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Full Paper

Enantiopure Iridium Complexes

Proline and α-Methylproline as Chiral Auxiliaries for the Synthesis of Enantiopure Bis-Cyclometalated Iridium(III) Complexes

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Abstract: A convenient proline- and α-methylproline-mediated method for the synthesis of enantiomerically pure bis-cyclometalated iridium(III) complexes is reported. The reactions of L-proline or L-α-methylproline with $[Ir(\mu\text{-}Cl)(C^{\wedge}N)_2]_2$ ($C^{\wedge}N$ = cyclometalating 2-phenylpyridine, 2-phenylbenzoxazole, or 2-phenylbenzothiazole ligand) afforded diastereomeric mixtures of intermediate prolinatoiridium(III) complexes from which the Λ-(*S*) diastereomers were isolated with excellent diastereomeric purity by washing, precipitation, or crystallization. A subsequent trifluoroacetic acid (TFA) induced substitution of the prolinate ligands with 2,2′-bipyridine with the retention of configuration provided the chiral-only-at-metal complexes with >99 % *ee*.

Introduction

Bis-cyclometalated iridium(III) complexes have recently gained significant attention as metal-containing bioactive compounds, biological probes, and catalysts (Figure 1),[1–5] which, at least in part, has been driven by the high constitutional and configurational stability of the bis-cyclometalating unit. The iridium center fulfills an exclusive[4] or partial[5] structural role and often features the sole source of chirality in the form of metal-centered chirality (octahedral centrochirality).[6] These octahedral complexes exist as Λ (left-handed propeller) and Δ (right-handed propeller) enantiomers, and single enantiomers with high enantiomeric purity are required for applications in asymmetric catalysis.

We recently introduced an auxiliary-mediated strategy[7] for the asymmetric synthesis of polypyridine-ruthenium(II) complexes[8] and later applied it to the synthesis of enantiopure bis-cyclometalated iridium(III)[4,5,9] and rhodium(III)[10] complexes. In this strategy, a chiral auxiliary in the form of a chiral bidentate ligand induces asymmetry at the metal (ruthenium) center or serves as a handle for the resolution of metal-centered stereoisomers (iridium and rhodium). The auxiliary ligands are afterwards removed in a traceless fashion with the retention of the metal-centered configuration. For the synthesis of bis-cyclometalated iridium complexes, we typically employed chiral salicyloxazoline or salicylthiazoline ligands as the chiral auxiliaries.[4,5,9] However, owing to our extensive use of chiral bis-cyclometalated iridium(III) complexes in asymmetric catalysis, we wondered if we could use less expensive and more readily available chiral bidentate ligands as chiral auxiliaries.[11]

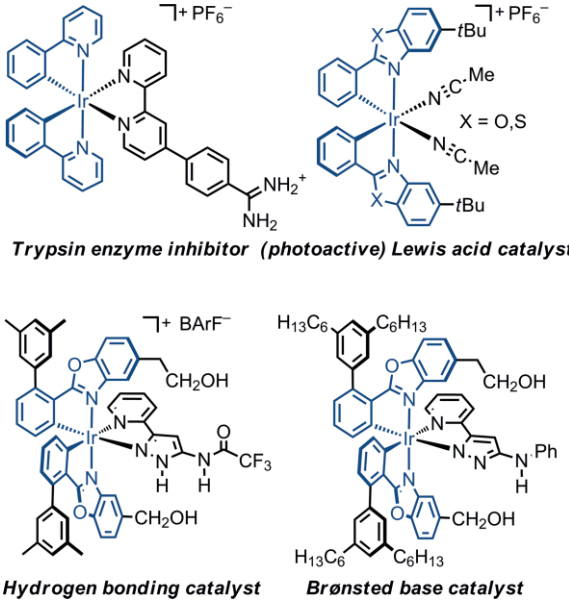

Figure 1. Examples of chiral, nonracemic bis-cyclometalated iridium(III) complexes from our lab used for medicinal chemistry and asymmetric catalysis; BArF = tetrakis[(3,5-di-trifluoromethyl)phenyl]borate.

In a previous study, we employed the amino acid L-proline[12,13] as a readily available chiral auxiliary to resolve diastereomeric mixtures of bis-cyclometalated L-prolinatoiridium(III) complexes by silica gel chromatography, followed by a substitution of the prolinate ligand for an achiral bidentate ligand with the retention of the configuration to provide a chiral-only-at-metal hydrogen-bonding catalyst.[14] Here, we now report that proline and the derived and commercially available α-methylproline are very suitable for the synthesis of enantiopure bis-cyclometalated iridium(III) complexes in a straightfor-

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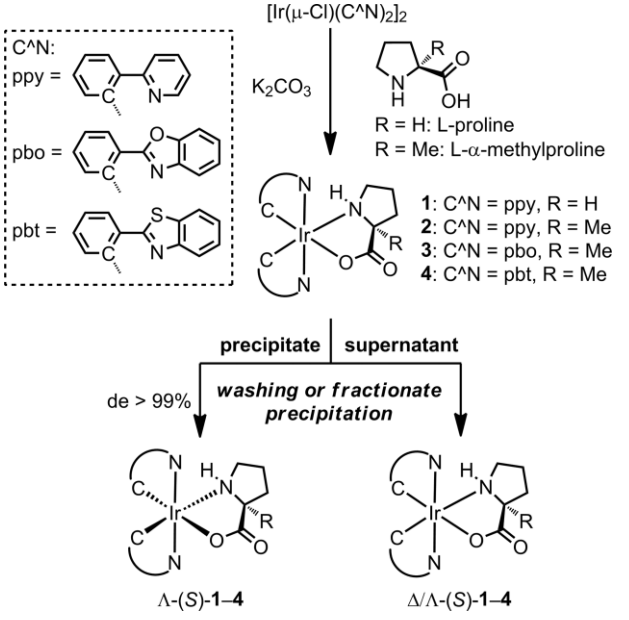
ward and convenient fashion without the need for any tedious chromatographic separation of the intermediate diastereomers.

Results and Discussion

The method starts with the readily available racemic μ-dichlorido-bridged iridium(III) dimers $[Ir(\mu\text{-}Cl)(C^\wedge N)_2]_2$ [C^N = 2-phenylpyridine (ppy), 2-phenylbenzoxazole (pbo), or 2-phenylbenzothiazole (pbt) as the cyclometalating ligands], which were treated with L-proline and L-α-methylproline to yield the corresponding prolinato- and methylprolinatoiridium(III) complexes as mixtures of diastereomers [Λ/Δ-(*S*)-**1**–**4**, Scheme 1].



Scheme 1. Synthesis of L-prolinatoiridium(III) complexes and isolation of the Λ-(*S*) diastereomers by washing, precipitation, or crystallization.

Accordingly, the reaction of racemic $[Ir(\mu\text{-}Cl)(ppy)_2]_2$ with L-proline in the presence of potassium carbonate afforded the prolinatoiridium complex **1** as a precipitated crude mixture of the Λ-(*S*) and Δ-(*S*) diastereomers with a diastereomeric ratio (*dr*) of 2.0:1 in favor of Λ-(*S*)-**1**. This observed diastereoselectivity apparently reflects a combination of the different solubilities and thermal stabilities of the two diastereomers.[15] Through the repeated washing of the product mixture with EtOH, the Λ-(*S*) diastereomer could be enriched, and Λ-(*S*)-**1** was isolated in an overall yield of 39 % with an excellent diastereomeric excess (*de*) of more than 99 %. Excerpts of the ^{1}H NMR spectra recorded before and after the washing procedure are shown in Figure 2, and the very high diastereomeric purity of the isolated Λ-(*S*)-**1** is clearly demonstrated.

We also investigated the sterically more demanding and also more lipophilic proline derivative L-α-methylproline. The reaction with racemic $[Ir(\mu\text{-}Cl)(ppy)_2]_2$ afforded the diastereomers Λ-(*S*)-**2** and Δ-(*S*)-**2** as a diastereomeric mixture with a slight excess of Λ-(*S*)-**2** (2.0:1 *dr*). The repeated precipitation of the diastereomeric mixture from a solution in CH_2Cl_2 layered with *n*-hexane finally provided Λ-(*S*)-**2** in a yield of 39 % with high

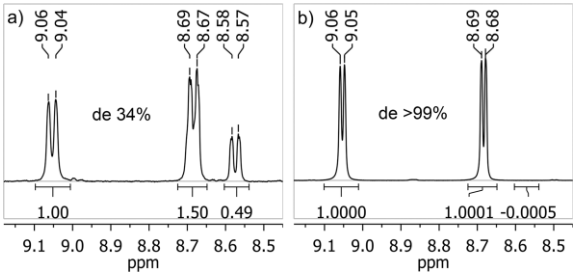


Figure 2. Excerpts from ^{1}H NMR spectra ([D$_6$]DMSO) of crude Λ-(*S*)-**1** (128 scans) and after washing with EtOH (1024 scans). The diastereomeric excess was determined by the integration of the signals at δ = 9.05 and 8.58 ppm.

diastereopurity (>99 % *de*). The structure of Λ-(*S*)-**2** is shown in Figure 3 and confirms the assigned metal-centered configuration.

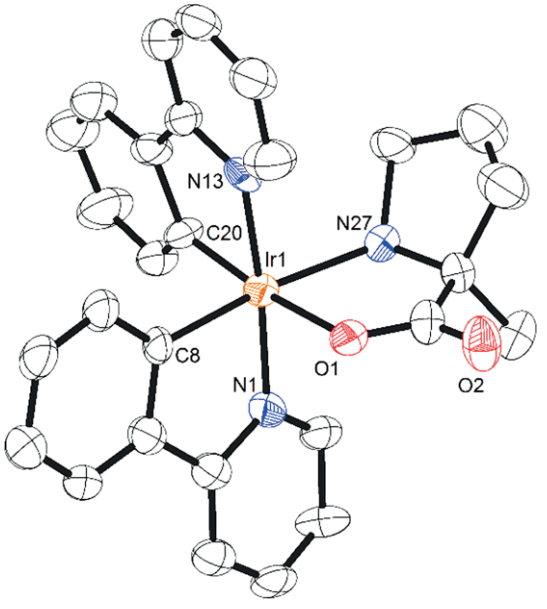


Figure 3. ORTEP drawing of Λ-(*S*)-**2** with 50 % probability thermal ellipsoids. The crystals were obtained by the slow evaporation of CH_2Cl_2. Only one of three independent molecules is shown. Solvent molecules are omitted for clarity. Selected bond lengths [Å] and angles [°]: O1–Ir1 2.122(11), N1–Ir1 2.038(12), Ir1–C20 1.980(17), Ir1–C8 2.024(13), Ir1–N13 2.047(13), Ir1–N27 2.184(13); C20–Ir1–C8 89.1(6), C20–Ir1–N1 97.8(6), C8–Ir1–N1 81.5(5), C8–Ir1–O1 94.3(5), N1–Ir1–O1 87.6(4), C20–Ir1–N27 98.0(6), N1–Ir1–N27 95.0(5).

This synthetic strategy was next applied to the corresponding complexes with pbo and pbt ligands. Although the reactions of racemic $[Ir(\mu\text{-}Cl)(pbo)_2]_2$ and $[Ir(\mu\text{-}Cl)(pbt)_2]_2$ with L-proline provided mixtures of diastereomers that did not differ enough in their solubilities in common solvents to enable us to achieve a resolution without chromatography, the reactions with L-α-methylproline were more useful and provided Λ/Δ-(*S*)-**3** (pbo ligands) and Λ/Δ-(*S*)-**4** (pbt ligands) as diastereomeric mixtures with a slight excess of the Λ-(*S*) diastereomers (1.2:1 *dr*). The Λ-(*S*) diastereomers were then isolated without chromatography by dissolving the mixtures of diastereomers in dichloromethane/acetonitrile, followed by the slow removal of the solvent until the product started to precipitate for Λ-(*S*)-**3** or crystallize for Λ-(*S*)-**4**. This procedure was repeated four

times to provide diastereomerically pure Λ-(*S*)-**3** (19 % yield, >99 % *de*) and twice for Λ-(*S*)-**4** (41 % yield, >99 % *de*).

Next, we investigated the Brønsted acid induced substitution of the chiral prolinate ligands with an achiral ligand and we chose 2,2′-bipyridine (bpy) as an exemplary achiral ligand (Table 1). For example, the treatment of Λ-(*S*)-**1** with 8 equiv. of trifluoroacetic acid (TFA) provided Λ-**5** after counterion exchange in 96 % yield. No traces of the unwanted Δ-enantiomer (> 99.9 % *ee*) could be detected by HPLC analysis with a chiral stationary phase (Table 1, Entry 1 and Figure 4). Similar results were achieved with the benzoxazole [Λ-(*S*)-**3** → Λ-**6**] and benzothiazole complexes [Λ-(*S*)-**4** → Λ-**7**], which provided the respective bpy complexes in satisfactory yields and with very high enantiopurity (Table 1, Entries 3 and 4). Interestingly, the use of the weaker acid NH_4PF_6 (8 equiv.) resulted in inferior results. For example, at room temperature, no full conversion could be achieved for Λ-(*S*)-**1** → Λ-**5**, and an increased temperature of 50 °C for 2 d was necessary to afford Λ-**5** with 84 % yield but with a slightly reduced enantioselectivity of 98.7 % *ee*. Thus, it can be concluded that the prolinatoiridium complexes require a stronger acid to achieve a smooth replacement than is required for our previously established salicyloxazoline and salicylthiazoline auxiliaries.

Table 1. Brønsted acid induced substitution of the chiral auxiliary with the retention of configuration.

Entry	Substrate	Acid	*T* [°C]	Time	Yield [%][a]	*ee* [%][b]
1	Λ-(*S*)-**1**	TFA (8 equiv.)	r.t.	2.5 h	96 (Λ-**5**)	>99.9
2	Λ-(*S*)-**1**	NH_4PF_6 (8 equiv.)	50 °C[c]	2 d	84 (Λ-**5**)	98.7
3	Λ-(*S*)-**3**	TFA (8 equiv.)	r.t.	2 h	75 (Λ-**6**)	99.6
4	Λ-(*S*)-**4**	TFA (8 equiv.)	r.t.	15 min	77 (Λ-**7**)	99.5

[a] Isolated as hexafluorophosphate salts. [b] Determined by HPLC with a chiral stationary phase. [c] Initially stirred at room temperature for 13 d without complete conversion.

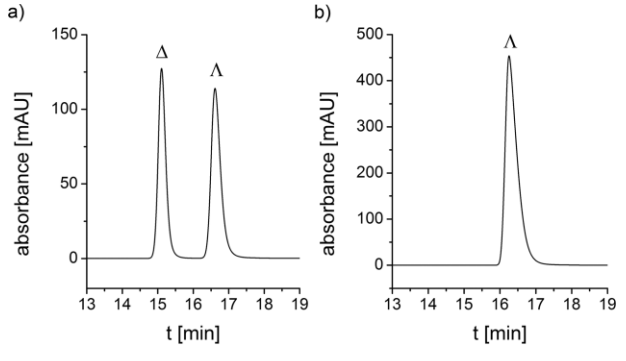


Figure 4. Chiral HPLC traces of (a) *rac*-**5** and (b) Λ-**5** obtained from Λ-(*S*)-**1** and TFA (Table 1, Entry 1). HPLC conditions: Daicel Chiralpak IA column (250 × 4.6 mm), solvent A: 0.1 % TFA, solvent B: MeCN, linear gradient of B 45 % to 60 % in 20 min, flow rate: 0.5 mL min^{-1}, column temperature: 40 °C, UV absorption detected at λ = 254 nm.

Conclusions

We have reported the use of L-proline and L-α-methylproline as chiral auxiliaries for the synthesis of nonracemic bis-cyclometalated iridium(III) complexes containing only achiral ligands. In this work, we exploited the different solubilities of the intermediate prolinatoiridium diastereomers and demonstrated that the Λ-(*S*) diastereomers feature lower solubilities and can be isolated with high diastereomeric purity by washing, precipitation, or crystallization. The subsequent TFA-induced substitution of the prolinate ligand with 2,2′-bipyridine provided the final chiral-only-at-metal complexes with very high enantiomeric purities of >99 % *ee*. Therefore, this method complements our previously developed salicyloxazoline and salicylthiazoline auxiliaries, and the application of this proline-mediated strategy to the simplified and more economic synthesis of asymmetric catalysts is underway in our laboratory.

Experimental Section

General Methods and Materials: All reactions were performed under a nitrogen or argon atmosphere. Stereoselective coordination chemistry was performed in the dark as a precaution against light-induced decomposition and isomerization. Acetonitrile and CH_2Cl_2 were distilled under nitrogen from calcium hydride, and Et_2O was distilled from sodium. MeOH was degassed by flushing with argon and stored over molecular sieves (3 Å). Chemicals were purchased from Acros Organics, Sigma–Aldrich, or Alfa Aesar and used without further purification. Column chromatography was performed with non-silylated synthetic amorphous silica gel 60 M from Macherey–Nagel (irregularly shaped, 230–400 mesh). The ^1H and ^{13}C NMR spectra were recorded with Bruker Avance 300 (300 MHz), Avance 500 (500 MHz), or DRX-500 (500 MHz) spectrometers at ambient temperature. The NMR standards used were as follows: ^1H NMR spectroscopy δ = 2.50 ppm {[D_6]dimethyl sulfoxide ([D_6]DMSO)}, ^{13}C NMR spectroscopy δ = 39.52 ppm ([D_6]DMSO). The CD spectra were recorded with a JASCO J-810 CD spectropolarimeter (200 to 600 nm, 1 nm bandwidth, scanning speed of 50 nm min^{-1}, accumulation of 5 scans). The HRMS spectra were recorded with a Finnigan LTQ-FT instrument with either atmospheric-pressure chemical ionization (APCI) or ESI as well as with a Bruker En Apex ultra 7.0 TFT-MS instrument by the ESI technique. The diastereomeric excesses were determined by ^1H NMR spectroscopy (1024 scans, 500 MHz). The enantiomeric excesses were determined with an Agilent 1200 or 1260 Series HPLC system with a Daicel Chiralpak IA (250 × 4.6 mm) HPLC column. The flow rate was 0.5 mL min^{-1}, the column temperature was 40 °C, and the UV absorption was measured at λ = 254 nm. Solvent A: 0.1 % TFA, solvent B: MeCN, linear gradient of B (Λ-**5**: 45 % to 60 % B in 20 min; Λ-**6** and Λ-**7**: 50 % to 65 % B in 20 min).

[Ir(μ-Cl)(C^N)$_2$]$_2$: Iridium(III) chloride trihydrate was treated with 2.5 equiv. of 2-phenylpyridine (C^N = ppy), 2-phenylbenzoxazole (C^N = pbo), or 2-phenylbenzothiazole (C^N = pbt) in pure 2-methoxyethanol (50 mM) at 150 °C inside a pressure tube for 12 h.[16] The resulting precipitate was isolated by filtration, washed with water and diethyl ether, and dried to yield the products [Ir(μ-Cl)(ppy)$_2$]$_2$ (yellow powder, 88 %), [Ir(μ-Cl)(pbo)$_2$]$_2$ (yellow powder, 86 %), and [Ir(μ-Cl)(pbt)$_2$]$_2$ (red powder, 84 %), which were used without further purification.

Λ-(*S*)-1: A suspension of [Ir(μ-Cl)(ppy)$_2$]$_2$ (100 mg, 93.3 μmol), L-proline (25.8 mg, 224 μmol), and potassium carbonate (32.2 mg, 233 μmol) in methanol (2 mL) was heated to 90 °C inside a pressure tube for 13 h. The yellow suspension was cooled to room temperature and transferred into a centrifuge tube with a minimal amount of methanol (3 mL). The excess solvent was removed until ca. 2 mL remained. Water (40 mL) was added, and the suspension was stored at 10 °C for 2 h. The precipitate was isolated by centrifugation and

washed with water (3 × 10 mL). Crude Λ/Δ-(*S*)-**1** was obtained as a yellow solid (108.3 mg) with a diastereomeric ratio of 2.0:1 in favor of the Λ-(*S*) diastereomer, as determined by ^{1}H NMR spectroscopy. To separate the diastereomers, a suspension of the product (94.9 mg) in ethanol (4.6 mL, 34 mM) inside a centrifuge tube was sonicated for 5 min, and the remaining precipitate was isolated by centrifugation. This procedure was repeated twice. The pure diastereomer Λ-(*S*)-**1** was dried under vacuum and obtained as a yellow solid (44.8 mg, 39 % overall yield) with >99 % *de*, as determined by ^{1}H NMR spectroscopy. ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 9.05 (d, ^3J = 5.6 Hz, 1 H), 8.68 (d, ^3J = 5.1 Hz, 1 H), 8.20 (d, ^3J = 8.2 Hz, 1 H), 8.17 (d, ^3J = 8.0 Hz, 1 H), 8.01–7.93 (m, 2 H), 7.75 (d, ^3J = 7.3 Hz, 1 H), 7.71 (d, ^3J = 7.4 Hz, 1 H), 7.52–7.45 (m, 1 H), 7.47–7.40 (m, 1 H), 6.82–6.74 (m, 2 H), 6.68–6.63 (m, 1 H), 6.63–6.57 (m, 1 H), 6.32 (d, ^3J = 7.3 Hz, 1 H), 5.95–5.86 (m, 2 H), 3.80 (td, ^3J = 8.8, 6.4 Hz, 1 H), 2.24–2.15 (m, 1 H), 2.05–1.94 (m, 1 H), 1.84–1.73 (m, 1 H), 1.61–1.50 (m, 1 H), 1.47–1.29 (m, 2 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 182.4, 168.6, 167.7, 152.3, 149.9, 147.7, 147.6, 144.6, 144.1, 137.9, 137.7, 132.5, 131.8, 128.8, 128.6, 124.4, 124.0, 122.7, 122.6, 120.5, 119.9, 119.2, 119.1, 61.3, 47.7, 30.5, 25.9 ppm. CD (MeCN): λ ($\Delta\varepsilon$, M^{-1} cm^{-1}) = 204 (+38), 217.5 (–33), 256.5 (+29), 273 (–8), 304.5 (+13), 329 (+4), 361 (+9) nm. HRMS: calcd. for $C_{27}H_{24}IrN_3O_2Na$ [M + Na]$^+$ 638.1391; found 638.1409.

Λ-(*S*)-2: A suspension of [Ir(μ-Cl)(ppy)$_2$]$_2$ (50.4 mg, 47.0 μmol), L-α-methylproline (18.2 mg, 141 μmol), and potassium carbonate (16.2 mg, 118 μmol) in methanol (1 mL) was heated to 90 °C inside a pressure tube for 2 h. The reaction mixture was cooled to room temperature and transferred into a centrifuge tube with a minimal amount of methanol (1 mL). Water (10 mL) was added, and the suspension was stored at 10 °C overnight. The precipitate was isolated by centrifugation and washed with water (3 × 2 mL). Crude Λ/Δ-(*S*)-**2** was obtained as a yellow solid (50.3 mg) with a diastereomeric ratio of 2.0:1 in favor of the Λ-(*S*) diastereomer, as determined by ^{1}H NMR spectroscopy. To separate the diastereomers, the product (43.6 mg) was dissolved in dichloromethane (23 mL, 3 mM), layered with hexane (92 mL), and stored at 10 °C until both phases mixed completely. The resulting precipitate was isolated by decantation. This procedure was repeated twice. Λ-(*S*)-**2** was dried under vacuum and obtained as a yellow solid (20.0 mg, 39 %) with >99 % *de*, as determined by ^{1}H NMR spectroscopy. ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 9.28 (d, ^3J = 5.8 Hz, 1 H), 8.66 (d, ^3J = 5.7 Hz, 1 H), 8.21 (d, ^3J = 8.2 Hz, 1 H), 8.18 (d, ^3J = 8.2 Hz, 1 H), 7.97 (q, ^3J = 7.5 Hz, 2 H), 7.76 (d, ^3J = 7.6 Hz, 1 H), 7.73 (d, ^3J = 7.7 Hz, 1 H), 7.47 (dt, ^3J = 12.1, 6.5 Hz, 2 H), 6.79 (t, ^3J = 7.3 Hz, 2 H), 6.65 (t, ^3J = 7.3 Hz, 1 H), 6.60 (t, ^3J = 7.3 Hz, 1 H), 6.39 (d, ^3J = 7.6 Hz, 1 H), 5.81 (d, ^3J = 7.6 Hz, 1 H), 5.50 (t, ^3J = 5.9 Hz, 1 H), 2.57–2.52 (m, 1 H), 1.89 (dt, ^2J = 13.8, ^3J = 7.3 Hz, 1 H), 1.71 (dq, ^2J = 11.6, ^3J = 6.0 Hz, 1 H), 1.58 (dt, ^2J = 12.6, ^3J = 6.2 Hz, 1 H), 1.44 (tt, ^2J = 14.1, ^3J = 7.1 Hz, 1 H), 1.35 (s, 3 H), 0.97 (dp, ^2J = 11.3, ^3J = 5.6, 5.1 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 185.0, 168.5, 167.8, 151.3, 150.3, 148.5, 147.6, 144.7, 144.0, 137.9, 137.7, 132.4, 131.7, 128.6, 128.4, 124.5, 123.9, 122.3, 121.8, 120.5, 119.8, 119.2, 119.0, 68.0, 48.7, 38.7, 27.3, 24.9 ppm. CD (MeCN): λ ($\Delta\varepsilon$, M^{-1} cm^{-1}) = 205 (+28), 217 (–29), 257 (+21), 271 (–7), 303 (+10), 327.5 (+3), 361 (+6) nm. HRMS: calcd. for $C_{28}H_{26}IrN_3O_2Na$ [M + Na]$^+$ 652.1548; found 652.1573.

Λ-(*S*)-3: A suspension of [Ir(μ-Cl)(pbo)$_2$]$_2$ (100 mg, 81.2 μmol), L-α-methylproline (26.2 mg, 203 μmol), and potassium carbonate (33.6 mg, 244 μmol) in methanol (1.6 mL) was heated to 90 °C inside a pressure tube for 18.5 h. The reaction mixture was cooled to room temperature, and water (3 mL) was added. The precipitate was isolated by filtration through a fritted glass filter and washed with water (3 × 10 mL). The crude product was purified by column chromatography (CH_2Cl_2/MeOH 50:1 → 20:1). Crude Λ/Δ-(*S*)-**3** was obtained as a yellow solid (89.9 mg) with a diastereomeric ratio of 1.2:1 in favor of the Λ-(*S*) diastereomer, as determined by ^{1}H NMR spectroscopy. To separate the diastereomers, the product (46.7 mg) was dissolved in a minimal amount of dichloromethane (7 mL), acetonitrile (1.3 mL, 50 mM) was added, and the solvent was evaporated (20 °C, up to 250 mbar) until the product started to precipitate. The flask was closed with a septum, and the suspension was stored at 10 °C for 2 d until precipitation was complete. The resulting precipitate was isolated by decantation. This procedure was repeated three times. Λ-(*S*)-**3** was dried under vacuum and obtained as a yellow solid (11.2 mg, 19 %) with >99 % *de*, as determined by ^{1}H NMR spectroscopy. ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 8.55–8.47 (m, 1 H), 8.07–8.00 (m, 2 H), 7.85 (dd, ^3J = 7.8, ^4J = 0.6 Hz, 1 H), 7.74 (dd, ^3J = 7.6, ^4J = 0.6 Hz, 1 H), 7.71 (dd, ^3J = 7.6, ^4J = 0.8 Hz, 1 H), 7.67–7.58 (m, 3 H), 7.55 (td, ^3J = 7.7, ^4J = 1.1 Hz, 1 H), 6.98–6.89 (m, 2 H), 6.76 (tt, ^3J = 7.3, ^4J = 1.4 Hz, 2 H), 6.65 (d, ^3J = 7.7 Hz, 1 H), 6.12 (d, ^3J = 7.7 Hz, 1 H), 5.62 (t, ^3J = 6.8 Hz, 1 H), 2.76 (dq, ^2J = 11.8, ^3J = 6.1 Hz, 1 H), 1.95–1.80 (m, 2 H), 1.60–1.43 (m, 2 H), 1.27 (s, 3 H), 1.08 (dp, ^2J = 12.1, ^3J = 6.0, 5.5 Hz, 1 H) ppm. ^{13}C NMR (126 MHz, [D$_6$]DMSO): δ = 185.3, 177.8, 177.6, 150.6, 149.9, 149.5, 147.8, 137.8, 137.3, 135.2, 132.9, 131.7, 131.3, 130.0, 128.8, 126.7, 126.3, 126.0, 125.8, 125.6, 121.6, 120.6, 118.1, 117.0, 112.4, 112.3, 69.0, 50.0, 38.0, 26.8, 24.8 ppm. CD (MeCN): λ ($\Delta\varepsilon$, M^{-1} cm^{-1}) = 209 (+84), 244.5 (–13), 262 (+1), 276 (–22), 307 (+21) nm. HRMS: calcd. for $C_{32}H_{26}IrN_3O_4Na$ [M + Na]$^+$ 732.1446; found 732.1449.

Λ-(*S*)-4: A suspension of [Ir(μ-Cl)(pbt)$_2$]$_2$ (200 mg, 154 μmol), L-α-methylproline (59.8 mg, 463 μmol), and potassium carbonate (64.3 mg, 463 μmol) in methanol (3 mL) was heated to 90 °C inside a pressure tube for 3.5 h. The reaction mixture was cooled to room temperature, and water (6 mL) was added. The precipitate was isolated by filtration through a fritted glass filter and washed with water (3 × 10 mL). Crude Λ/Δ-(*S*)-**4** was obtained as a red solid (225.5 mg) with a diastereomeric ratio of 1.2:1 in favor of the Λ-(*S*) diastereomer, as determined by ^{1}H NMR spectroscopy. To separate the diastereomers, the product (212.2 mg) was dissolved in a minimal amount of dichloromethane (10 mL), acetonitrile (1.4 mL, 200 mM) was added, and the solvent was evaporated (40 °C, up to 500 mbar) until the product started to crystallize. The flask was cooled slowly to room temperature, closed with a septum, and stored at 10 °C for 2 d until crystallization was complete. The resulting precipitate was isolated by decantation. This procedure was repeated twice. Λ-(*S*)-**4** was dried under vacuum and obtained as a yellow solid (88.5 mg, 41 %) with >99 % *de*, as determined by ^{1}H NMR spectroscopy. ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 8.42–8.39 (m, 1 H), 8.39–8.36 (m, 1 H), 8.32–8.30 (m, 1 H), 8.29–8.26 (m, 1 H), 7.84 (dd, ^3J = 7.6, ^4J = 0.7 Hz, 1 H), 7.77 (dd, ^3J = 7.6, ^4J = 0.8 Hz, 1 H), 7.66–7.58 (m, 2 H), 7.55 (td, ^3J = 8.1, 7.7, ^4J = 1.3 Hz, 1 H), 7.50 (ddd, ^3J = 8.3, 7.3, ^4J = 1.4 Hz, 1 H), 6.93–6.86 (m, 2 H), 6.74 (d, ^3J = 7.2 Hz, 1 H), 6.69 (td, ^3J = 7.9, 7.5, ^4J = 1.3 Hz, 1 H), 6.60 (td, ^3J = 7.7, ^4J = 1.3 Hz, 1 H), 5.92 (d, ^3J = 7.8 Hz, 1 H), 5.45 (t, ^3J = 6.9 Hz, 1 H), 2.78 (dt, ^2J = 11.0, ^3J = 5.6 Hz, 1 H), 1.79–1.71 (m, 1 H), 1.67–1.58 (m, 1 H), 1.51–1.37 (m, 2 H), 1.03–0.91 (m, 4 H) ppm. ^{13}C NMR (126 MHz, [D$_6$]DMSO): δ = 184.7, 181.5, 180.1, 151.0, 150.0, 149.5, 148.9, 141.7, 140.7, 135.6, 133.5, 131.3, 131.0, 130.5, 129.6, 127.6, 127.1, 126.5, 125.78, 125.75, 124.0, 123.7, 121.6, 121.4, 120.6, 120.5, 68.7, 50.0, 38.2, 27.1, 24.5 ppm. CD (MeCN): λ ($\Delta\varepsilon$, M^{-1} cm^{-1}) = 215 (+167), 227 (–55), 238.5 (–2), 248 (–15), 268 (+3), 312.5 (+18), 326.5 (+30) nm. HRMS: calcd. for $C_{32}H_{26}IrN_3O_2S_2Na$ [M + Na]$^+$ 764.0986; found 764.0999.

Λ-5: A freshly prepared solution of TFA in acetonitrile (400 mM, 0.34 mL, 135 μmol) was added to a mixture of prolinatoiridium complex Λ-(*S*)-**1** (10.4 mg, 16.9 μmol) and 2,2′-bipyridine (39.6 mg,

254 μmol). The resulting suspension was stirred at room temperature for 2.5 h until a clear solution was obtained. The reaction mixture was concentrated to dryness and subjected to silica gel chromatography (CH_2Cl_2/MeOH, 50:1 to 10:1). The combined product eluents were again concentrated to dryness, and the resulting material was dissolved in a minimum amount of methanol (0.3 mL). The product was precipitated by the addition of a few drops of a saturated, aqueous solution of NH_4PF_6, and water (10 mL) was added. The yellow precipitate was isolated by centrifugation, washed with water (3 × 2 mL) and diethyl ether (3 × 2 mL), and dried under high vacuum to afford Λ-**5** as a PF_6 salt (13.1 mg, 96 %) as a single enantiomer. Alternatively, a suspension of Λ-(*S*)-**1** (15.0 mg, 24.4 μmol), 2,2′-bipyridine (57.2 mg, 366 μmol), and NH_4PF_6 (31.8 mg, 195 μmol) in acetonitrile was stirred at room temperature for 13 d. As TLC (CH_2Cl_2/MeOH, 10:1) showed incomplete conversion after this time, the reaction mixture was heated to 50 °C for 2 d. The solvent was removed, and the crude product was subjected to silica gel chromatography (CH_2Cl_2/MeOH, 200:1 → 100:1). The combined product eluents were dissolved in MeCN (0.5 mL), precipitated by the addition of diethyl ether (10 mL), washed with diethyl ether (3 × 2 mL), and dried under high vacuum to afford Λ-**5** as a PF_6 salt (16.5 mg, 84 %) with an enantiomeric excess of 98.7 %. The analytical data were consistent with the data reported previously.[9]

Λ-6: A freshly prepared solution of TFA in acetonitrile (400 mM, 0.40 mL, 161 μmol) was added to a mixture of Λ-(*S*)-**3** (14.3 mg, 20.2 μmol) and 2,2′-bipyridine (47.3 mg, 303 μmol). The yellow suspension was stirred at room temperature for 15 min until a clear solution was obtained. The reaction mixture was concentrated to dryness and subjected to silica gel chromatography (CH_2Cl_2/MeOH, 20:1 → 10:1). The combined product eluents were again concentrated to dryness, and the resulting material was dissolved in a minimum amount of methanol (0.4 mL). The product was precipitated by the addition of a few drops of a saturated, aqueous solution of NH_4PF_6, and water (10 mL) was added. The yellow precipitate was isolated by centrifugation, washed with water (3 × 2 mL) and diethyl ether (3 × 2 mL), and dried under high vacuum to afford Λ-**6** as a PF_6 salt (13.4 mg, 75 %) with 99.6 % *ee*. The analytical data were consistent with the data reported previously for the racemic mixture.[17] CD (MeCN): λ ($\Delta\varepsilon$, M^{-1} cm^{-1}) = 206.5 (+84), 234 (–38), 249.5 (+3), 300.5 (+38), 321 (+18), 333 (+32), 345 (+25), 355.5 (+32), 408 (–15) nm.

Λ-7: A freshly prepared solution of TFA in acetonitrile (400 mM, 0.32 mL, 130 μmol) was added to a mixture of methylprolinatoiridium complex Λ-(*S*)-**4** (10.2 mg, 16.2 μmol) and 2,2′-bipyridine (38.0 mg, 243 μmol). The orange suspension was stirred at room temperature for 2 h, and the resulting yellow solution was concentrated to dryness and subjected to silica gel chromatography (CH_2Cl_2/MeOH, 20:1). The combined product eluents were again concentrated to dryness, and the resulting material was dissolved in a minimum amount of methanol (0.3 mL). The product was precipitated by the addition of a few drops of a saturated, aqueous solution of NH_4PF_6, and water (10 mL) was added. The yellow precipitate was isolated by centrifugation, washed with water (3 × 2 mL) and diethyl ether (3 × 2 mL), and dried under high vacuum to afford Λ-**7** as a PF_6 salt (11.3 mg, 77 %) with 99.5 % *ee*. The analytical data were consistent with the data reported previously.[9]

Single-Crystal X-ray Diffraction Studies: The Crystallographic data and structure-refinement statistics are provided in the Supporting Information. See the Supporting Information for the structures of Λ-(*S*)-**1**, -**3**, and -**4** and Λ-**6**.

CCDC 1472294 [for Λ-(*S*)-**2**] contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

Supporting Information (see footnote on the first page of this article): Crystallographic data and structure-refinement statistics.

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Keywords: Asymmetric synthesis · Chirality · Chiral auxiliaries · Amino acids · Iridium

[1] For reviews covering bis-cyclometalated iridium(III) complexes as bioactive compounds and biological probes, see: a) V. Fernández-Moreira, F. L. Thorp-Greenwood, M. P. Coogan, *Chem. Commun.* **2009**, *46*, 186–202; b) K. K.-W. Lo, S. P.-Y. Li, K. Y. Zhang, *New J. Chem.* **2011**, *35*, 265–287; c) K. K.-W. Lo, K. Y. Zhang, *RSC Adv.* **2012**, *2*, 12069–12083; d) C.-H. Leung, H.-J. Zhong, D. S.-H. Chan, D.-L. Ma, *Coord. Chem. Rev.* **2013**, *257*, 1764–1776; e) D.-L. Ma, Z. Zhang, M. Wang, L. Lu, H.-J. Zhong, C.-H. Leung, *Chem. Biol.* **2015**, *22*, 812–828; f) K. K.-W. Lo, *Acc. Chem. Res.* **2015**, *48*, 2985–2995.

[2] For individual studies on the use of bis-cyclometalated iridium(III) complexes as bioactive compounds and biological probes, see: a) K. K.-W. Lo, C.-K. Li, J. S.-Y. Lau, *Organometallics* **2005**, *24*, 4594–4601; b) K. K.-W. Lo, J. S.-Y. Lau, *Inorg. Chem.* **2007**, *46*, 700–709; c) F. Shao, B. Elias, W. Lu, J. K. Barton, *Inorg. Chem.* **2007**, *46*, 10187–10199; d) F. Shao, J. K. Barton, *J. Am. Chem. Soc.* **2007**, *129*, 14733–14738; e) D.-L. Ma, W.-L. Wong, W.-H. Chung, F.-Y. Chan, P.-K. So, T.-S. Lai, Z.-Y. Zhou, Y.-C. Leung, K.-Y. Wong, *Angew. Chem. Int. Ed.* **2008**, *47*, 3735–3739; *Angew. Chem.* **2008**, *120*, 3795; f) J. S.-Y. Lau, P.-K. Lee, K. H.-K. Tsang, C. H.-C. Ng, Y.-W. Lam, S.-H. Cheng, K. K.-W. Lo, *Inorg. Chem.* **2009**, *48*, 708–718; g) Q. Zhao, M. Yu, L. Shi, S. Liu, C. Li, M. Shi, Z. Zhou, C. Huang, F. Li, *Organometallics* **2010**, *29*, 1085–1091; h) M. Graf, K. Sünkel, *Inorg. Chim. Acta* **2011**, *379*, 40–43; i) B. Y.-W. Man, H.-M. Chan, C.-H. Leung, D. S.-H. Chan, L.-P. Bai, Z.-H. Jiang, H.-W. Li, D.-L. Ma, *Chem. Sci.* **2011**, *2*, 917–921; j) H.-Y. Shiu, M.-K. Wong, C.-M. Che, *Chem. Commun.* **2011**, *47*, 4367–4369; k) C.-H. Leung, H.-J. Zhong, H. Yang, Z. Cheng, D. S.-H. Chan, V. P.-Y. Ma, R. Abagyan, C.-Y. Wong, D.-L. Ma, *Angew. Chem. Int. Ed.* **2012**, *51*, 9010–9014; *Angew. Chem.* **2012**, *124*, 9144; l) W. H.-T. Law, K.-K. Leung, L. C.-C. Lee, C.-S. Poon, H.-W. Liu, K. K.-W. Lo, *ChemMedChem* **2014**, *9*, 1316–1329; m) D. Maggioni, M. Galli, L. D'Alfonso, D. Inverso, M. V. Dozzi, L. Sironi, M. Iannacone, M. Collini, P. Ferruti, E. Ranucci, G. D'Alfonso, *Inorg. Chem.* **2015**, *54*, 544–553; n) M. Graf, Y. Gothe, N. Metzler-Nolte, R. Czerwieniec, K. Sünkel, *Z. Anorg. Allg. Chem.* **2015**, *641*, 1798–1802; o) P. Göbel, F. Ritterbusch, M. Helms, M. Bischof, K. Harms, M. Jung, E. Meggers, *Eur. J. Inorg. Chem.* **2015**, 1654–1659.

[3] Z.-Y. Cao, W. D. G. Brittain, J. S. Fossey, F. Zhou, *Catal. Sci. Technol.* **2015**, *5*, 3441–3451.

[4] For bis-cyclometalated iridium(III) complexes as structural templates for asymmetric catalysis, see: a) L.-A. Chen, W. Xu, B. Huang, J. Ma, L. Wang, J. Xi, K. Harms, L. Gong, E. Meggers, *J. Am. Chem. Soc.* **2013**, *135*, 10598–10601; b) L.-A. Chen, X. Tang, J. Xi, W. Xu, L. Gong, E. Meggers, *Angew. Chem. Int. Ed.* **2013**, *52*, 14021–14025; *Angew. Chem.* **2013**, *125*, 14271; c) H. Huo, C. Fu, C. Wang, K. Harms, E. Meggers, *Chem. Commun.* **2014**, *50*, 10409–10411.

[5] For bis-cyclometalated iridium(III) complexes as (photoactivatable) chiral Lewis acid catalysts, see: a) H. Huo, C. Fu, K. Harms, E. Meggers, *J. Am. Chem. Soc.* **2014**, *136*, 2990–2993; b) H. Huo, X. Shen, C. Wang, L. Zhang, P. Röse, L.-A. Chen, K. Harms, M. Marsch, G. Hilt, E. Meggers, *Nature* **2014**, *515*, 100–103; c) C. Wang, Y. Zheng, H. Huo, P. Röse, L. Zhang, K. Harms, G. Hilt, E. Meggers, *Chem. Eur. J.* **2015**, *21*, 7355–7359; d) C. Wang, J. Qin, X. Shen, R. Riedel, K. Harms, E. Meggers, *Angew. Chem. Int. Ed.* **2016**, *55*, 685–688; *Angew. Chem.* **2016**, *128*, 695–698; e) C. Tian, L. Gong, E. Meggers, *Chem. Commun.* **2016**, *52*, 4207–4210.

[6] For different aspects of metal-centered chirality, see: a) U. Knof, A. von Zelewsky, *Angew. Chem. Int. Ed.* **1999**, *38*, 302–322; *Angew. Chem.* **1999**, *111*, 312; b) H. Brunner, *Angew. Chem. Int. Ed.* **1999**, *38*, 1194–1208; *Angew. Chem.* **1999**, *111*, 1248; c) P. D. Knight, P. Scott, *Coord. Chem. Rev.* **2003**, *242*, 125–143; d) M. Fontecave, O. Hamelin, S. Ménage, *Top. Organomet. Chem.* **2005**, *15*, 271–288; e) H. Amouri, M. Gruselle, *Chirality in Transition Metal Chemistry*, Wiley, Chichester, UK, **2008**; f) J. Crassous, *Chem. Soc. Rev.* **2009**, *38*, 830–845; g) E. Meggers, *Eur. J. Inorg. Chem.* **2011**, 2911–2926; h) J. Crassous, *Chem. Commun.* **2012**, *48*, 9684–9692; i) E. C. Constable, *Chem. Soc. Rev.* **2013**, *42*, 1637–1651; j) L. Gong, L.-A. Chen, E. Meggers, *Angew. Chem. Int. Ed.* **2014**, *53*, 10868–10874; *Angew. Chem.* **2014**, *126*, 11046.

[7] For a review on auxiliary-mediated asymmetric coordination chemistry, see: E. Meggers, *Chem. Eur. J.* **2010**, *16*, 752–758.

[8] a) L. Gong, S. P. Mulcahy, K. Harms, E. Meggers, *J. Am. Chem. Soc.* **2009**, *131*, 9602–9603; b) L. Gong, M. Wenzel, E. Meggers, *Acc. Chem. Res.* **2013**, *46*, 2635–2644.

[9] M. Helms, Z. Lin, L. Gong, K. Harms, E. Meggers, *Eur. J. Inorg. Chem.* **2013**, 4164–4172.

[10] C. Wang, L.-A. Chen, H. Huo, X. Shen, K. Harms, L. Gong, E. Meggers, *Chem. Sci.* **2015**, *6*, 1094–1100.

[11] Lusby and co-workers recently reported the synthesis of Δ- and Λ-[(μ-Cl)Ir(ppy)$_2$]$_2$ (ppy = cyclometalating 2-phenylpyridine) with readily available L-serine and D-serine as chiral auxiliaries, respectively, see: O. Chepelin, J. Ujma, X. Wu, A. M. Z. Slawin, M. B. Pitak, S. J. Coles, J. Michel, A. C. Jones, P. E. Barran, P. J. Lusby, *J. Am. Chem. Soc.* **2012**, *134*, 19334–19337.

[12] For bis-cyclometalated L-prolinatoiridium(III) complexes, see: a) R. Urban, R. Krämer, S. Mihan, K. Polborn, B. Wagner, W. Beck, *J. Organomet. Chem.* **1996**, *517*, 191–200; b) M. Graf, K. Sünkel, *Inorg. Chim. Acta* **2011**, *371*, 42–46.

[13] For a report on the use of proline as a chiral auxiliary for the asymmetric synthesis of chiral ruthenocene complexes, see: U. Koelle, K. Bücken, U. Englert, *Organometallics* **1996**, *15*, 1376–1383.

[14] J. Liu, L. Gong, E. Meggers, *Tetrahedron Lett.* **2015**, *56*, 4653–4656.

[15] The ^{1}H NMR spectroscopy analysis of the evaporated entire crude reaction mixture in [D$_6$]DMSO revealed a diastereomeric ratio of 1.3:1 in favor of Λ-(*S*)-**1**. When the reaction was executed instead at a lower temperature (40 °C), a diastereomeric ratio of exactly 1:1 was observed.

[16] M. Nonoyama, *Bull. Chem. Soc. Jpn.* **1974**, *47*, 767–768.

[17] F. Gärtner, S. Denurra, S. Losse, A. Neubauer, A. Boddien, A. Gopinathan, A. Spannenberg, H. Junge, S. Lochbrunner, M. Blug, S. Hoch, J. Busse, S. Gladiali, M. Beller, *Chem. Eur. J.* **2012**, *18*, 3220–3225.

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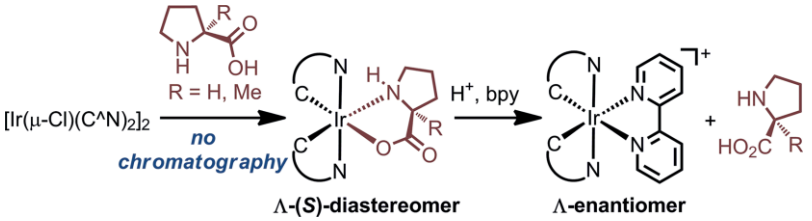

Proline and α-methylproline are very suitable chiral auxiliaries for the synthesis of enantiopure bis-cyclometalated iridium(III) complexes in a straightforward and convenient fashion without the tedious chromatographic separation of the intermediate diastereomers.

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