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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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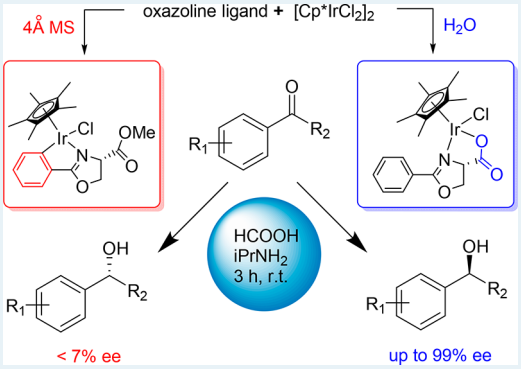
Supporting Information

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. While 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 while the N,C-analogue R alcohols. Further study revealed that the nature of the base additive considerably impacts 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

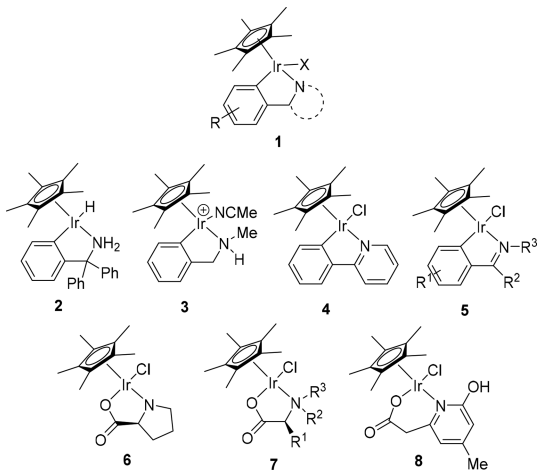


Figure 1. Selected examples of N,C- and N,O-chelated half-sandwich iridium complexes.

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-amino acids, 2-pyridylacetic acid, picolinic acid, or even peptide ligands have been known for decades.[7] However, they have only scarcely been used in catalysis. Examples are found in the α-amino-acid-derived N,O-chelated complex **6**, which catalyzes the asymmetric transfer hydrogenation (ATH) of ketones,[7n]

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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]

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] However, the outcome of

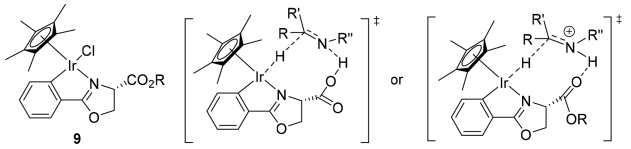


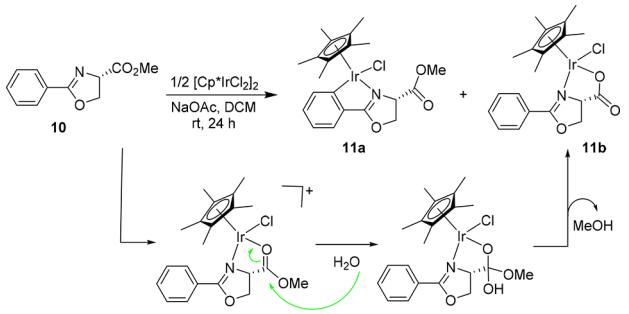
Figure 2. Target catalyst and proposed mode of asymmetric reduction of imines involving secondary interactions.

our endeavor is 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. While 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 $[Cp^*IrCl_2]_2$ 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 (Table 1, entry 1). Delightfully, the ratio of **11a** to **11b** was found to be variable with the amount of water in the solvent. Thus, when CH_2Cl_2 dried over CaH_2 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 CH_2Cl_2 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 occurs with or without water (See Section 8 in the Supporting Information (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), because of the presence of chiral centers at iridium and the ligand. ^{1}H NMR monitoring of the freshly prepared solution of **11b** in dry $CDCl_3$ or CD_3OD in the −50 °C to +40 °C range indicated that the diastereomeric ratio does not

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



entry	solvent	additive	yield[b] (%)	11a:11b[c]
1	CH_2Cl_2[d]	no	94	1:3.5
2	dried CH_2Cl_2[e]	no	92	1:1
3	dried CH_2Cl_2[e]	4 Å MS (50 mg/mL)	89	>99:1
4	CH_2Cl_2[d]	H_2O (2%, v/v)	97	<1:99

[a]Conditions: ligand (0.49 mmol), $[Cp^*IrCl_2]_2$ (0.22 mmol), NaOAc (4.9 mmol), DCM (10 mL), rt, 24 h. [b]Isolated yield. [c]Product ratio determined by ^{1}H NMR of the crude reaction mixture. [d]Used as received. [e]Dried over CaH_2.

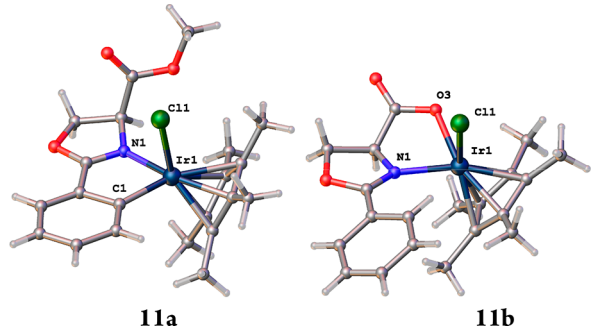


Figure 3. Molecular structures of **11a** and **11b** determined by single-crystal X-ray diffraction (XRD). For **11a**, the selected bond distances are as follows: Ir1−Cl1, 2.4138(10) Å; Ir1−N1, 2.078(5) Å; Ir1−C1, 2.056(6) Å; Ir1-avgC(Cp*), 2.189(15) Å. For **11a**, the selected bond angles are as follows: N1−Ir1−Cl1, 87.47(15)°; C1−Ir1−Cl1, 86.84(18)°; C1−Ir1−N1, 77.7(3)°. For **11b** (solvent omitted for clarity), the selected bond distances (Å) are as follows: Ir1−Cl1, 2.404(2) Å; Ir1−O3, 2.152(7) Å; Ir1−N1, 2.092(8) Å; Ir1-avgC(Cp*), 2.142(23) Å. For **11b** (solvent omitted for clarity), the selected bond angles (deg) are as follows: O3−Ir1−Cl1, 83.6(2)°; N1−Ir1−Cl1, 88.3(3)°; N1−Ir1−O3, 77.0(2)°.

change noticeably by varying the temperature or solvent, even after 24 h. No changes in the diastereomeric ratio were also observed upon the addition of $[Bu_4N]Br$ or $[Bu_4N]I$ (5 equivs). Prolonged heating of the mixture with $[Bu_4N]Br$ or $[Bu_4N]I$ (40 °C, longer than 1 h) resulted in the gradual change of the solution color from orange to red, presumably indicating the replacement of the chloride with Br or I. The 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, however, is 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 in the SI).

The fact that **11a** and **11b** differs mainly in the coordination mode of the chiral ligand prompted us to compare their ability

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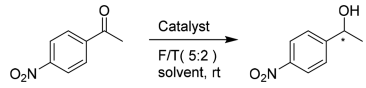
Table 2. Comparison of ATH of *p*-Nitroacetophenone under Various Conditions[a]



entry	catalyst	solvent	time (h)	conversion[b] (%)	enaniomeric excess, ee[c] (%)
1	**11a**	CH_2Cl_2	15	75	4 (*R*)
2	**11b**	CH_2Cl_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_2O	15	54	3 (*R*)
12	**11b**	H_2O	15	85	27 (*S*)
13[e]	**11a**	aq. solution of HCO_2H/HCO_2Na	15	58	0
14[e]	**11b**	aq. solution of HCO_2H/HCO_2Na	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).

of catalyzing ATH reactions.[10] First, 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_2Cl_2 at room temperature. However, the outcome is remarkably different. Thus, while 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, reinforcing the contrast brought about by a simple change in ligand coordination mode and the superiority of the N,O-chelated **11b** (Table 2, entries 5−14). The best enantioselectivity was observed in CH_2Cl_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 the mechanism of how they affect the ATH and, particularly, the step of hydride transfer, where the enantioselectivity is likely to be determined.

Bearing in mind that the 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 enaniomeric excess (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 considerably affect the enantioselectivity of the ATH*. Among the tested amines, the HCO_2H-*i*$PrNH_2$ (2:1) mixture gave the highest enantioselectivity, with a significantly widened window of effective HCOOH/amine ratios. While 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]

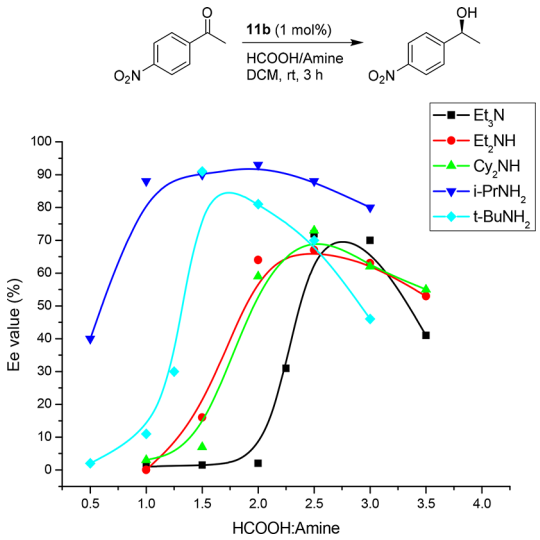


Figure 4. Effect of amines and the molar ratio of HCOOH/amine on the enantioselectivity of the ATH with catalyst **11b**. Conditions: *p*-nitroacetophenone (0.2 mmol), catalyst (0.002 mmol), HCOOH/amine solution (0.5 mL), DCM (2 mL), room temperature. The ee value was determined by high-performance liquid chromatography (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 ring (Table 3). As with the reduction using an azeotropic mixture of F/T as hydrogen source, the **11b**-catalyzed ATH of all four tested acetophenones with the HCO_2H−*i*$PrNH_2$ (2:1) mixture gave excellent enantioselectivity in each case (see Table 3, entries 2, 4, 6, 8, and 10), while the performance of **11a** was much poorer (Table 3, entries 1, 3, 5, 7, and 9). These observations substantiate further the assertion that the coordination mode of ligands can exert a significant effect on the activity and enantioselectivity of ATH reactions.

The scope of substrates was subsequently examined with complex **11b** using the HCO_2H-*i*$PrNH_2$ (2:1) mixture

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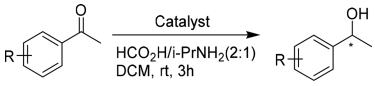
Table 3. Comparison of ATH of Aromatic Ketones Catalyzed by 11a and 11b[a]



entry	R	catalyst	conversion[b] (%)	enaniomeric excess, 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*-NO_2	**11a**	30	5 (R)
10	*p*-NO_2	**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 ^{1}H NMR of the crude reaction mixture. [c]Determined by HPLC.

as a hydrogen source (see Figure 5). All aromatic ketones could be reduced with excellent enantioselectivities (90%–99% ee). However, the catalyst shows a low activity toward acetophenones that 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.

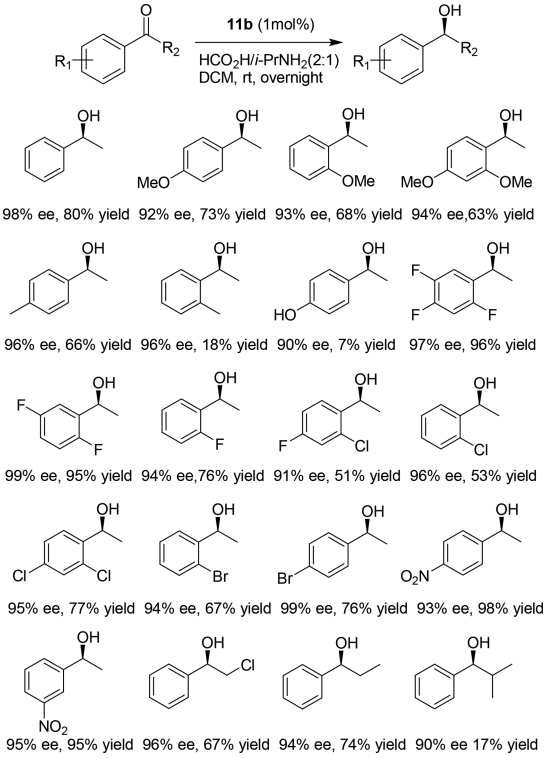


Figure 5. ATH of various aromatic ketones with complex **11b**. Isolated yields are given. For more details, see the SI.

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. Density functional theory (DFT) modeling of the hydride-transfer step revealed that the isopropylammonium cation can indeed participate in the transition state and further showed, consistent with the experiment, that it is the S alcohol that is to be favored ($\Delta\Delta G^{\ddagger}$ = 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)

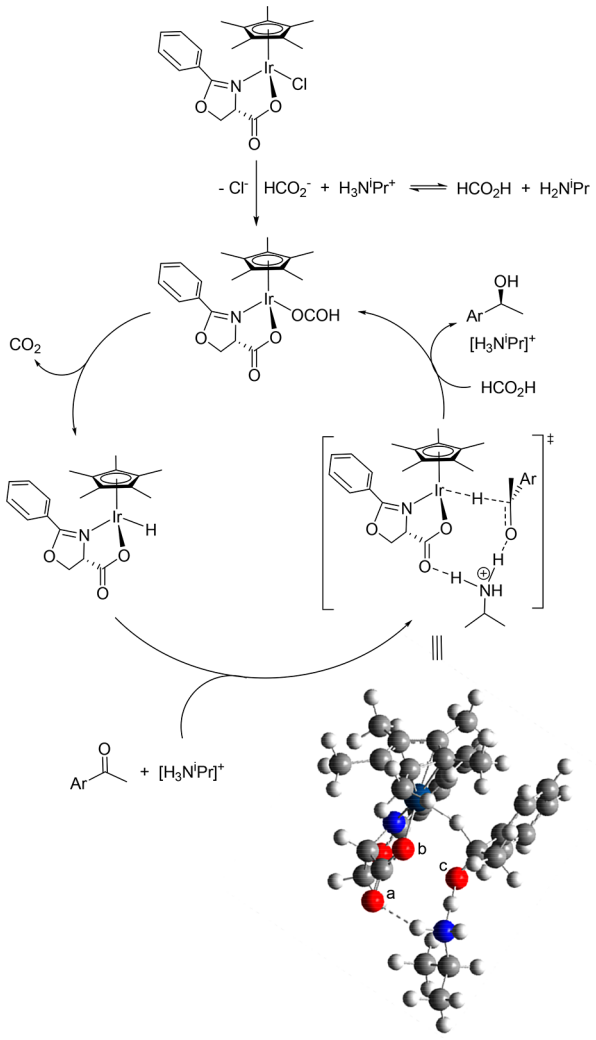


Figure 6. Suggested mechanism for the ATH of ketones with the N,O-chelated iridium complex. The ammonium cation may hydrogen bond with the N,O-ligand throughout the catalytic cycle. The suggested transition state of hydride transfer is supported by a DFT calculation. (Ar = Ph. For details, see Section 13 of the SI.)

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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 and 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 Hashiguchi;[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; and (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 Publications website at DOI: 10.1021/acscatal.8b02068.

Experimental procedures and characterization data, ^1H and ^{13}C NMR spectra, and HPLC traces (PDF)
Crystallographic information for $C_{21}H_{25}ClIrNO_3$ (CIF)
Crystallographic information for $C_{21}H_{25}Cl_3IrNO_3$ (CIF)

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Notes

The authors declare no competing financial interest.

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