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Scope and Mechanistic Studies of the Cationic Ir/Me-BIPAM-Catalyzed Asymmetric Intramolecular Direct Hydroarylation Reaction

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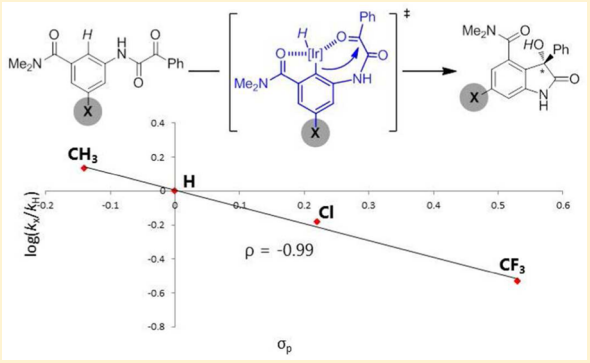
Supporting Information

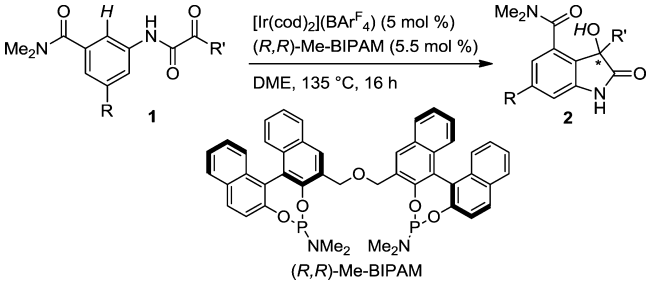
ABSTRACT: Results of mechanistic studies on asymmetric hydroarylation of α-keto amides via direct C−H bond addition to a carbonyl group catalyzed by a cationic Ir/Me-BIPAM complex are presented in this paper. A catalytic cycle involving C−H bond cleavage to give an Ar-[Ir]$^+$ intermediate, insertion of a carbonyl group into the aryl-iridium bond, giving iridium alkoxide, and finally reductive elimination to reproduce active [Ir]$^+$ species is proposed. The mechanistic insight for the iridium hydride species indicated that the C−H bond cleavage is caused in a reversible manner. Furthermore, the kinetic isotope effect was measured by product analysis of the reaction to compare H/D, and it was determined that k_H/k_D was 1.85. These experimental results suggest that the C−H bond cleavage step is not included in the turnover-limiting step. In addition, Hammett studies of substrates (ρ = −0.99) demonstrated that electron-donating groups at the *para* position to the reactive C−H bond accelerate the reaction rate. This linear relationship obtained in the Hammett plot indicates that the nucleophilicity of the aryl-iridium intermediate is an important factor in this reaction. All of the data indicate that carbonyl insertion into aryl-iridium is included in the turnover-limiting step of the catalytic cycle.



INTRODUCTION

Asymmetric control in the construction of quaternary carbon centers is an important methodology to synthesize various pharmaceuticals and natural products. The asymmetric addition[1] of aryl boron reagents to C−O or C−N double bonds such as ketones[2−5] and ketimines[6] is a general synthetic route for tertiary alcohols or amines having chiral quaternary carbon skeletons. However, these methods generate stoichiometric metal salt wastes as byproducts. Thus, an enantioselective direct C−H bond addition reaction that does not require an organometallic reagent is highly desirable in terms of the atom and synthetic step economy. However, there have been few reports on asymmetric nucleophilic addition of a C−H bond to the carbonyl group by a transition metal catalyst.[7] Our group recently reported cationic Ir/Me-BIPAM-catalyzed enantioselective intramolecular direct hydroarylation of α-keto amides (Scheme 1).[8] This transformation provides a convenient synthetic route for chiral 3-substituted 3-hydroxy-2-oxindole derivatives with asymmetric induction. While some pioneering works have been reported,[9] only limited mechanistic information is available for aryl sp^2 C−H bond addition to carbonyl groups. Herein, we report the results of mechanistic studies of our newly developed intramolecular enantioselective hydroarylation reaction.

Scheme 1. Cationic Ir/Me-BIPAM-Catalyzed Enantioselective Intramolecular Direct Hydroarylation



RESULTS AND DISCUSSION

Substrate Scope. The cationic Ir/Me-BIPAM catalyst system achieves highly reactive and enantioselective hydroarylation of a wide range of α-keto amides. In optimized reaction conditions, the reaction occurred solely at the sandwiched C−H bond between the *N*,*N*-dimethyl carbamoyl group and keto amide group[10] to provide the corresponding oxindole products. Our developed method is the first example of highly enantioselective direct C−H bond addition to carbonyl compounds and displays broad functional group

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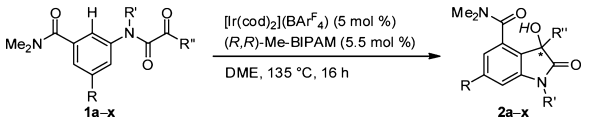
tolerance (Table 1). Although the *N,N*-dimethyl carbamoyl group serves as the best directing group, other directing groups

Table 1. Substrate Scope[a]



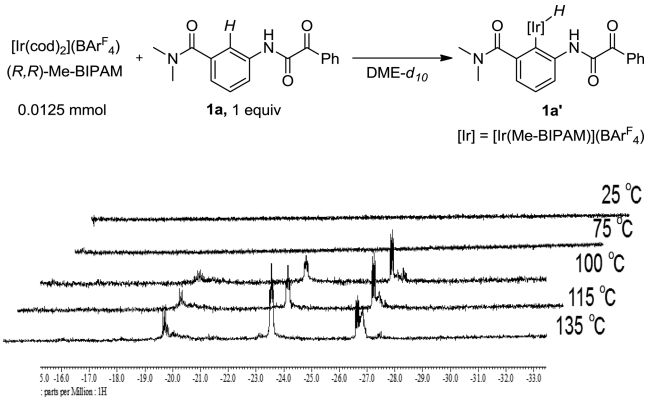
Entry	R =	R′ =	R″ =	yield [%]	ee [%][b]
1	H	H	C_6H_5 (**1a**)	>99 (**2a**)	98 (*S*)
2	H	H	4-$CF_3C_6H_4$ (**1b**)	98 (**2b**)	98
3	H	H	4-FC_6H_4 (**1c**)	99 (**2c**)	90
4	H	H	4-BrC_6H_4 (**1d**)	80 (**2d**)	98
5	H	H	4-PhC_6H_4 (**1e**)	94 (**2e**)	91
6	H	H	4-$CH_3C_6H_4$ (**1f**)	93 (**2f**)	91
7[c]	H	H	4-$PhOC_6H_4$ (**1g**)	97 (**2g**)	84
8	H	H	3-$CF_3C_6H_4$ (**1h**)	97 (**2h**)	97
9[c]	H	H	3-$CH_3C_6H_4$ (**1i**)	90 (**2i**)	92
10	H	H	2-FC_6H_4 (**1j**)	87 (**2j**)	97
11[c]	H	H	2-naphthyl (**1k**)	88 (**2k**)	94
12	H	H	3,5-$(CF_3)_2C_6H_3$ (**1l**)	97 (**2l**)	98
13[c]	H	H	3,4-$(CH_2O_2)C_6H_3$ (**1m**)	85 (**2m**)	80
14	CH_3	H	C_6H_5 (**1n**)	90 (**2n**)	93
15	CF_3	H	C_6H_5 (**1o**)	96 (**2o**)	91
16	Cl	H	C_6H_5 (**1p**)	85 (**2p**)	95
17	H	H	CH_3 (**1q**)	96 (**2q**)	94
18	H	H	CH_2CH_3 (**1r**)	95 (**2r**)	92
19	H	H	$CH(CH_3)_2$ (**1s**)	93 (**2s**)	90
20	H	CH_3	C_6H_5 (**1t**)	85 (**2t**)	92
21	H	CH_3	4-$CF_3C_6H_4$ (**1u**)	92 (**2u**)	87
22	H	CH_3	4-FC_6H_4 (**1v**)	95 (**2v**)	86
23	H	CH_3	4-$CH_3C_6H_4$ (**1w**)	86 (**2w**)	90
24	H	CH_3	4-$CH_3OC_6H_4$ (**1x**)	66 (**2x**)	70

[a]Reaction conditions: α-keto amides (0.25 mmol), $[Ir(cod)_2](BAr^F_4)$ (5 mol %), and (*R,R*)-Me-BIPAM (1.1 equiv to Ir) in DME (1 mL) was stirred for 16 h at 135 °C. [b]The letter within the parentheses indicates the absolute configuration of the chiral center within the product. [c]5 mol % of $[Ir(cod)((R,R)\text{-Me-bipam})](BAr^F_4)$ was used as the catalyst.

such as acetyl and benzoyl groups are also effective. In most cases, complete regioselectivity, high yield, and excellent enantioselectivity were obtained. This transformation demonstrates a broad functional group tolerance on the aromatic ketone (entries 1−13). Additionally, high enantioselectivity was maintained even when the aromatic ring of the aniline side has a substituent such as a CH_3, Cl, or CF_3 group (entries 14−16). Similarly, the method can be extended easily to a variety of aliphatic α-keto amides to produce 3-alkyl-3-hydroxy-2-oxindoles in high enantioselectivities (90−94% ee; entries 17−19). Finally, the reaction of α-keto amides bearing a methyl group on the nitrogen atom was also attempted. In most cases, desired products were obtained with good yields and enantioselectivities (entries 20−23), but a moderate result was observed only in the case of electron-donating methoxy-bearing substrate (entry 24).

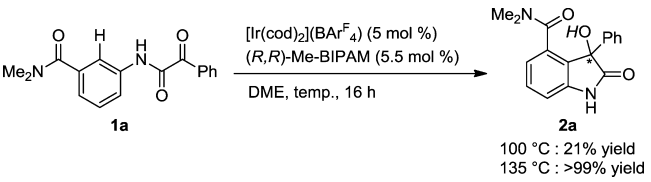
Mechanistic Studies. For mechanistic investigations, we first observed iridium hydride species that form via C−H bond cleavage (Scheme 2). In order to ascertain the C−H bond cleavage step, monitoring of ^{1}H NMR spectra of a mixture of Ir/Me-BIPAM complex and **1a** in DME-d_{10} at various temperatures was conducted. As a result, some signals, such

Scheme 2. Formation of Iridium Hydride Species



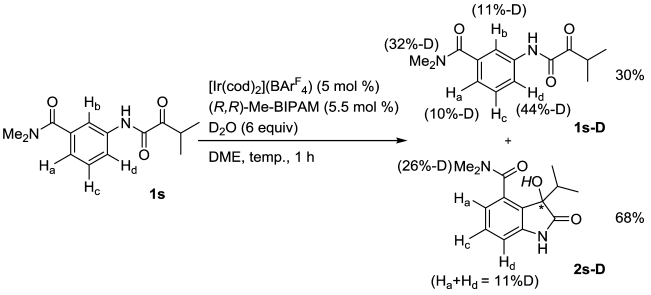
as those for iridium hydride species, were observed between −20 to −30 ppm at temperatures over 100 °C. While iridium hydride was detected at 100 °C, the product was obtained in only 21% yield for catalytic reaction conditions (Scheme 3). These results clearly demonstrate that a high temperature (135 °C) is essential for the steps except for C−H bond cleavage in the catalytic cycle.

Scheme 3. Effect of Temperature



To obtain additional data for the reaction mechanism, we carried out an asymmetric hydroarylation reaction of substrate **1s** in the presence of D_2O (6 equiv) under our optimized conditions (Scheme 4). The reaction was quenched in 1 h, and

Scheme 4. Deuterium Labeling Experiment



the mixture was purified to produce the unreacted substrate **1s-D** (30%) and product **2s-D** (68%). Deuterium incorporation was observed at the *ortho* position of the keto amide group (11%-D at H_b and 44%-D at H_d), the *ortho* position of the *N,N*-dimethyl carbamoyl group (10%-D at H_a) in the substrate, and the 5- and 7-positions of the product (11%-D at H_a and H_d) on the integration ratio of the ^{1}H NMR spectra of **1s-D** and **2s-D**. These results may arise from the fact that the C−H bond cleavage occurs in a fast and reversible manner prior to the carbonyl insertion.[7,9g,h] In addition, deuterium incorporation was also observed at the *N,N*-dimethyl carbamoyl group in both the substrate (**1s-D**) and product (**2s-D**).

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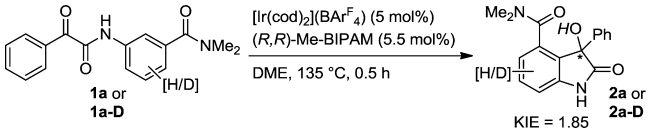
Next, isotope labeling studies were undertaken, with separate rate constants being measured for reactions. The intermolecular kinetic isotope effect (KIE) of the reaction employing substrates **1a** and **1a-D** was found to be 1.85 at the early stage of the reaction (Scheme 5).[9h,j] These experimental

Scheme 5. Kinetic Isotope Effect



observations for the C−H bond cleavage step suggest that C−H bond cleavage occurs before the turnover-limiting step in the catalytic cycle (secondary isotope effect can be observed) (Figure 1).[11] In Figure 1, the turnover-limiting step is the

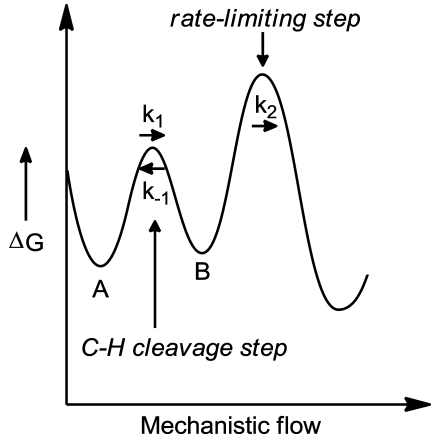


Figure 1. Proposed energy diagram.

second step, and the reaction rate is shown as k_2[B]. The concentration of B depends on the equilibrium of reversible C−H bond cleavage/formation having rate constants k_1 and k_{-1}, respectively. Due to the deuterium substitution, the equilibrium is greatly affected, and thus the concentration of B is reduced. As explained above, although iridium hydride species formed easily at a low temperature (100 °C), the reaction only proceeded smoothly at a high temperature (135 °C) to give the desired product, and H/D scrambling was observed in the deuterium labeling experiment. These results indicated that the k_{-1} step is much faster than the k_2 step, and the obtained value of the kinetic isotope effect (1.85) results from an equilibrium isotope effect on the C−H bond cleavage step.

To finally determine the turnover-limiting step of this reaction, a Hammett study was performed. The investigation focused on insertion of a carbonyl group into the aryl-iridium bond. First, substrates having an electron-donating or electron-withdrawing substituent (X) at the *para* position to the reactive C−H bond were subjected to competing reactions. Hammett plot analysis using substrates (**1a**, **1n**−**1p**) provided a linear relationship in a plot of $\log(k_X/k_H)$ versus σ, where ρ was determined to be −0.99 (Figure 2). This result shows that the reaction rate of a substrate having an electron-donating substituent at the *para* position to the reactive C−H bond is faster than that of a substrate having an electron-withdrawing substituent, and it can be considered that this relationship displays the reactivity for insertion of a carbonyl group into the

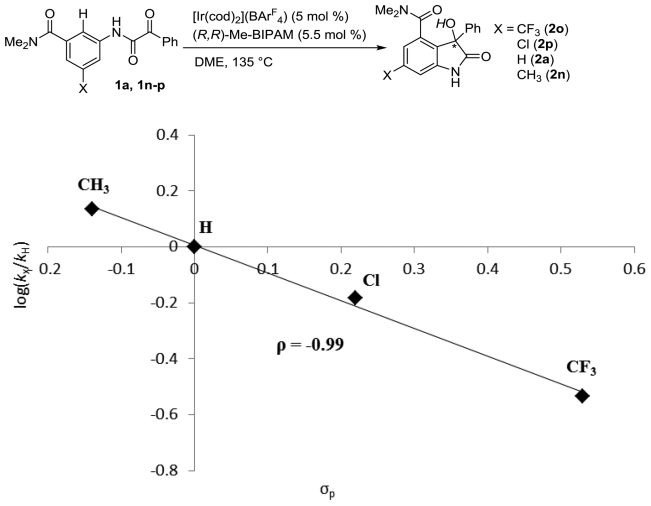


Figure 2. Hammett plot using substrates **1a** and **1n**−**p**.

aryl-iridium intermediate (an electron-donating substituent increases the nucleophilicity of the aryl-iridium species).

Next, the Hammett plot for substituents (Y) at the *para* position to the ketone group was also attempted to confirm the hypothesis as mentioned above (Figure 3). If the Hammett plot

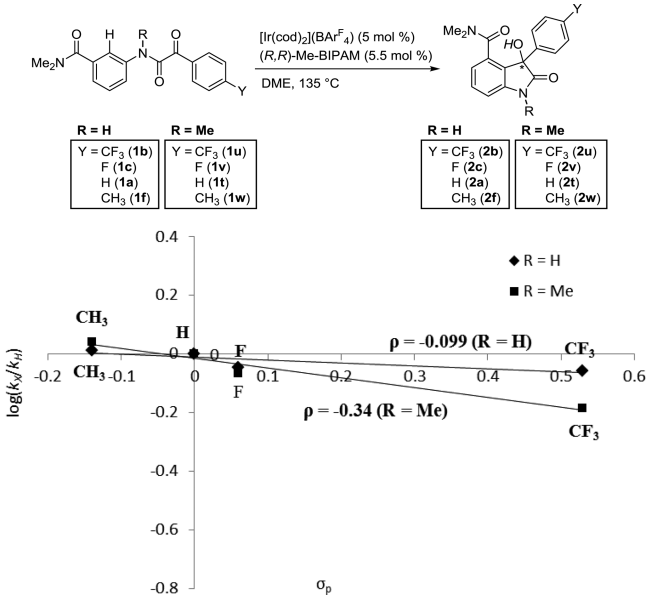


Figure 3. Hammett plot using substrates **1a**−**c** and **1f** (NH) or **1t**−**1w** (NMe).

shown in Figure 2 displays reactivity for carbonyl insertion into aryl-iridium, a linear relationship having a positive gradient should be obtained in Figure 3. Unfortunately, a clear substituent effect was not observed. The Hammett plot displayed a linear relationship between $\log(k_X/k_H)$ and σ, resulting in a small ρ value of −0.099. This result is probably due to a keto amide skeleton being activating by the electron-withdrawing amide group, and the substituent effect was thus neutralized. In other words, the reactivity for the insertion step is determined by nucleophilicity of the aryl-iridium intermediate. In order to ascertain the effect by the electron-withdrawing amide group, we further tested by changing the electronic nature of the amide moiety. The Hammett plot using

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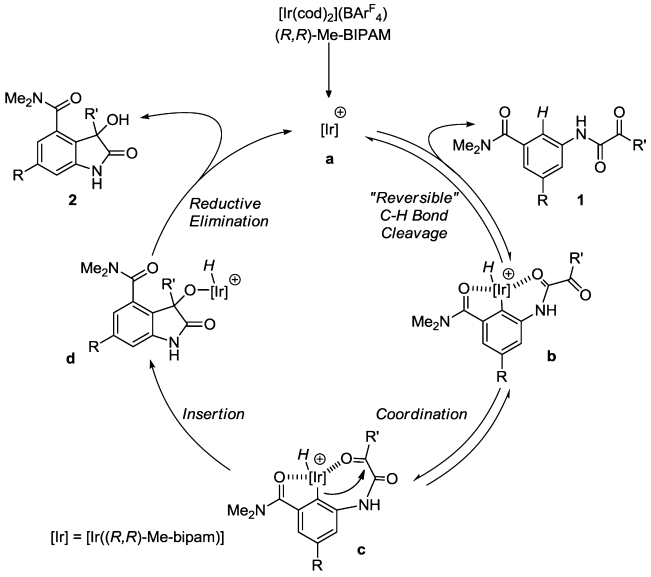
N-Me substrates displayed an insufficient ρ value of −0.34. These experiments demonstrate the strong activation of amide group. In our developed reaction, the electronic effect of the substituent X in Figure 2 plays a key role in control of reactivity.

These experimental and kinetic data suggest that the turnover-limiting step in this reaction is more closely related to the insertion of a carbonyl group into the aryl-iridium intermediate than to the C−H bond cleavage step.[9h]

We propose a catalytic cycle for the cationic Ir/Me-BIPAM-catalyzed enantioselective intramolecular direct hydroarylation (Scheme 6). First, the precatalyst mixture of $[Ir(cod)_2](BAr^F{}_4)$ and (*R*,*R*)-Me-BIPAM forms active complex **a**. Subsequently, a cationic active species reacts with substrate **1** to afford aryl-iridium intermediate **b**, which is coordinated with the two carbonyl groups of the amides. In this state, an equilibrium exists between complex **b** and **c**. Asymmetric hydroarylation of the ketone carbonyl group would proceed from **c**, thus producing enantiomerically enriched iridium alkoxide species **d**. Finally, reductive elimination occurs to give product **2** and regenerate the active species.

Scheme 6. Proposed Catalytic Cycle



The absolute configuration of oxindole product **2a** was established to be *S* by X-ray analysis.[8] However, no X-ray structure of an active chiral catalyst is yet available because of the difficulty in synthesizing a single crystal of the cationic Ir/Me-BIPAM complex. To further investigate the carbonyl insertion process (intermediate **c** in Scheme 6), DFT calculations were performed with B3LYP/LANL2DZ level of theory. At first, the two minimum energy modes of Ar-[Ir((*R*,*R*)-Me-BIPAM)]-H (intermediate **b** in Scheme 6) were calculated (Figure 4). Next, the turnover-limiting and stereo-determining step, which is coordinated with the two carbonyl groups (the aryl-iridium intermediate **c** in Scheme 6) were calculated (Figure 5). The conformation **c2** giving the experimentally observed *S* product has a low energy for reaction from the intermediate in which the carbonyl oxygen is coordinated to the iridium center at the Si-face after the C−H bond cleavage process. Conversely, coordination at the Re-face of the carbonyl group (**c1**) has a higher energy than Si-face coordination (**c2**) ($\Delta E_{c1\text{-}c2}$ = 3.10 kcal/mol). Thus, the enantioselective insertion to Si-face of the carbonyl group can be rationalized by less steric congestion intermediate **c2**.

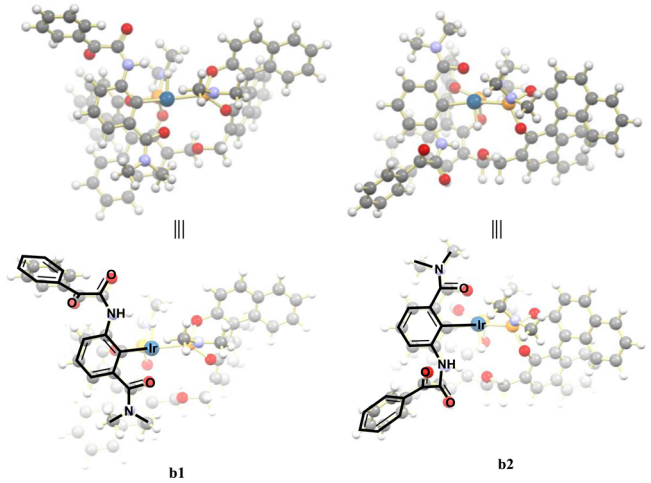


Figure 4. DFT calculations of aryl-iridium intermediate optimized at the B3LYP/LANL2DZ level.

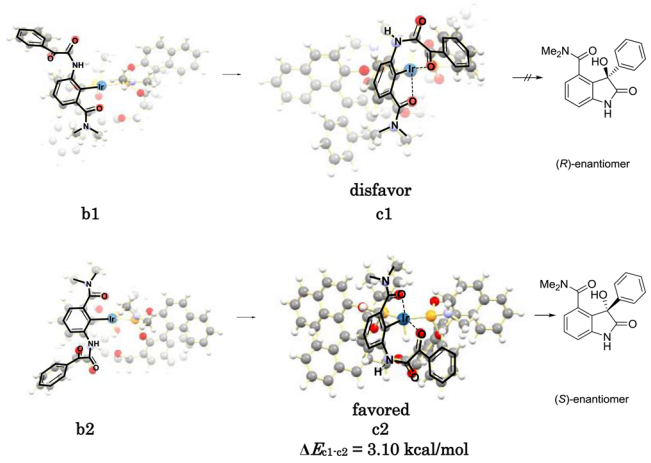


Figure 5. DFT calculations of enantioselection models at the B3LYP/LANL2DZ level.

CONCLUSION

In conclusion, the detailed mechanism for enantioselective intramolecular direct hydroarylation of α-keto amides catalyzed by a cationic iridium/Me-BIPAM complex is described. The turnover-limiting step in the catalytic cycle was determined to be the carbonyl insertion step to the aryl-iridium bond by ^{1}H NMR experiments, kinetic isotope effect studies, and Hammett studies.

EXPERIMENTAL SECTION

General Procedure. To a flame-dried flask, $[Ir(cod)_2](BAr^F{}_4)$ (0.0125 mmol, 5 mol %) and (*R*,*R*)-Me-BIPAM (0.0138 mmol, 5.5 mmol %) and dry dimethoxyethane (1.0 mL) were added under an N_2 atmosphere. The solution was stirred at room temperature for 30 min, followed by the addition of α-keto amides (0.25 mmol). The reaction mixture was then heated at 135 °C. After being stirred for 16 h, the mixture was purified with silica gel column chromatography (eluent: *n*-hexane/ethyl acetate) to afford pure 3-substituted 3-hydroxy-2-oxindole.

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■ ASSOCIATED CONTENT

Supporting Information

Text, tables, and figures providing experimental details, spectral and/or analytical data for all new compounds. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/om501260w.

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Notes

The authors declare no competing financial interest.

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