97, 127.92, 127.68, 124.50, 124.14, 123.30, 122.79, 122.43, 121.97, 121.75, 119.49, 119.16, 114.08, 58.33. The de value is >98% (determined by NMR). For Δ-**4**, yield, 89%; CD ($\Delta\varepsilon/M^{-1}$ cm^{-1}, DCM): 279 (+144), 316 (−90), 356 (−151), 407 nm (+35). For Λ-**4**, yield, 94%; CD ($\Delta\varepsilon/M^{-1}$ cm^{-1}, DCM): 280 (−109), 318 (+75), 355 (+129), 411 nm (−28).

(R,S)-HLO-Me. ESI-MS: *m/z* = 155 $[M-H]^-$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.28 (s, 1H), 7.39 (t, 1H), 7.10 (d, *J* = 7.7 Hz, 1H), 6.98 (d, *J* = 8.4 Hz, 1H), 6.94 (t, 1H), 2.98 (s, 3H). For (*R*)-HLO-Me, yield, 45% (on the basis of *rac*-sulfoxide); ee, 98.6% (chiral HPLC analysis, mobile phase: hexane/(EtOH:MeOH)/TEA = 90/(3:1)10/0.1); CD ($\Delta\varepsilon/M^{-1}$ cm^{-1}, DCM): 247 nm (+97), 287 nm (−24). For (*S*)-HLO-Me, yield, 46% (on the basis of *rac*-sulfoxide); ee, 99.2%; CD ($\Delta\varepsilon/M^{-1}$ cm^{-1}, DCM): 246 (−84), 287 nm (+21).

(R,S)-HLO-Et. ESI-MS: *m/z* = 169 $[M-H]^-$; ^{1}H NMR (400 MHz, $CDCl_3$): 10.38 (s, 1H), 7.38 (t, 1H), 7.08 (d, *J* = 7.6 Hz, 1H), 6.94 (t, 2H), 3.13 (q, 2H), 1.33 (t, 3H). For (*R*)-HLO-Et, yield 47% (on the basis of *rac*-sulfoxide); ee, 98.7% (chiral HPLC analysis, mobile phase:

DOI: 10.1021/acs.inorgchem.6b02494
Inorg. Chem. XXXX, XXX, XXX−XXX

hexane/(EtOH:MeOH)/TEA = 90/(3:1)10/0.1); CD ($\Delta\varepsilon$/M^{-1} cm^{-1}, DCM): 248 (+77), 287 nm (−22). For (*S*)-HLO-Et, yield 46% (on the basis of *rac*-sulfoxide); ee, 97.3%; CD ($\Delta\varepsilon$/M^{-1} cm^{-1}, DCM): 248 (−86), 289 nm (+27).

(R,S)-HLO-^{i}Pr. ESI-MS: m/z = 183 $[M-H]^-$; ^{1}H NMR (400 MHz, $CDCl_3$): 10.65 (s, 1H), δ 7.39 (t, 1H), 7.02 (d, J = 7.6 Hz, 1H), 6.93 (dd, J = 15.4, 8.0 Hz, 2H), 3.30−3.15 (m, 1H), 1.39 (d, J = 6.8 Hz, 3H), 1.29 (d, J = 6.8 Hz, 3H). For (*R*)-HLO-^{i}Pr, yield 46% (on the basis of *rac*-sulfoxide); ee, 99.8% (chiral HPLC analysis, mobile phase: hexane/(EtOH:MeOH)/TFA = 92/8(6:2)/0.1); CD ($\Delta\varepsilon$/M^{-1} cm^{-1}, DCM): 251 (+75), 288 nm (−22). For (*S*)-HLO-^{i}Pr, yield 46% (on the basis of *rac*-sulfoxide); ee, 99.8%; CD ($\Delta\varepsilon$/M^{-1} cm^{-1}, DCM): 251 (−56), 289 nm (+20).

(R,S)-HLO-Bn. ESI-MS: m/z = 231 $[M-H]^-$; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.24 (s, 1H), 7.40−7.30 (m, 4H), 7.06 (d, J = 7.4 Hz, 2H), 6.92 (d, J = 8.3 Hz, 1H), 6.79 (t, 1H), 6.69 (d, J = 7.7 Hz, 1H), 4.36 (q, 2H). For (*R*)-HLO-Bn, yield 46% (on the basis of *rac*-sulfoxide); ee, 98.6% (chiral HPLC analysis, mobile phase: hexane/(EtOH:MeOH)/TEA = 88/(9:3)12/0.1). CD ($\Delta\varepsilon$/M^{-1} cm^{-1}, DCM): 230 (−41), 254 (+65), 290 nm (−30). For (*S*)-HLO-Bn, yield 47% (on the basis of *rac*-sulfoxide); ee, 97.1%; CD ($\Delta\varepsilon$/M^{-1} cm^{-1}, DCM): 229 (+49), 254 (−63), 290 nm (+30).

Synthesis of *rac*-[Ir(ppy)$_2$(LO-^{i}Pr)] (*rac*-3). $[(Ir(ppy)_2Cl)_2]$ (20.0 mg, 0.0275 mmol), HLO-^{i}Pr (7.59 mg, 0.0413 mmol), Et_3N (11.5 μL, 0.0826 mmol), and MeOH (5 mL) were added into a three-neck flask, and the mixture was stirred at 50 °C under a N_2 atmosphere for 5 h. The reaction mixture was cooled to room temperature and then concentrated to dryness. The residue material was dissolved in EtOH (0.5 mL), and then a mixture of Et_2O (2 mL) and hexane (15 mL) was added to the above solution to produce precipitate. The precipitate was filtrated and washed with Et_2O−hexane (1:5) to get a yellow solid. The product was recrystallized from DCM. Yield, 84%. Anal. Calcd for $C_{31}H_{27}N_2O_2IrS$: C 54.45, H 3.98, N 4.10, S 4.69. Found: C 54.31, H 3.82, N 3.85, S 4.38; ESI-MS: m/z = 685.1 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.97 (d, J = 5.5 Hz, 1H), 8.84 (d, J = 5.7 Hz, 1H), 7.99 (d, J = 8.1 Hz, 1H), 7.86 (dd, J = 15.8, 7.6 Hz, 2H), 7.73 (t, 1H), 7.63 (d, J = 7.3 Hz, 1H), 7.57 (d, J = 7.5 Hz, 1H), 7.49 (d, J = 6.7 Hz, 1H), 7.23 (t, 1H), 7.19−7.11 (m, 2H), 6.96−6.89 (m, 3H), 6.88−6.77 (m, 2H), 6.64 (d, J = 7.1 Hz, 1H), 6.56 (t, 1H), 5.77 (d, J = 7.5 Hz, 1H), 2.80 (m, 1H), 1.09 (d, J = 6.7 Hz, 3H), 0.52 (d, J = 6.9 Hz, 3H). Single crystals of *rac*-**3** were grown by evaporation of a MeOH solution of *rac*-**3**.

Single-Crystal X-ray Crystallography. The diffraction intensities for Λ-**3** and Δ-**3** were collected on an Oxford Gemini S Ultra CCD area detector diffractometer with graphite-monochromated Cu Kα radiation (λ = 1.54178 Å), and *rac*-**3** was collected on an R-AXIS Spider IP-Mo Kα radiation (λ = 0.71073) at 150 K. All of the data were corrected for absorption effect using the multiscan technique. The structures were solved via direct methods (olex2.-solve)[16] and refined by iterative cycles of least-squares refinement on F^2 followed by difference Fourier synthesis.[17] All non-hydrogen atoms were refined anisotropically. All hydrogen atoms were included in the final structure factor calculation at idealized positions and were allowed to ride on the neighboring atoms. The crystal data and the details of data collection and refinement for the complexes are summarized in Table 1. Additional crystallographic information is available in the Supporting Information.

RESULTS AND DISCUSSION

Diastereoselective Recognition between Chiral Ir(III) Complexes and Sulfoxide. Chiral sulfoxide compounds have been found to have enantioselective interaction with octahedral Ru(II) complexes, in which the configuration at the Ru(II) center was changed to match up with the configuration of sulfoxide ligand, and thus were applied on asymmetric synthesis of chiral Ru(II) complexes.[18] Compared to octahedral Ru(II) complexes, enantiopure octahedral Ir(III) complexes bearing bidentate ligands are more inert in terms of configuration,

Table 1. Crystallographic Data for *rac*-3, Λ-3, and Δ-3

complex	*rac*-**3**	Λ-**3**	Δ-**3**
molecular formula	$C_{31}H_{27}N_2O_2SIr$	$C_{31}H_{27}N_2O_2SIr$	$C_{31}H_{27}N_2O_2SIr$
M_r	683.80	683.80	683.80
crystal system	monoclinic	orthorhombic	orthorhombic
space group	$P2_1/c$	$P2_12_12_1$	$P2_12_12_1$
a/Å	15.7792(10)	9.41597(13)	9.4262(3)
b/ Å	9.7493(6)	15.5922(2)	15.5922(7)
c/ Å	16.6251(15)	17.5922(3)	17.5770(8)
β/°	92.118(3)	90.00	90.00
V/Å^3	2555.8(3)	2582.81(7)	2583.40(18)
Z	4	4	4
D_c (g cm^{-3})	1.777	1.7610	1.761
μ (mm^{-1})	5.338	11.016	11.013
no. data of collected	23252	15022	13829
no. observed reflections	5810	4092	4096
$R_1[I > 2\sigma(I)]^a$	0.0466	0.0222	0.0439
$wR_2{}^b$ (all data)	0.1009	0.0567	0.1236
Flack parameter		−0.011(6)	−0.013(18)
GOF on F^2	1.036	1.073	1.114

$^aR_1 = \sum||F_0| - |F_c||/\sum|F_0|$. $^bwR_2 = [\sum w(F_0^2 - F_c^2)^2/\sum w(F_0^2)^2]^{1/2}$

showing no racemization of the enantiomer metal complexes in solution under the usual conditions. Therefore, they appear to be ideal entities for observation of enentioselective recognition processes and resolution of racemic sulfoxides. *rac*-HLO-^{i}Pr ligand is selected as an example because it has been used as a chiral auxiliary for asymmetric synthesis,[18c] and the chelate coordination ensures the stability of the formation complex when separated from the free ligand. More importantly, the coordinated phenol group can modulate its binding strength to the metal center by deprotonation or reprotonation, leading to assembly or release, respectively, of the sulfoxide ligand being reversible.

The diastereoselective recognition between Λ-[Ir(ppy)$_2$(MeCN)$_2$](PF$_6$) (receptor) and *rac*-HLO-^{i}Pr in CD_2Cl_2 solution in the presence of Et_3N as a base was observed and monitored by ^{1}H NMR spectroscopy because the diastereomers have distinguishable NMR spectra. As shown in Figure 1, Λ-receptor could immediately react with *rac*-HLO-^{i}Pr and reach thermodynamic equilibrium at 45 °C in ∼1 h. Upon addition of 0.5 equiv of *rac*-HLO-^{i}Pr to a receptor solution, the spectrum became complicated, demonstrating coexistence of multiple species. The resonance peak at 9.03 ppm assigned to the α-H of the pyridyl ring decreases, and the new resonance peaks appear at 9.95 and 8.79 ppm (assigned to Λ-**3**), 9.28 and 8.39 ppm (assigned to Λ-R_1), and 8.66 and 8.47 ppm (assigned to Λ-$R_2$and Λ-R_1, where Λ-R_2 are the products generated by the reaction of Λ-receptor and (*S*)-HLO-^{i}Pr in various coordinated modes; see Figure S1 in Supporting Information). The molar ratio is ∼1.3 for Λ-**3** to (Λ-R_1 + Λ-R_2). Increasing the amount of sulfoxide to 1 equiv, the resonance peaks belonging to Λ-**3** increase markedly, concomitant with the almost disappearance of the peak at 9.03 ppm (see Figure 1c), demonstrating that the Λ-receptor precursor is nearly exhausted and converted into sulfoxide complexes. Upon continually increasing the amount of sulfoxide to 1.5 equiv, we are surprised to find that the intensity of the peaks assigned to Λ-**3** continually increases while the peaks belonging to Λ-R_1 and Λ-R_2 become weak, indicating that the ligand (*S*)-LO-^{i}Pr in complexes Λ-R_1 and Λ-R_2 is displaced by (*R*)-LO-^{i}Pr; a new

DOI: 10.1021/acs.inorgchem.6b02494
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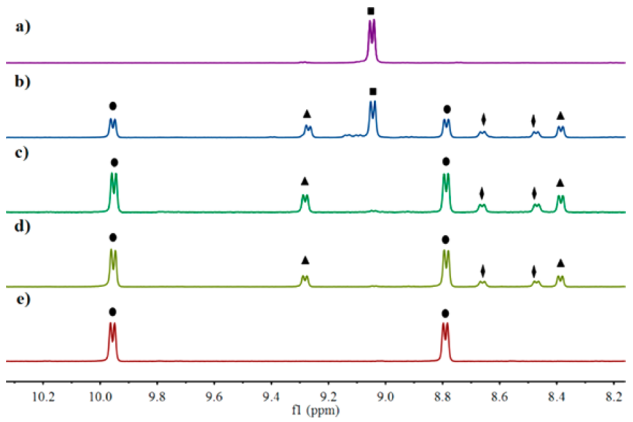
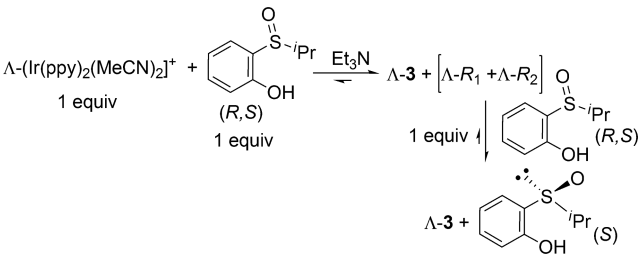


Figure 1. Excerpts of ^{1}H NMR spectra of Λ-[Ir(ppy)$_2$(MeCN)$_2$](PF$_6$) (receptor) and HLO-^{i}Pr in CD_2Cl_2 at 45 °C for 1 h: (a) receptor, (b) receptor and 0.5 equiv of HLO-^{i}Pr with 1 equiv of Et_3N, (c) receptor and 1 equiv of HLO-^{i}Pr with 2 equiv of Et_3N, (d) receptor and 1.5 equiv of HLO-^{i}Pr with 3 equiv of Et_3N, and (e) receptor and 2 equiv of HLO-^{i}Pr with 4 equiv of Et_3N (●, Λ-**3**; ▲, Λ-R_1; ◆, Λ-R_2; ■, receptor).

equilibrium is achieved by dynamic coordination bonding between the components, forming the thermodynamically more stable single diastereomer Λ-**3**.[18e] This is indeed the case; when we tried to isolate the diastereomers Λ-R_1 and Λ-R_2 by a chromatography technique, however, they decomposed. Up to 2 equiv of *rac*-HLO-^{i}Pr ligand is added, the NMR signals of Λ-R_1 and Λ-R_2 disappear, and the spectrum becomes simple and clear, as shown in Figure 1e, indicating that the ligand-substituent reaction between (*S*)-LO-^{i}Pr and (*R*)-LO-^{i}Pr is thoroughly achieved and the unstable intermediate Λ-R_1 and Λ-R_2 complexes are completely converted into the thermodynamically stable complex Λ-**3** under the experimental conditions. These processes can be seen in Scheme 1. The

Scheme 1. Possible Mechanism of the Enantioselective Recognition between Λ-[Ir(ppy)$_2$(MeCN)$_2$](PF$_6$) and *rac*-HLO-^{i}Pr under Thermodynamic Control

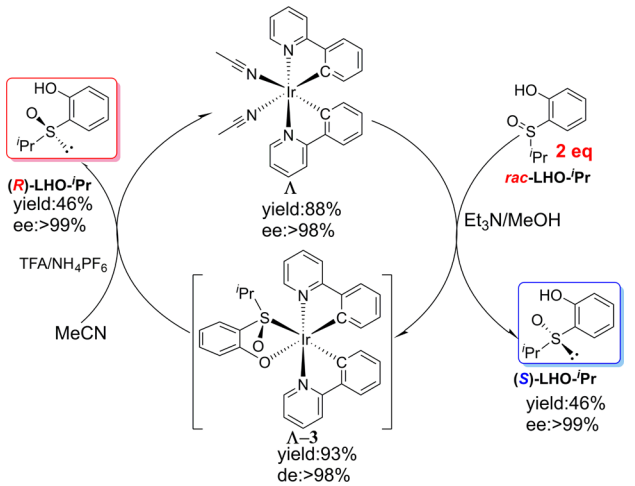


reaction of Λ-[Ir(ppy)$_2$(MeCN)$_2$](PF$_6$) with 1 equiv of (*R*,*S*)-HLO-^{i}Pr initially produces a mixture of diastereomers Λ-**3**, Λ-R_1, Λ-R_2. By continually increasing *rac*-HLO-^{i}Pr to 2 equiv, the metastable Λ-R_1 and Λ-R_2 are subsequently converted into the more stable Λ-**3** in a dynamic transformation under thermodynamic control. It should be pointed out that no racemization occurred during these processes, as seen in that no enantiomer Δ-**3** was found when checking the purity of Λ-**3** by NMR spectroscopy in the presence of shift reagent (vide infra).

A similar case was also observed in the diastereoselective recognition between Δ-[Ir(ppy)$_2$(MeCN)$_2$](PF$_6$) and 2 equiv of *rac*-HLO-^{i}Pr in identical conditions, but leading to formation of Δ-**3** enantiomer and (*R*)-HLO-^{i}Pr.

Enantioeselective Resolution of Sulfoxides by Chiral Ir(III) Complex on the Basis of Dynamic Thermodynamic Control. From the aforementioned observations, we can find that the reaction between Λ-[Ir(ppy)$_2$(MeCN)$_2$](PF$_6$) and 2 equiv of *rac*-HLO-^{i}Pr is quantitative and highly enantioselective, and the product is a single diastereomer under thermodynamic control. Moreover, the properties of the sulfoxide Ir(III) complex and the free sulfoxide ligand are distinguishable; thus, a facile protocol can be designed to separate the enantiomers of sulfoxides using a chiral-at-metal strategy. As shown in Scheme 2, mixing Λ-[Ir(ppy)$_2$(MeCN)$_2$](PF$_6$) (receptor) with 2 equiv

Scheme 2. Diagram of the Resolution and Recycle Processes of *rac*-Sulfoxide via a Chiral-at-Metal Strategy



of rac-HLO-^{i}Pr in MeOH in the presence of Et_3N as a base leads to diastereoselective assembly of the receptor with (*R*)-HLO-^{i}Pr, producing Λ-**3** under thermodynamic equilibrium. Complex Λ-**3** was easily isolated from the uncoordinated sulfoxide in an excellent yield of 93%, and the uncoordinatedly enantiopure (*S*)-HLO-^{i}Pr was also isolated in 46% yield (50% in theory).

Moreover, the enantiopure (*R*)-HLO-^{i}Pr sulfoxide can be obtained by release of the sulfoxide ligand from complex Λ-**3** in the presence of TFA and MeCN, because the coordination strength of the sulfoxide ligand to metal would be reduced by protonation of the phenol group and then displaced by the coordinated solvent CH_3CN.[15] Indeed, (*R*)-HLO-^{i}Pr sulfoxide was isolated and purified by silica gel chromatography in a yield of 46% (on the basis of *rac*-HLO-^{i}Pr).

The resolved enantiomers (*S*)-HLO-^{i}Pr and (*R*)-HLO-^{i}Pr were characterized by NMR, MS, and CD spectroscopies (see Experimental Section). As shown in Figure 2, they are optically active with mirror images and have a positive Cotton effect at 250 nm and a negative Cotton effect at 288 nm for (*R*)-HLO-^{i}Pr, and a negative Cotton effect at 251 nm and a positive Cotton effect at 289 nm for (*S*)-HLO-^{i}Pr. Furthermore, the enantiopurities of (*S*)-HLO-^{i}Pr and (*R*)-HLO-^{i}Pr were determined by chiral HPLC analyses (see Figure 3), and the ee values were found to be >99%. These also demonstrated that no significant racemization occurred in the sulfur atom center during the resolution processes. The preparation of (*S*)-HLO-^{i}Pr has been reported by Alcudia's group using the Andersen method[19] and by our group recently using in situ coordination oxidation.[15] Here, a new resolution approach is

DOI: 10.1021/acs.inorgchem.6b02494
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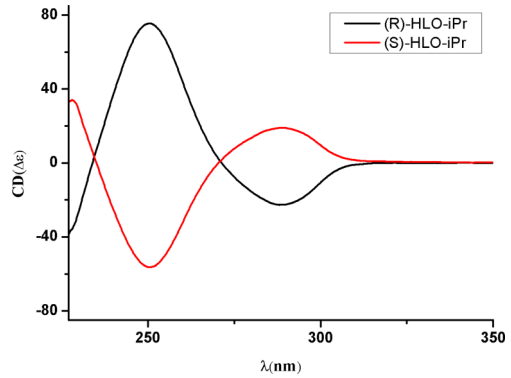

Figure 2. CD spectra of (*R*)-HLO-^{i}Pr and (*S*)-HLO-^{i}Pr in DCM (5×10^{-4} M).

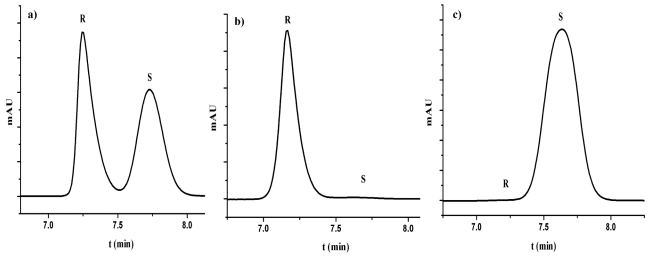

Figure 3. HPLC traces of *rac*-HLO-^{i}Pr (a), (*R*)-HLO-^{i}Pr (b), and (*S*)-HLO-^{i}Pr (c). HPLC conditions: Daicel Chiralpak AD-H column, 250 mm × 4.6 mm, flow rate = 1 mL/min, column temperature = 35 °C, 300 nm, hexane/(EtOH:MeOH)/TFA = 92/8(6:2)/0.1 as eluent.

also developed to complement the asymmetric synthesis of chiral sulfoxides in high enantiopurities.

The enantiomeric sulfoxide complexes Λ-**3** and Δ-**3** were also characterized by NMR, MS, and CD spectroscopies. Their CD spectra are mirror images with positive Cotton effect at 323 and 357 nm and negative Cotton effect at 287 and 420 nm for Λ-**3**, and negative Cotton effect at 319 and 356 nm and positive Cotton effect at 285 and 414 nm for Δ-**3**, as shown in Figure 4.

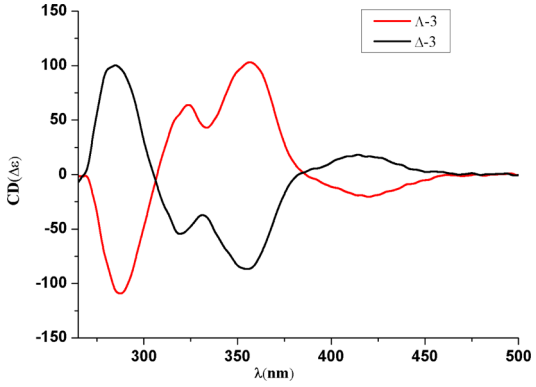

Figure 4. CD spectra of Λ-**3** and Δ-**3** in DCM (2.5×10^{-5} M).

The chemical shift of the α-H of the pyridine ring at 9.03 ppm is split into 9.96 and 8.83 ppm in *rac*-**3** due to the fact that the C_{2v} symmetry is broken upon being coordinated with sulfoxide ligand (see Figure 1). The significant low-field shift (9.96 ppm) can be attributed to the hydrogen bonding between the α-H and sulfoxide oxygen atom (vide infra). The resonance peak at 8.83 ppm of *rac*-**3** is split into two peaks at 8.76 and 8.68 ppm in the presence of 60 equiv of (*S*)-1,1′-binaphthol (*S*-binol) as a chiral shift reagent, as shown in Figure 5, which are in accord with those of Λ-**3** and Δ-**3** enantiomers. These peaks can be

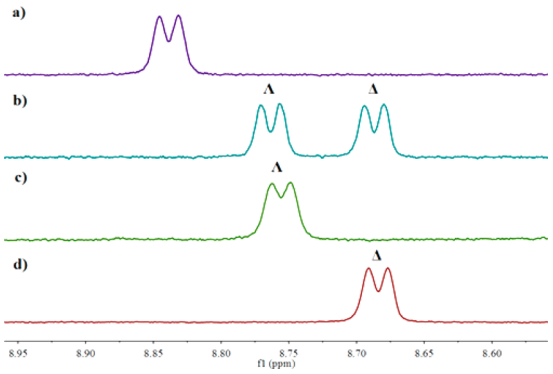

Figure 5. Excerpts of ^{1}H NMR spectra in $CDCl_3$: (a) *rac*-**3**, (b) *rac*-**3** with 60 equiv of *S*-binol, (c) Λ-**3** with 60 equiv of *S*-binol, and (d) Δ-**3** with 60 equiv of *S*-binol.

used to evaluate the enantiopurities of Λ-**3** and Δ-**3** enantiomers and show the ee values to be >98% from the ratio of the integrals of the α-H peaks of the two enantiomers. These results also demonstrate that no racemization occurred in the metal center under the experimental conditions.

The crystal structure of *rac*-**3** has been determined by X-ray crystallography. It crystallizes in the $P2_1/c$ space group. Each Ir(III) ion is coordinated by two ppy and one LO-^{i}Pr ligand in a distorted octahedral geometry. The N1 and N2 atoms are at trans position with the angle of N1−Ir1−N2 = 170.4(2)°; this is consistent with its parent. The Ir1−S1 distance of 2.357(1) Å is in accord with the reported distance for the Ir(III) sulfoxide complexes.[20,21] The S−O bond distance of 1.499(3) Å is consistent with that reported in sulfoxide complexes.[15,20−22] A pair of enantiomers Δ-*R* and Λ-*S* are found in the crystal structure; thus, the complex is racemate. Two pairs of diastereomers Δ-*R* and Δ-*S*, and Λ-*R* and Λ-*S*, would be generated when *rac-trans*(*N*)-[(Ir(ppy)$_2$Cl)$_2$] reacted with *rac*-HLO-^{i}Pr in the experimental conditions. Structural analyses show that only two configurations Δ-*R* and Λ-*S* are found, demonstrating that the configurations of the Ir(III) center enantioselectively assemble with the chiral sulfoxides. That is, the Δ Ir(III)-centered configuration favors the *R* configuration sulfoxide while the Λ configuration center prefers the *S* configuration sulfoxide, leading to enantioselective recognition between the metal center receptors and chiral sulfoxides. These are consistent with the previous observations in Ru(II) sulfoxide complexes by Meggers' group and our group.[15,17,22] To understand this selectivity, a density functional theory (DFT) calculation was carried out for Ru(II) and LO-^{i}Pr complexes by Meggers' group, and they found that the Λ-*S* enantiomer is more stable than the Δ-*S* enantiomer.[18e] As shown in Figure 6, the O2 of the sulfoxide group is hydrogen bonded to the C22−H of the pyridine ring (C22···O2 = 3.197 Å, H22···O2 = 2.338 Å, ∠C22−H−O2 = 153.6°); the ^{i}Pr group is far from the α-H of the pyridine ring to relieve the steric congestion and forms C−H···π interaction (2.92 Å) with the ppy ligand to stabilize the diastereomer. We would assume that the positions of O2 and ^{i}Pr group around the sulfur atom were interchanged in the isomer of Λ-*R*. The bulky ^{i}Pr group should be close to the pyridine ring and sterically interferes with the α-H. As a consequence, Λ-*R* diastereomer decomposes or

DOI: 10.1021/acs.inorgchem.6b02494
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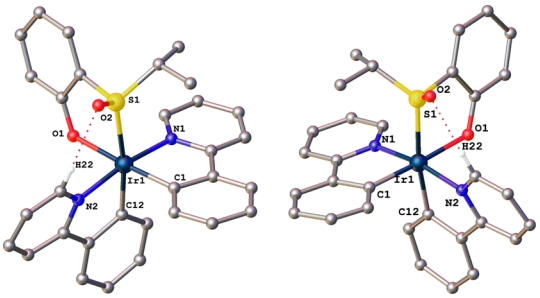

Figure 6. View of a pair of enantiomeric structures (Λ-S, left; Δ-R, right) in *rac*-**3**. Selected bond distances: Ir1−S1 = 2.357(1), Ir1−O1 = 2.136(4), Ir1−N1 = 2.047(4), Ir1−N2 = 2.067(4), Ir1−C1 = 1.998(5), Ir1−C12 = 2.037(4), and S1−O2 = 1.499(3) Å. ORTEP drawing with 50% probability thermal ellipsoids.

converts into Λ-*S* through the displacement of the *S*-sulfoxide by *R*-sulfoxide ligand under thermodynamic equilibrium.

To compare and confirm the absolute configuration at Ir(III) and sulfur centers, crystal structures of enantiopure sulfoxide complexes Δ-**3** and Λ-**3** were also measured by X-ray crystallography, respectively (see Figure S2 in the Supporting Information). They crystallize in a chiral space group $P2_12_12_1$. As expected, the absolute configurations at the Ir(III) centers and sulfur atoms in Δ-**3** and Λ-**3** are Δ and Λ, and *R* and *S* configurations, respectively, which are consistent with the configurations of their parents and also demonstrate that no racemization occurs at metal and sulfur centers in the reactions. The Flack parameters of Δ-**3** (−0.013(18)) and Λ-**3** (−0.011(6)) are close to zero, demonstrating that the assignments of chirality at the metal and sulfur centers are correct.

The highly stable configuration of Ir(III) center and reversibly coordinated capability of chiral sulfoxide ligand encourages us to recycle and reuse the chiral Ir(III) complex. Indeed, chiral Λ-$[Ir(ppy)_2(MeCN)_2](PF_6)$ was isolated in a yield of 88% after a facile purification. Its enantiopurity was examined by treatment with (*R*)-LO-^{i}Pr and conversion into Λ-**3** complex and found to be >98%. No diastereomer Δ-*S* was observed in the ^{1}H NMR spectra, indicating no racemization at the Ir(III) center in these processes. Moreover, the recovered chiral Λ-$[Ir(ppy)_2(MeCN)_2](PF_6)$ was reused in the second resolution cycle without loss of activity and enantioselectivity.

Next, we extend the developed methodology to separate other sulfoxides with various substituents, such as *rac*-HLO-Me, *rac*-HLO-Et, and *rac*-HLO-Bn. Indeed, the chiral Λ-$[Ir(ppy)_2(MeCN)_2](PF_6)$ complex can efficiently perform enantioselective recognition and resolution of the sulfoxide compounds with excellent yields and ee values (see Experimental section). The CD spectra of Δ-**1** and Λ-**1**, Δ-**2** and Λ-**2**, Δ-**4** and Λ-**4**, (*R*)-HLO-Me and (*S*)-HLO-Me, (*R*)-HLO-Et and (*S*)-HLO-Et, and (*R*)-HLO-Bn and (*S*)-HLO-Bn are mirror images with intense Cotton effect as shown in Figures S3−S8 in the Supporting Information. The enantiopurities of sulfoxides are determined by chiral HPLC analyses, and the ee values for (*R*)-HLO-Me, (*S*)-HLO-Me, (*R*)-HLO-Et, (*S*)-HLO-Et, (*R*)-HLO-Bn, and (*S*)-HLO-Bn are found to be 98.6%, 99.2%, 98.7%, 97.3%, 98.6%, and 97.1%, respectively, as shown in Figures S9−S11.

CONCLUSIONS

The chiral recognition and resolution of sulfoxide enantiomers under thermodynamic control was first achieved by the optically active complex Λ-$[Ir(ppy)_2(MeCN)_2](PF_6)$ with a chiral-at-metal strategy. The enantioselectivity may involve the hydrogen-bonding interaction between the sulfoxide O and the α-H of the pyridine ring as well as the steric repulsion between the bulky substituent groups of sulfoxide and the α-H of pyridine ring. Moreover, the enantioreceptor Λ-$[Ir(ppy)_2(MeCN)_2](PF_6)$ can be recycled and reused without loss of reaction activity and enantioselectivity. This finding would provide a complemental method for the resolution of sulfoxide enantiomers and may open a new avenue in enantioselective recognition and resolution via a chiral-at-metal strategy.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.inorgchem.6b02494. CCDC data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

CD, ^{1}H NMR, and HPLC figures for the compounds (PDF)

Supplementary crystallographic data for CCDC reference numbers 1509172 (for Λ-**3**), 1509171 (for Δ-**3**), and 1509173 (for *rac*-**3**) (CIF)

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This work was supported by the NSF of China (21272284 and 21571195).

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DOI: 10.1021/acs.inorgchem.6b02494
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