Preparation of single enantiomers of chiral at metal bis-cyclometallated iridium complexes

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Reaction of [Ir(C^N)₂Cl]₂ with chiral bidentate N^OH ligands provides complexes [Ir(C^N)₂(N^O)] as a 1:1 mixture of diastereomers which can be separated by crystallisation. A pure diastereomer can be converted to [Ir(C^N)₂(bipy)][CF₃CO₂] with complete retention of stereochemistry at the metal.

Complexes of the type [Ir(C^N)₂(X^Y)] usually occur as a single geometric isomer, with *cis* carbon atoms and *trans* nitrogen atoms of the cyclometallated ligand (Fig. 1).[1] The complexes have a stereogenic metal centre and exist as a mixture of Λ and Δ enantiomers. However, unlike [Ru(bipy)₃]²⁺ the resolution of Ir(III) complexes is still in its infancy and very few reports have been published so far.[2-6] Separation by HPLC of the enantiomers of [Ir(ppy)₃] (Hppy = phenylpyridine) was reported in 2007,[3] and of [Ir(ppy-R)₂(acac)] (R = F, OMe, Ph) in 2008.[4] Single diastereomers have been isolated e.g. [Ir(C^N*)]₃ and [Ir(C^N*)₂(acac)] with enantiopure cyclometallating ligands,[7] or [Ir(C^N)₂(X^Y*)] (X^Y* = amino acidate[5, 8, 9], phenol oxazoline[6]) with enantiopure X^Y ligands. However, these complexes have chirality at the ligand as well as the metal; hence, the aim of this work was to prepare, on a synthetically useful scale, homochiral cyclometallated Ir(III) complexes which are only chiral at the metal.

Our strategy was to prepare diastereomeric complexes [Ir(C^N)₂(X^Y*)], separate the diastereomers, then remove the chiral auxiliary by protonation and replace it with another bidentate ligand. A similar strategy has recently been applied by Meggers for the synthesis of homochiral trisbidentate ruthenium complexes,[10] and in 2012 was applied to iridium complexes for the first time.[5]

The dimer [Ir(ppz)₂Cl]₂(**a,** Hppz = phenylpyrazole) was reacted with 2.2 equiv of (S)-Na(L1)[11,12] in a mixture of DCM/ methanol (2:1) at room temperature for 2-4 hrs, to give **1a** as a

Scheme 1
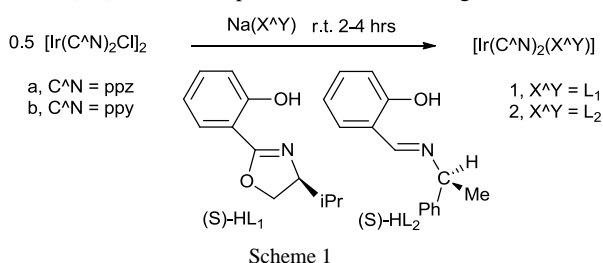
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†Electronic Supplementary Information (ESI) available: Synthetic procedures and characterization data for **1a,b, 2a,b** and **3a**and cif files forΛS- and ΔS-**1a,** ΛS-**1b,**ΔS-**2a,** ΛS- and ΔS-**2b.**CCDC 922561-922566.

(1:1) mixture of diastereomers, ΔS and ΛS, in good combined yields (>75%) (Scheme 1). The reaction was repeated with only 0.8 equiv of (S)-Na(L1) per dimer and the ¹H NMR spectrum of the product showed a 1:1 ratio of the two diastereomers along with the unreacted excess dimer. This suggests that there is no diastereoselectivity in the synthesis and there is an equal probability for the formation of the two diastereomers.

The diastereomers of **1a** could be separated by crystallisation from different solvents and they do not interconvert in solution, suggesting the chirality at the metal is stable at room temperature. The absolute configuration of both diastereomers was determined by X-ray crystallography[13] and the structures of ΛS- and ΔS-**1a** are shown in Fig. 2.[14] The structures show that both isomers have *cis* carbon atoms and *trans* nitrogen atoms for the C^N ligands and S configuration at the chiral carbon atom of the oxazoline ligand; one isomer has a Λ configuration at the Ir centre (Fig. 2 left), whereas the other isomer shows a Δ configuration (Fig. 2 right). The change in chirality at the metal leads to different orientations of L1 with respect to the [Ir(C^N)₂] fragment. In the ΛS isomer the pyrazole [N(4)-C(12)] pointing towards the oxazoline nitrogen is on the unsubstituted side of the oxazoline and there is no steric conflict. In contrast, in the ΔS isomer, the pyrazole [N(2)-C(3)] pointing towards the oxazoline nitrogen is on the same side as the isopropyl which leads to steric congestion which is clearly evident in the planarity of L1 (Fig. 2 right). Thus, in the ΛS isomer the angle between the planes of the phenol and the oxazoline is less than 3° whilst in the ΔS isomer the corresponding angle is > 20°.

The structures are retained in solution as determined by key NOEs between the X^Y ligand and the [Ir(C^N)₂] fragment (see ESI Fig S1). In ΛS-**1a** the isopropyl group lies above a ppz ligand so is significantly affected by a ring current and the signals are observed upfield (δ 0.53, 0.20 and 0.28 for H₈, MeₐA and MeᵦB respectively) and an NOE is observed between Meₐ and pyrazole proton Hg′. In contrast, in the ΔS isomer, the isopropyl chemical shifts are more normal (δ 2.01, 0.89 and 0.33 for H₈, Meₐ and
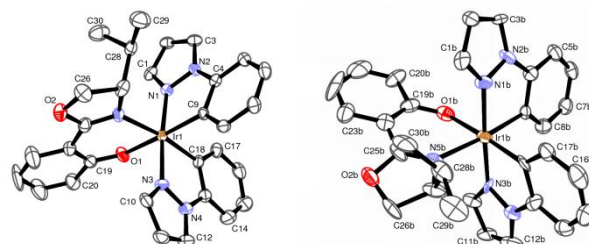

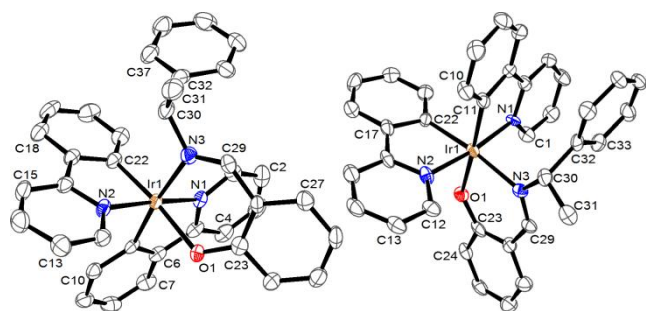Fig 2 X-ray structures of ΛS-**1a** (left) andΔS-**1a** (right).

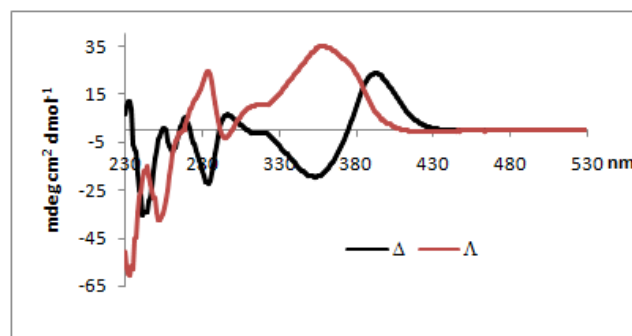Fig 3 X-ray structures of ΛS-**2b** (left)and ΔS-**2b**(right)

Fig 4 CD spectra of ΔS and ΛS-**1a**

Me$_B$ respectively). However, protons H$_5$ and H$_7$ [δ 3.76 (H$_5$) and 3.04 (H$_7$)] are now affected by a ring current of a ppz and so are at higher field than in the ΛS isomer [*ca.* δ 4.3 (H$_5$) and 3.93 (H$_7$)]. The compounds are chiral with a specific rotation in CHCl$_3$, of +582° for the ΛS isomer compared to -593° for the ΔS isomer; these are much higher than the free ligand (-29° in CHCl$_3$). This suggests that the chirality imposed by the metal has a bigger effect on the specific rotation than the chirality at the carbon of the ligand.

A similar reaction of (S)-Na(L1) with [Ir(ppy)$_2$Cl]$_2$ gave **1b** as a 1:1 mixture of diastereomers. In this case both diastereomers crystallised from the same solvent mixture but the crystals could be separated by hand picking due to a significant variation in colour and shape. Partial separation was also achieved by column chromatography over alumina, providing a pure fraction of the ΛS isomer which was characterised by X-ray crystallography (ESI Fig S2). The ^{1}H and ^{13}C-{^{1}H} NMR spectra of **1b** are similar to those of **1a**.

Using a similar procedure, chiral imine (S)-Na(L2)[15] reacted with dimers **a, b** to form compounds **2a, b,** each as a 1:1 ratio of diastereomers, (ΔS and ΛS), in good combined yield (>75%). For **2a** crystallisation from methanol gave pure ΔS-**2a**, the mother liquors being significantly enriched in ΛS-**2a**. For **2b** both diastereomers crystallised together but they could be separated by hand-picking due to a significant variation in colour and shape of the crystals.

The crystal structures[16] of ΛS- and ΔS-**2b** are shown in Fig. 3; (that of ΔS-**2a** is in Fig S3). In complexes **2** there is free rotation about the N-CH(Me)Ph bond of the ligand which can alleviate steric congestion. In ΔS-**2b**, the salicylimine fragment is almost planar and the phenyl substituent [C(32)-C(37)] and ppy [C(1)-C(11) including N(1)] are in a face to face orientation (a similar interaction is present in ΔS-**2a**). In ΛS-**2b** (Fig 3 left) there is some distortion of the imine, the N is 0.34 Å out of the best plane of the rest of the salicylimine and the N^O chelate angle is smaller, at 85.90(11)°, than in the ΔS isomer, 88.50(19)°.

The optical properties of the complexes were investigated *via* circular dichroism. Where the ΔS and ΛS-isomers were obtained pure, **1a** (Fig 4) and **2b** (Fig S4) the CD spectra are almost mirror images suggesting that the configuration at the metal is the dominant factor in the appearance of the spectra.

To our knowledge there are no studies on the stability of chirality at the metal in complexes of the type [Ir(C^N)$_2$(X^Y)]. The lack of diastereoselectivity in the syntheses and the fact that solutions of single diastereomers show no epimerisation (by ^{1}H NMR spectroscopy) over several days suggests that chirality at the metal is stable at room temperature. To investigate this further

a sample of ΔS**2a** was heated in DMSO-d$_6$ and no epimerisation took place up to 120 °C. Similarly a mixture of ΔS-**2b**:ΛS-**2b** (1:1.4) showed no change in ratio by ^{1}H NMR spectroscopy when heated to 120 °C in DMSO-d$_6$. Therefore we conclude that the chirality is stable up to 120 °C. This is consistent with conversion of *mer* to *fac* isomers of [Ir(ppy)$_3$] requiring heating to > 200 °C.[17] The previous reports of non-equal ratio of diastereomers with amino acidates[5, 8] and phenol oxazolines[6] may reflect difficulties in isolation by column chromatography rather than an intrinsic diastereoselectivity.

Having separated single diastereomers the next step was to remove the X^Y ligand by protonation without racemisation at the metal. Bubbling HCl gas through a dichloromethane solution of ΔS-**2a** led to formation of [Ir(ppz)$_2$Cl]$_2$. However when this was reacted with (S)-Na(L2) **2a** was reformed as a 1.3:1 ΔS:ΛS mixture of diastereomers showing some racemisation had occurred.[18] Hence a milder acid treatment was used; ΔS-**2a** was reacted with TFA in a biphasic mixture of DCM:H$_2$O (1:1) at room temperature for 48 hrs. Monitoring the reaction by ^{1}H NMR spectroscopy showed a spectrum very similar to that of [Ir(ppz)$_2$Cl]$_2$. The FAB mass spectrum showed an ion at *m/z* 1071 corresponding to [Ir$_2$(ppz)$_4$(CF$_3$CO$_2$)]$^+$ hence the product is proposed to be ΛΛ-[Ir(ppz)$_2$(CF$_3$CO$_2$)]$_2$ **3a**.[19] To determine the chirality at the metal centre, **3a** was reacted separately with (S)-Na(L1) and (S)-Na(L2) which gave ΔS-**1a** and ΔS-**2a** respectively, in good yields (>70%). In each case the ΔS-diastereomer was formed, and the ΛS isomer was hardly detectable by ^{1}H NMR spectroscopy (< 2%) in either case. Thus, the overall process of removal of the original chiral ligand and replacement with a second ligand occurred with complete retention of configuration at the metal with no significant racemisation.

To make the process more efficient we combined removal of the chiral auxiliary and coordination of a new ligand. Thus, ΔS-**2a** was reacted with TFA in the presence of bipy to form Δ-[Ir(ppz)$_2$(bipy)][CF$_3$CO$_2$] **4a** in which the only chirality is at the metal, in 72% yield. Using a similar procedure Λ-**4a** was synthesised from ΛS-**1a** via ΛΛ-**3a**. Thus the two enantiomers of **4a** were synthesised independently from two different precursors. The enantiomeric excesses of Δ-**4a** and Λ-**4a** were assessed by ^{1}H NMR spectroscopy in the presence of Δ [Bu$_4$N][trisphat].[20] The spectra (see Fig 5) show very high enantiopurity, in both cases the minor isomer is not observed. The enantiopurity of Λ-**4a** was also checked by HPLC (see ESI) and. was found to be >98% ee. The CD spectra of the two enantiomers are mirror images (see ESI).
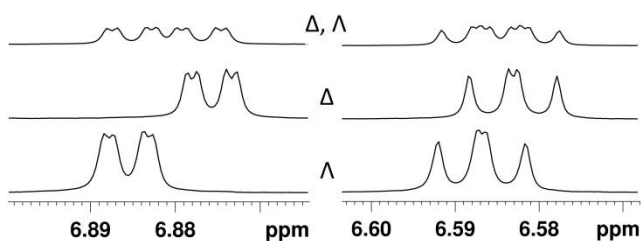
Fig 5 Selected parts of 1H NMR spectra of **4a**, racemic (top), Δ (middle) and Λ (bottom)

Conclusions

Diastereomeric complexes [Ir(C^N)₂(X^Y)] **1a, b** and **2a, b** are easily prepared as a 1:1 ratio of diastereomers. In all cases at least one diastereomer can be obtained pure by crystallisation. The chirality at the metal is stable in solution up to 120 °C. The X^Y ligands can be easily removed from the metal by treatment with TFA to give a homochiral dimer which can be used to make homochiral complex Δ- or Λ- [Ir(ppz)₂(bipy)][CF₃CO₂] **4a** which is only chiral at the metal. The use of an appropriate strength acid is crucial since, unlike corresponding [Ru(bipy)₃]²⁺ derivatives the chirality is not stable to moderately strong acid. This work will pave the way for the use of enantiopure Ir(III) complexes in many fields such as DNA probes which have previously relied heavily on Ru(II) polypyridine complexes.

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12. L1 was synthesised from l-valinol and L2 from 1-phenylethylamine, both of 98% optical purity. The optical rotation of the ligands was checked against the literature values and was the same within 0.5%

13. Crystal data for Λ-1a: C30H28IrN5O2•0.5C6H14, M = 725.86, hexagonal, a = 19.805(7) Å, b = 19.805(7) Å, c = 12.370(6) Å, α = 90.00°, β = 90.00°, γ = 120.00°, V = 4202(3) Å3, T = 150(2) K, space group P6(5), Z = 6, 35447 reflections measured, 6093 independent reflections (Rint = 0.0719). The final R1 values were 0.0292 (I > 2σ(I)). The final wR(F2) values were 0.0586 (I > 2σ(I)). The final R1 values were 0.0336 (all data). The final wR(F2) values were 0.0595 (all data). Flack parameter = 0.013(7).

Crystal data for Δ-1a: C30H28IrN5O•H2O, M = 700.79, monoclinic, a = 9.286(5) Å, b = 27.646(16) Å, c = 16.326(9) Å, α = 90.00°, β = 94.865(10)°, γ = 90.00°, V = 4176(4) Å3, T = 150(2) K, space group P2(1), Z = 6, 32410 reflections measured, 16038 independent reflections (Rint = 0.1149). The final R1 values were 0.0681 (I > 2σ(I)). The final wR(F2) values were 0.1225 (I > 2σ(I)). The final R1 values were 0.0970 (all data). The final wR(F2) values were 0.1319 (all data). Flack parameter = 0.007(10).
In all cases the Flack parameter was close to zero showing the assignment of chirality at the metal is correct.

14. The Δ-isomer shows three independent molecules in the unit cell. Isomer b is shown in the figure.

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16. Crystal data for Λ-2b: C37H30IrN3O, M = 724.84, orthorhombic, a = 8.1790(18) Å, b = 12.986(3) Å, c = 27.068(6) Å, α = 90.00°, β = 90.00°, γ = 90.00°, V = 2875.0(11) Å3, T = 150(2) K, space group P2(1)2(1)2(1), Z = 4, 23997 reflections measured, 6235 independent reflections (Rint = 0.0382). The final R1 values were 0.0239 (I > 2σ(I)). The final wR(F2) values were 0.0498 (I > 2σ(I)). The final R1 values were 0.0288 (all data). The final wR(F2) values were 0.0511 (all data). Flack parameter = 0.002(6).
Crystal data for Δ-2b: (C37H30IrN3O)2.5(CH4O), M = 804.95, orthorhombic, a = 9.541(2) Å, b = 12.508(3) Å, c = 28.060(7) Å, α = 90.00°, β = 90.00°, γ = 90.00°, V = 3348.8(14) Å3, T = 150(2) K, space group P2(1)2(1)2(1), Z = 4, 25945 reflections measured, 6587 independent reflections (Rint = 0.0471). The final R1 values were 0.0398 (I > 2σ(I)). The final wR(F2) values were 0.0832 (I > 2σ(I)). The final R1 values were 0.0428 (all data). The final wR(F2) values were 0.0841 (all data). Flack parameter = 0.026(10).

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