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

David L. Davies,* Kuldip Singh, Shalini Singh and Barbara Villa-Marcos

Cite this: *Chem. Commun.*, 2013, **49**, 6546Received 26th April 2013,
Accepted 5th June 2013

DOI: 10.1039/c3cc43121e

www.rsc.org/chemcomm

Reaction of $[\text{Ir}(\text{C}^*\text{N})_2\text{Cl}]_2$ with chiral bidentate N^*OH ligands provides complexes $[\text{Ir}(\text{C}^*\text{N})_2(\text{N}^*\text{O})]$ as a 1 : 1 mixture of diastereomers which can be separated by crystallisation. A pure diastereomer can be converted to $[\text{Ir}(\text{C}^*\text{N})_2(\text{bipy})][\text{CF}_3\text{CO}_2]$ with complete retention of stereochemistry at the metal.

Complexes of the type $[\text{Ir}(\text{C}^*\text{N})_2(\text{X}^*\text{Y})]$ usually occur as a single geometric isomer, with *cis* carbon atoms and *trans* nitrogen atoms of the cyclometallated ligand.¹ The complexes have a stereogenic metal centre and exist as a mixture of Λ and Δ enantiomers. However, unlike $[\text{Ru}(\text{bipy})_3]^{2+}$ 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 $[\text{Ir}(\text{ppy})_3]$ (Hppy = phenylpyridine) was reported in 2007,³ and of $[\text{Ir}(\text{ppy-R})_2(\text{acac})]$ (R = F, OMe, Ph) in 2008.⁴ Single diastereomers have been isolated *e.g.* $[\text{Ir}(\text{C}^*\text{N}^*)_3]$ and $[\text{Ir}(\text{C}^*\text{N}^*)_2(\text{acac})]$ with enantiopure cyclometallating ligands,⁷ or $[\text{Ir}(\text{C}^*\text{N})_2(\text{X}^*\text{Y}^*)]$ (X^*Y^* = amino acidate,^{5,8,9} phenol oxazoline⁶) 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 $[\text{Ir}(\text{C}^*\text{N})_2(\text{X}^*\text{Y}^*)]$, 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 $[\text{Ir}(\text{ppz})_2\text{Cl}]_2$ (**a**, Hppz = phenylpyrazole) was reacted with 2.2 equiv. of $(S)\text{-Na}(\text{L1})$ ^{11,12} in a mixture of DCM–methanol (2 : 1) at room temperature for 2–4 hours, to give **1a** as a (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 $(S)\text{-Na}(\text{L1})$ 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 crystallography¹³ and the structures of ΔS - and ΛS -**1a** are shown in Fig. 1.¹⁴ 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. 1, left), whereas the other isomer shows a Δ configuration (Fig. 1, right). The change in chirality at the metal leads to different orientations of **L1** with respect to the

Fig. 1 X-ray structures of ΔS -**1a** (left) and ΛS -**1a** (right).

Department of Chemistry, University of Leicester, Leicester LE1 7RH, UK.

E-mail: dld3@le.ac.uk; Fax: +44 (0)116-2523789; Tel: +44 (0)116-2522092

† Electronic supplementary information (ESI) available: Synthetic procedures and characterization data for **1a**, **b**, **2a**, **b** and **3a** and cif files for ΔS - and ΛS -**1a**, ΔS -**1b**, ΔS -**2a**, ΔS - and ΔS -**2b**. CCDC 922561–922566. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3cc43121e

Fig. 2 X-ray structures of **2a** (left) and **2b** (right).

[Ir(C[^]N)₂] fragment. In the *ΔS* 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. 1, right). Thus, in the *ΔS* 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 *ΔS*-**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 H_B, Me_A and Me_B respectively) and an NOE is observed between Me_A and pyrazole proton H_G. In contrast, in the *ΔS* isomer, the isopropyl chemical shifts are more normal (δ 2.01, 0.89 and 0.33 for H_B, Me_A and Me_B respectively). However, protons H₅ and H₇ [δ 3.76 (H₅) and 3.04 (H₇)] are now affected by a ring current of a ppz and so are at higher field than in the *ΔS* isomer [*ca.* δ 4.3 (H₅) and 3.93 (H₇)]. The compounds are chiral with a specific rotation in CHCl₃, of +582° for the *ΔS* isomer compared to –593° for the *ΔS* isomer; these are much higher than the free ligand (–29° in CHCl₃). 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(ppz)₂Cl]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 *ΔS* isomer which was characterised by X-ray crystallography (ESI,[†] Fig. S2). The ¹H and ¹³C-{¹H} 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 *ΔS*), in good combined yield (>75%). For **2a** crystallisation from methanol gave pure *ΔS*-**2a**, the mother liquors being significantly enriched in *ΔS*-**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 structures¹⁶ of *ΔS*- and *ΔS*-**2b** are shown in Fig. 2; (that of *ΔS*-**2a** is in Fig. S3, ESI[†]). In complexes **2** there is free

Fig. 3 CD spectra of **1a** and **2a**.

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 ppz [C(1)–C(11) including N(1)] are in a face to face orientation (a similar interaction is present in *ΔS*-**2a**). In *ΔS*-**2b** (Fig. 2, 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 *ΔS*-isomers were obtained pure, **1a** (Fig. 3) and **2b** (Fig. S4, ESI[†]) 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 ¹H 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** : *ΔS*-**2b** (1 : 1.4) showed no change in ratio by ¹H 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(ppz)₃] requiring heating to >200 °C.¹⁷ The previous reports of non-equal ratio of diastereomers with amino acidates^{5,8} and phenol oxazolines⁶ 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)₂Cl]₂. However when this was reacted with (*S*)-Na(L2) **2a** was reformed as a 1.3 : 1 *ΔS* : *ΔS* 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 : H₂O (1 : 1) at room temperature for 48 hours. Monitoring the reaction by ¹H NMR spectroscopy showed a spectrum very similar to that of [Ir(ppz)₂Cl]₂. The FAB mass spectrum showed an ion at *m/z* 1071 corresponding to [Ir₂(ppz)₄(CF₃CO₂)₂]⁺ hence the product is proposed to be *ΔΔ*-[Ir(ppz)₂(CF₃CO₂)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

Fig. 4 Selected parts of ^1H NMR spectra of **4a**, racemic (top), Δ (middle) and Λ (bottom).

was formed, and the ΛS isomer was hardly detectable by ^1H 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)][CF₃CO₂]**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 $\Lambda\Lambda$ -**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 ^1H NMR spectroscopy in the presence of Δ -[Bu₄N][trisphat].²⁰ The spectra (see Fig. 4) 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[†]).

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.

The authors thank the University of Leicester for funding, Johnson Matthey for a loan of IrCl₃, Chiral Technologies Europe technical team for the chiral HPLC analysis and referees for helpful suggestions on how to measure the enantiomeric excess.

Notes and references

- For exceptions see, J. M. Fernández-Hernández, C.-H. Yang, J. I. Beltrán, V. Lemaire, F. Polo, R. Fröhlich, J. Cornil and L. De Cola, *J. Am. Chem. Soc.*, 2011, **133**, 10543–10558; J.-Y. Hung, Y. Chi, I. H. Pai, Y.-C. Yu, G.-H. Lee, P.-T. Chou, K.-T. Wong, C.-C. Chen and C.-C. Wu, *Dalton Trans.*, 2009, 6472–6475; E. Baranoff, S. Suárez, P. Bugnon, C. Barolo, R. Buscaino, R. Scopelliti, L. Zuppiroli, M. Graetzel and M. K. Nazeeruddin, *Inorg. Chem.*, 2008, **47**, 6575–6577.
- A. Auffrant, A. Barbieri, F. Barigelli, J. Lacour, P. Mobian, J. P. Collin, J. P. Sauvage and B. Ventura, *Inorg. Chem.*, 2007, **46**, 6911–6919.

- X. M. Chen, Y. Okamoto, T. Yano and J. Otsuki, *J. Sep. Sci.*, 2007, **30**, 713–716.
- F. J. Coughlin, M. S. Westrol, K. D. Oyler, N. Byrne, C. Kraml, E. Zysman-Colman, M. S. Lowry and S. Bernhard, *Inorg. Chem.*, 2008, **47**, 2039–2048.
- O. Chepelin, J. Ujma, X. Wu, A. M. Z. Slawin, M. B. Pitak, S. J. Coles, J. Michel, A. C. Jones, P. E. Barran and P. J. Lusby, *J. Am. Chem. Soc.*, 2012, **134**, 19334–19337.
- E. Marchi, R. Sinisi, G. Bergamini, M. Tragni, M. Monari, M. Bandini and P. Ceroni, *Chem.-Eur. J.*, 2012, **18**, 8765–8773.
- C. Schaffner-Hamann, A. von Zelewsky, A. Barbieri, F. Barigelli, G. Muller, J. P. Riehl and A. Neels, *J. Am. Chem. Soc.*, 2004, **126**, 9339–9348; L. R. Yang, A. von Zelewsky, H. P. Nguyen, G. Muller, G. Labat and H. Stoeckli-Evans, *Inorg. Chim. Acta*, 2009, **362**, 3853–3856.
- R. Urban, R. Krämer, S. Mihan, K. Polborn, B. Wagner and W. Beck, *J. Organomet. Chem.*, 1996, **517**, 191–200.
- M. Graf and K. Sünkel, *Inorg. Chim. Acta*, 2011, **371**, 42–46.
- L. Gong, S. P. Mulcahy, D. Devarajan, K. Harms, G. Frenking and E. Meggers, *Inorg. Chem.*, 2010, **49**, 7692–7699; L. Gong, S. P. Mulcahy, K. Harms and E. Meggers, *J. Am. Chem. Soc.*, 2009, **131**, 9602–9603; E. Meggers, *Chem.-Eur. J.*, 2010, **16**, 752–758.
- D. Franco, M. Gómez, F. Jiménez, G. Muller, M. Rocamora, M. A. Maestro and J. Mahía, *Organometallics*, 2004, **23**, 3197–3209.
- L1 was synthesised from L-valinol and L2 from S-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%.
- 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 *P*6(5), *Z* = 6, 35 447 reflections measured, 6093 independent reflections (*R*_{int} = 0.0719). The final *R*₁ values were 0.0292 (*I* > 2σ(*I*)). The final *wR*(*F*²) values were 0.0586 (*I* > 2σ(*I*)). The final *R*₁ values were 0.0336 (all data). The final *wR*(*F*²) 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 *P*2(1), *Z* = 6, 32 410 reflections measured, 16 038 independent reflections (*R*_{int} = 0.1149). The final *R*₁ values were 0.0681 (*I* > 2σ(*I*)). The final *wR*(*F*²) values were 0.1225 (*I* > 2σ(*I*)). The final *R*₁ values were 0.0970 (all data). The final *wR*(*F*²) 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.
- The Λ -isomer shows three independent molecules in the unit cell. Isomer **b** is shown in the figure.
- H. Nozaki, H. Takaya, S. Moriuti and R. Noyori, *Tetrahedron*, 1968, **24**, 3655–3669.
- 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 *P*2(1)2(1)2(1), *Z* = 4, 23 997 reflections measured, 6235 independent reflections (*R*_{int} = 0.0382). The final *R*₁ values were 0.0239 (*I* > 2σ(*I*)). The final *wR*(*F*²) values were 0.0498 (*I* > 2σ(*I*)). The final *R*₁ values were 0.0288 (all data). The final *wR*(*F*²) values were 0.0511 (all data). Flack parameter = 0.002(6). Crystal data for Δ -**2b**: (C₃₇H₃₀IrN₃O)·2.5(CH₃OH), *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 *P*2(1)2(1)2(1), *Z* = 4, 25 945 reflections measured, 6587 independent reflections (*R*_{int} = 0.0471). The final *R*₁ values were 0.0398 (*I* > 2σ(*I*)). The final *wR*(*F*²) values were 0.0832 (*I* > 2σ(*I*)). The final *R*₁ values were 0.0428 (all data). The final *wR*(*F*²) values were 0.0841 (all data). Flack parameter = 0.026(10).
- A. B. Tamayo, B. D. Alleyne, P. I. Djurovich, S. Lamansky, I. Tsyba, N. N. Ho, R. Bau and M. E. Thompson, *J. Am. Chem. Soc.*, 2003, **125**, 7377–7387; H.-C. Böttcher, M. Graf, H. Krüger and C. Wagner, *Inorg. Chem. Commun.*, 2005, **8**, 278–280.
- It is likely that cyclometallation is reversed by strong acid; *mer* to *fac* isomerisation of [Ir(C[^]N)₃] is known to be catalysed by phenol, see A. R. McDonald, M. Lutz, L. S. von Chranowski, G. P. M. van Klink, A. L. Spek and G. van Koten, *Inorg. Chem.*, 2008, **47**, 6681–6691.
- It could be a monomer with a chelating trifluoroacetate.
- J. Lacour, C. Ginglinger, C. Grivet and G. Bernardinelli, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 608–610; M. Brissard, M. Gruselle, B. Malézieux, R. Thouvenot, C. Guyard-Duhayon and O. Convert, *Eur. J. Inorg. Chem.*, 2001, 1745–1751.