N,O- vs N,C-Chelation in Half-Sandwich Iridium Complexes: A Dramatic Effect on Enantioselectivity in Asymmetric Transfer Hydrogenation of Ketones

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ABSTRACT: Cyclometalation of [Cp*IrCl$_2$]$_2$ with methyl (S)-2-phenyl-4,5-dihydrooxazole-4-carboxylate in the presence of NaOAc selectively led to a N,C- or N,O-chelated Cp*Ir(III) complex, depending on whether or not water was present in the reaction. Whilst derived from the same precursor, these two complexes behaved in a dramatically different manner in asymmetric transfer hydrogenation (ATH) of ketones by formic acid, with the N,O-chelated complex being much more selective and active. The sense of asymmetric induction is also different, with the N,O-complex affording S whilst the N,C-analogue R alcohols. Further study revealed that the nature of the base additive impacts considerably on the enantioselectivity and the effective HCOOH/amine ratios. These observations show the importance of ligand coordination mode and using the right base for ATH reactions.

KEYWORDS: N,O-chelation, N,C-chelation, half-sandwich iridium complexes, cyclometalation, asymmetric transfer hydrogenation

N,C-Chelated half-sandwich iridium complexes of type **1** have received a great deal of attention in the past decade, finding numerous applications in catalysis among others (Figure 1).[1] In 2008, Ikariya and co-workers reported that complex **2** catalyzes the aerobic oxidation of alcohols.[2] When the metalacycle was made chiral with a simple chiral amine, oxidative kinetic resolution of racemic alcohols was shown to be feasible. In the same year, Pfeffer, Janssen, Feringa, de Vries et al found that complex **3** with a simple amine ligand is a good catalyst for racemization of alcohols.[3] In 2009, Crabtree and co-workers disclosed complex **4** with 2-phenylpyridine as a ligand for water oxidation.[4] In 2010, one of our groups demonstrated that the ketimine-ligated complexes **5** are powerful catalysts for the reductive amination of a wide variety of carbonyl compounds.[5] The following years have witnessed flourishing applications of half-sandwich cyclometalated iridium complexes in catalysis, including hydrogenation, reductive amination, dehydrogenation, oxidation, alkylation, racemisation, hydrosilylation, hydroamination, polymerization and related reactions.[1,6]

The somewhat related N,O-chelated half-sandwich

complexes of iridium derived from α- and β-aminoacids, 2-pyridylacetic acid, picolinic acid, or even peptide ligands have been known for decades.[7] They have,
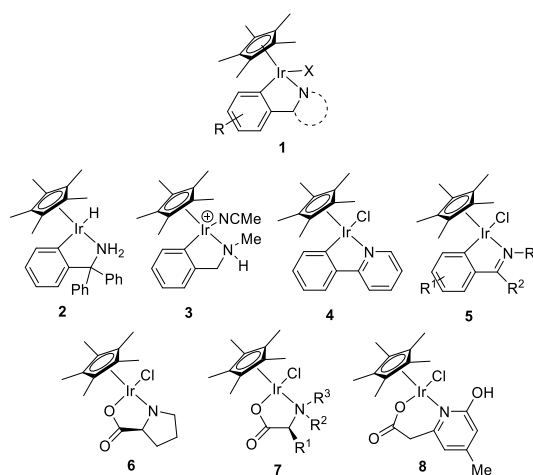
Figure 1. Selected examples of N,C- and N,O-chelated half-sandwich iridium complexes.

however, only scarcely been used in catalysis. Examples are found in the α-aminoacid derived N,O-chelated complex **6** which catalyzes ATH of ketones[7n] and complex **7** as a highly reactive and selective catalyst for the alkylation of amines with alcohols.[7p] The iridium complex **8** bearing a 2-pyridylacetic acid-derived ligand is an efficient catalyst for the dehydrogenation of alcohols.[7o]
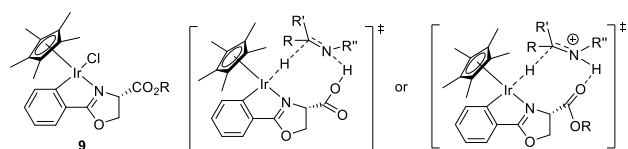
Figure 2. Target catalyst and proposed mode of asymmetric reduction of imines involving secondary interactions.

In continuing our exploration of N,C-chelated iridium complexes in catalysis,[1d] we targeted a simple chiral complex **9**, anticipating that it might enable asymmetric reduction of imines. The imino substrate could be activated by the carboxylic acid (R = H) or the ester (R = alkyl) via hydrogen bonding and thereby positioned, facilitating enantioselective hydride transfer as illustrated in Figure 2.[8] The outcome of our endeavor is, however, totally unexpected. The oxazoline ligand was found to form, surprisingly, either a N,C- or a N,O-chelated half-sandwich Ir(III)-complex and remarkably, this mode of chelation has a dramatic effect on the enantioselectivity of the Cp*Ir(III) complex-catalyzed ATH of ketones. Whilst both N,C- and N,O-chelated half-sandwich complexes have been well documented in the literature, little is known of how the difference in the coordination mode of the ligand may affect their catalytic activity and selectivity.

Cyclometalation through C–H activation is a well-established method for the synthesis of transition metal complexes bearing η^2-C,X (X = C, N, O) ligands.[1] According to a general procedure for the preparation of cyclometalated complexes,[5,9] methyl (S)-2-phenyl-4,5-dihydrooxazole-4-carboxylate **10** was reacted with [Cp*IrCl₂]₂ at room temperature in the presence of anhydrous NaOAc. The reaction afforded a mixture of two half-sandwich Cp*Ir(III) complexes, the expected N,C-chelated complex **11a** and an "abnormal" N,O-chelated complex **11b**, in a ratio of **11a:11b** = 1:3.5 (entry 1, Table 1). Delightfully, the ratio of **11a** to **11b** was found to be variable with the amount of water in the solvent. Thus, when CH₂Cl₂ dried over CaH₂ was used, the ratio of **11a** increased with **11a:11b** = 1:1 (entry 2, Table 1), and introducing 4 Å molecular sieves to this reaction afforded the N,C-chelated complex **11a** as the sole product (entry 3, Table 1). In sharp contrast, using wet CH₂Cl₂ led to the exclusive formation of the N,O-chelated complex **11b** (entry 4, Table 1). Most likely, **11b** is formed via initial coordination of the ester moiety to the Lewis acidic Ir(III) center followed by hydrolysis with water, as illustrated in Table 1. In the absence of an ester group, cyclometalation takes place with or without

Table 1. Synthesis of cyclometalated Cp*Ir(III) complexes **11a** and **11b**.[a]

Entry	Solvent	Additive	Yield (%)[b]	11a:11b[c]
1	CH₂Cl₂[d]	no	94	1:3.5
2	Dried CH₂Cl₂[e]	no	92	1:1
3	Dried CH₂Cl₂[e]	4 Å MS (50 mg/mL)	89	>99:1
4	CH₂Cl₂[d]	H₂O (2%, v/v)	97	<1:99

[a]Conditions: ligand (0.49 mmol), [Cp*IrCl₂]₂ (0.22 mmol), NaOAc (4.9 mmol), DCM (10 mL), rt, 24 h. [b]Isolated yield. [c]Product ratio determined by ¹H NMR of the crude reaction mixture. [d]Used as received. [e]Dried over CaH₂.
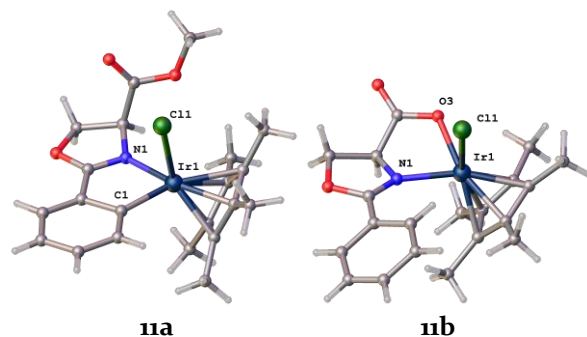
Figure 3. Molecular structures of **11a** and **11b** determined by single crystal X-ray diffraction. **11a**: selected bond distances (Å): Ir1-Cl1 2.4138(10); Ir1-N1 2.078(5); Ir1-C1 2.056(6); Ir1-avgC(Cp*) 2.189(15). Selected bond angles (°): N1-Ir1-Cl1 87.47(15); C1-Ir1-Cl1 86.84(18); C1-Ir1-N1 77.7(3). **11b**: solvent omitted for clarity; selected bond distances (Å): Ir1-Cl1 2.404(2); Ir1-O3 2.152(7); Ir1-N1 2.092(8); Ir1-avgC(Cp*) 2.142(23). Selected bond angles (°): O3-Ir1-Cl1: 83.6(2); N1-Ir1-Cl1 88.3(3); N1-Ir1-O3 77.0(2).
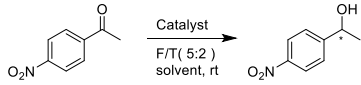
water (See Section 8 of the SI). Both **11a** and **11b** are air-stable complexes. Attempts to convert one to the other under various conditions, e.g. by adding an acid or a base or raising the temperature, have not been successful. The structures of **11a** and **11b** were determined by single crystal X-ray diffraction and are shown in Figure 3.

Pure **11b** exists in solution as a mixture of two diastereomers (ratio of 9.8:1) due to the presence of chiral centers at iridium and the ligand. ¹H NMR monitoring of the freshly prepared solution of **11b** in dry CDCl₃ or CD₃OD in the −50 to +40 °C range indicated that the diastereomeric ratio does not change noticeably with varying of the temperature or solvent even after 24 h. No changes in the diastereomeric ratio was also observed

upon addition of [Bu$_4$N]Br or [Bu$_4$N]I (5 equivs). Prolonged heating of the mixture with [Bu$_4$N]Br or [Bu$_4$N]I (40 °C, longer than 1 h) resulted in the gradual change of the solution color from orange to red, indicating presumably the replacement of the chloride with Br or I. Addition of an excess amount of acetic acid (5 equivs) or a mixture of acetic acid and isopropylamine did not alter the structure of **11b** or its diastereomeric ratio either. Similarly, **11a** appears as a mixture of two diastereomers, the ratio of which is, however, considerably higher (>20:1), and addition of acetic acid and isopropylamine to a solution of **11a** in CDCl$_3$ brought about no notable effect, as shown by ^{1}H NMR (see Section 7 of the SI).

The fact that **11a** and **11b** differs mainly in the coordination mode of the chiral ligand prompted us to compare their ability of catalyzing ATH reactions.[10] Firstly, we tested the catalytic performance of **11a** and **11b** in the ATH of ketones, choosing the reduction of *p*-nitroacetophenone as a model reaction. As can be seen from Table 2, in the presence of 1% of **11a** or **11b** *p*-nitroacetophenone could be reduced by using an azeotropic mixture of formic acid/triethylamine (F/T) in CH$_2$Cl$_2$ at room temperature. The outcome is remarkably different, however. Thus, whilst the N,C-chelated **11a** showed a very low catalytic activity (75% conversion in 15 h) and extremely low enantioselectivity (4% ee), the N,O-analogue **11b** was much more active and enantioselective (100% conversion in 2 h, 73% ee). Of further notice is that the configuration of the products obtained with **11a** and **11b** is opposite. This sharp difference was repeated in other solvents as well,

**Table 2.** Comparison of ATH of p-nitroacetophenone under various conditions.^{a}

Entry	Catalyst	Solvent	Time (h)	Conversion (%)^b	Ee (%)^c
1	**11a**	CH$_2$Cl$_2$	15	75	4 (R)
2	**11b**	CH$_2$Cl$_2$	2	100	73 (S)
3^d	**11a**	F/T	15	61	2 (R)
4^d	**11b**	F/T	15	96	38 (S)
5	**11a**	MeOH	15	80	4 (R)
6	**11b**	MeOH	15	97	53 (S)
7	**11a**	*i*PrOH	15	71	2 (R)
8	**11b**	*i*PrOH	15	99	40 (S)
9	**11a**	toluene	15	42	2 (R)
10	**11b**	toluene	15	100	42 (S)
11	**11a**	H$_2$O	15	54	3 (R)
12	**11b**	H$_2$O	15	85	27 (S)
13^e	**11a**	aq. solution of HCO$_2$H/HCO$_2$Na	15	58	0
14^e	**11b**	aq. solution of HCO$_2$H/HCO$_2$Na	15	100	37 (S)

^{a}Conditions: substrate (0.2 mmol), catalyst (0.002 mmol), azeotropic F/T solution (0.5 mL), solvent (2 mL), room temperature. ^{b}Determined by ^{1}H NMR of the crude reaction mixture. ^{c}Determined by HPLC. ^{d}Azeotropic F/T solution (2.5 mL) was used with no additional solvent. ^{e}Aqueous formate solution used (pH 4.5).

reinforcing the contrast brought about by a simple change in ligand coordination mode and the superiority of the N,O-chelated **11b** (entries 5-14, Table 2). The best enantioselectivity was observed in CH$_2$Cl$_2$ with **11b**. These observations suggest that although **11a** and **11b** bear chiral ligands of similar original structure, the differing coordination mode of the ligands impacts on the mechanism of how they effect the ATH and particularly on the step of hydride transfer, where the enantioselectivity is likely to be determined.

Bearing in mind that ratio of F/T may affect the enantioselectivity of ATH of ketones[11], we also examined the effect of this parameter on the ATH with the more effective catalyst **11b**. As shown in Figure 4, the F/T ratio indeed impacts on the ee of the ATH in question, with the highest ee observed in a narrow widow of ca 2.5-3. More interestingly, variation of the nature of the amine used brought about a hitherto little-noticed finding, i.e. *both the nature of the amine and its ratio with HCOOH affect considerably the enantioselectivity of the ATH*. Among the tested amines, the HCO$_2$H-*i*PrNH$_2$ (2:1) mixture gave the highest enantioselectivity, with a significantly widened window of effective HCOOH/amine ratios. Whilst the reason for the varying effect of amines on the ee is not entirely clear at the moment, the observation calls for attention when examining other catalysts for ATH reactions with formic acid, where NEt$_3$ has been used as a base almost exclusively in the past decades.[10a-d,g-n]
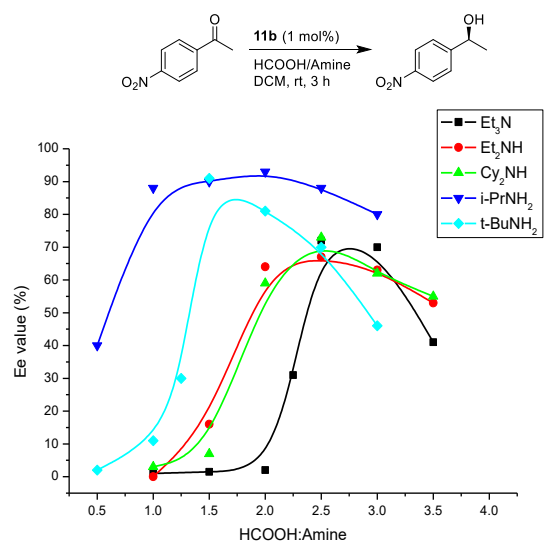
Figure 4. Effect of amines and the molar ratio of HCOOH/amine on the enantioselectivity of the ATH with catalyst **11b**. Conditions: *p*-nitroacetophenone (0.2 mmol), catalyst (0.002 mmol), HCOOH/amine solution (0.5 mL), DCM (2 mL), room temperature. The ee value was determined by HPLC.

Under the optimized conditions, we made further comparison of **11a** with **11b** in the ATH of acetophenones bearing either electron-donating or electron-withdrawing substituents on the aromatic (Table 3). As with the reduction using an azeotropic

Table 3. Comparison of ATH of aromatic ketones catalyzed by **11a** and **11b**[a]

| Entry	R	Catalyst	Conversion (%)[b]	Ee (%)[c]
1	H	**11a**	6	4 (R)
2	H	**11b**	23	98 (S)
3	o-OMe	**11a**	8	6 (R)
4	o-OMe	**11b**	20	93 (S)
5	p-OMe	**11a**	10	7 (R)
6	p-OMe	**11b**	23	92 (S)
7	p-Br	**11a**	20	3 (R)
8	p-Br	**11b**	65	99 (S)
9	p-NO₂	**11a**	30	5 (R)
10	p-NO₂	**11b**	100	93 (S)

[a]Conditions: substrate (0.2 mmol), catalyst (0.002 mmol), HCOOH/amine (2:1) solution (0.5 mL), DCM (2 mL), room temperature, 3 h. [b]Determined by ¹H NMR of the crude reaction mixture. [c]Determined by HPLC.
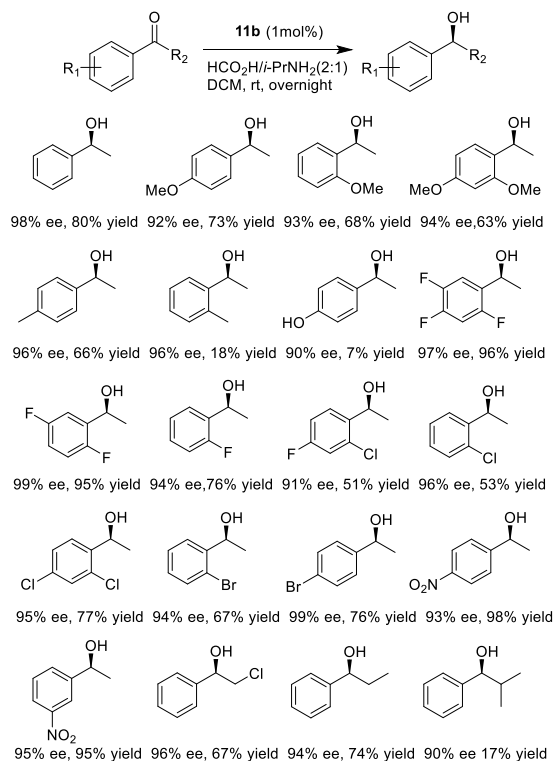
Figure 5. ATH of various aromatic ketones with complex **11b**. Isolated yields are given. For more details, see the SI.

mixture of F/T as hydrogen source, the **11b**-catalysed ATH of all four tested acetophenones with the HCO₂H-*i*PrNH₂ (2:1) mixture gave excellent enantioselectivity in each case (entries 2, 4, 6, 8 and 10, Table 3), whilst the performance of **11a** was much poorer (entries 1, 3, 5, 7 and 9, Table 3). These observations substantiate further the assertion that the coordination mode of ligands can exert significant effect on the activity and enantioselectivity of ATH reactions.

The scope of substrates was subsequently examined with complex **11b** using the HCO₂H-*i*PrNH₂ (2:1) mixture as hydrogen source (Figure 5). All aromatic ketones could be reduced with excellent enantioselectivities (90-99% ee). However, the catalyst shows a low activity towards acetophenones which bear highly electron-donating substituents or sterically more demanding ones, e.g. 4-hydroxyacetophenone and α-substituted acetophenones. We note that electron-rich ketones have been challenging for ATH catalysts in general, and only a few examples of ATH of hydroxyacetophenones are known.[12] Still disappointingly, neither **11b** nor **11a** was found to be enantioselective in the ATH of imines.
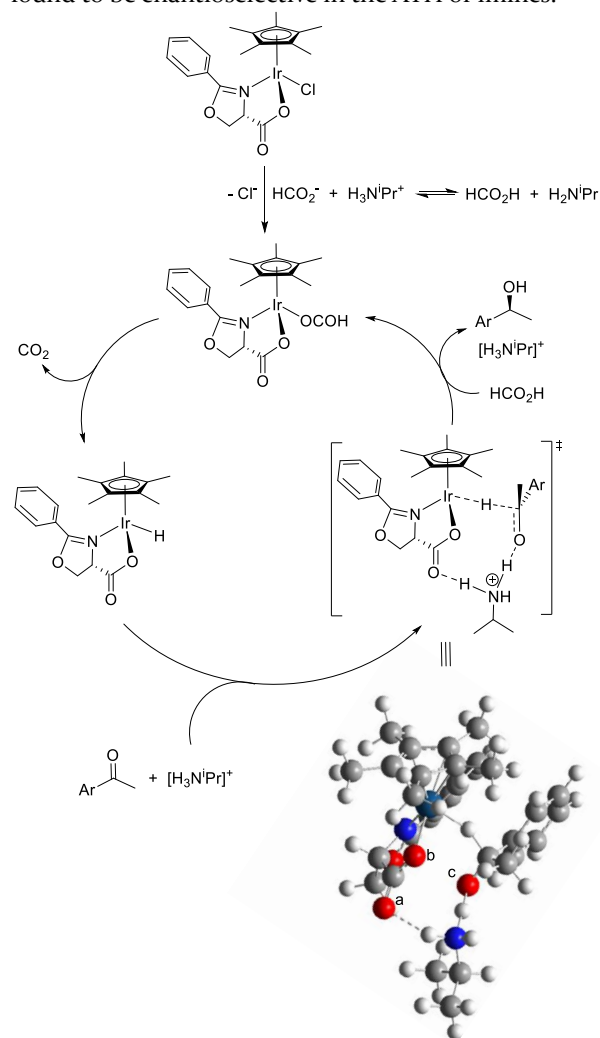
Figure 6. Suggested mechanism for the ATH of ketones with the N,O-chelated iridium complex. The ammonium cation may hydrogen bond with the N,O-ligand throughout the catalytic cycle. The suggested transition state of hydride transfer is supported by a DFT calculation (Ar = Ph. For details, see Section 13 of the SI).

A plausible mechanism for the **11b**-catalyzed ATH is shown in Figure 6. The steps leading to the iridium-hydride from **11b** would be expected to be similar to those proposed for the N,C-chelated iridacycles.[13] It is the hydride transfer step that sets this

catalyst apart from other N,O- or N,C-chelated iridium catalysts. We hypothesize that the ammonium cation participates in the transition state of this enantioselectivity-determining step, hydrogen-bonding both the N,O-ligand via its carboxylate oxygen and the ketone substrate through its carbonyl oxygen. Such a hydrogen bonding network would be expected to lower the barrier of the transition state and enhance the enantioselectivity of the hydride transfer. DFT modelling of the hydride-transfer step revealed that the isopropylammonium cation can indeed participate in the transition state and further showed, in line with the experiment, that it is the S alcohol that is to be favored ($\Delta\Delta G^{\neq}$ = 1.8 kcal/mol). As shown in Figure 6, the transition state of the hydride transfer involves two protons of the ammonium cation strongly hydrogen-bonding with the oxygen atom of the carboxylate ligand (a; O...H distance 1.92 Å) and the acetophenone oxygen (c; O...H distance 1.25 Å, indicating significant O-H bond formation) simultaneously. There also appear to be weaker interactions between these two protons and the ligand oxygen (b; 2.91, 2.90 Å, respectively) (See Section 13 of the SI for more details). The existence of the hydrogen bonding in question may not be unexpected, as ammonium cations are widely known to form moderately-strong hydrogen bonds with various carbonyl compounds.[14] In ATH reactions, ligand-induced hydrogen bonding has been well established since the pioneering work of Noyori and co-workers;[15] however, examples of hydrogen bonding enabled by carboxylate ligands are relatively rare.[16] The calculated transition state in Figure 6 also indicates why the nature of the ammonium cation affects significantly the enantioselectivity, with the cation directly involved in the enantioselectivity-determining step. What remains to be delineated is how the other cations, e.g. Et_3NH^+, participate in the transition state and thereby affect the ee, although primary ammonium cations appear to form stronger hydrogen bonds with ketones than tertiary ones.[14]

In summary, we have demonstrated that 1) a *N,C*- or a *N,O*-chelated half-sandwich Cp*Ir(III)-complex can be selectively prepared from the reaction of methyl (*S*)-2-phenyl-4,5-dihydrooxazole-4-carboxylate with [Cp*IrCl$_2$]$_2$ by simply changing the reaction conditions; 2) the mode of chelation has a dramatic effect on the enantioselectivity of the Cp*Ir(III) complex-catalyzed ATH of ketones; 3) The nature of the amine and its ratio with HCOOH significantly affect the enantioselectivity of the *N,O*-complex-catalyzed ATH reaction.

ASSOCIATED CONTENT

Supporting Information. The Supporting Information is available free of charge on the ACS Publication website at DOI: xxx-xxx
Experimental procedures and characterization data, ^{1}H and ^{13}C NMR spectra

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Notes
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