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**Theoretical study on the mechanism of iridium-catalyzed γ -
functionalization of primary alkyl C-H bonds**

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Abstract: The mechanism of the iridium-catalyzed functionalization of a primary C-H bond at the γ position of an alcohol (*Nature* **2012**, 483, 70) is investigated by density functional (DFT) calculations. A new Ir^{III}-Ir^V mechanism is found to be more feasible than the previously reported Ir^I-Ir^{III} mechanism (*Org. Lett.* **2013**, 15, 4066). In the Ir^{III}-Ir^V mechanism, the reaction begins with the initial formation of (Me₄phen)Ir^{III}(H)[Si(OR)Et₂]₂ from the catalyst precursor, [Ir(cod)OMe]₂ (cod=1,5-cyclooctadiene). The catalytic cycle includes five steps: 1) the insertion of norbornene into the Ir-H bond to produce (Me₄phen)Ir^{III}(norbornyl)[Si(OR)Et₂]₂ (R=CH(C₂H₅)C₃H₇); 2) the Si-H oxidative addition of HSi(OR)Et₂ to form (Me₄phen)Ir^VH(norbornyl)[Si(OR)Et₂]₃; 3) the reductive elimination of norbornane to furnish (Me₄phen)Ir^{III}[Si(OR)Et₂]₃; 4) the intramolecular C-H activation of the primary C-H bond at the γ position; and 5) the Si-C reductive elimination to produce the final product and regenerate the catalyst. The highest barrier in the Ir^{III}-Ir^V mechanism is 7.3 kcal/mol lower than that of the Ir^I-Ir^{III} mechanism. In addition, the regioselectivity of the C-H activation predicted by this new Ir^{III}-Ir^V mechanism is consistent with experimental observation.

Keywords: iridium catalysis, reaction mechanism, C-H functionalization, DFT calculation, regioselectivity

1. Introduction

Transition metal-catalyzed C-H functionalization of alkanes provides a powerful method for the synthesis of complex molecules.¹⁻³ A major challenge in alkyl C-H bond functionalization is to activate only one bond selectively among many similar C-H bonds. One popular strategy to realize high selectivity is to utilize a directing group.⁴ However, many reported C-H functionalization reactions of alkanes use directing groups that must be removed in a later step in order to obtain the desired products. C-H functionalization directed by commonly available functional groups is more efficient for organic synthesis. In this context, Hartwig developed an Ir-catalyzed γ -functionalization of a primary C-H bond directed by a hydroxyl substituent (Scheme 1).⁵ Various alcohols and ketones bearing a broad range of functional groups are suitable substrates for this silylation reaction.^{6,7} The selectivity of this reaction is fascinating: first, a primary C-H bond is favored over a secondary or tertiary C-H bond; second, the usually more reactive aromatic C-H bonds^{8,9} remain intact. In order to understand the selectivity of this reaction, mechanistic studies are required to elucidate the catalytic pathway.

Scheme 1. Ir-catalyzed γ -functionalization of alkyl C-H bonds.

A recent computational study by Sunoj found that the $[\text{IrH}(\text{nbe})(\text{phen})]$ (nbe=norbornene, phen=1,10-phenanthroline) is the active catalyst that reacts by an

Ir^I-Ir^{III} pathway.¹⁰ The Si-C reductive elimination is predicted to be the rate determining step (Scheme 2, cycle 1). However, a recent experimental study on the Ir-catalyzed silylation of secondary alkyl C-H bonds showed that the rate determining step should be the C-H bond cleavage.¹¹ On the other hand, the possible Ir^{III}-Ir^V catalytic pathway (Scheme 2, cycle 2) was not considered in the above report. Following the seminal work of Bergman,¹² many Ir catalysts involving the transformation of Ir^{III}-Ir^V have been developed.¹³⁻¹⁶ Sakaki reported that the Ir-catalyzed borylation of benzene involves a Ir^{III}-Ir^V catalytic cycle.¹⁷ The Ir-catalyzed borylation of the C-H bonds in alkylamines and alkylethers was also determined to be via an Ir^{III}-Ir^V mechanism recently.¹⁸ In addition, Su and Chu found that the oxidative addition of C-H bond to CpIr^IL (Cp=cyclopentadiene, L=PMe₃)^{19,20} complexes proceeds in a concerted pathway via a three-centered transition state.²¹ The selectivity of the CpIrL system is aromatic C-H > primary C-H > secondary C-H.^{11,12} This observation is in contrast to the regioselectivity observed in Hartwig's work. As a result, the Ir^{III}-Ir^V pathway should be compared with the Ir^I-Ir^{III} one to determine the correct mechanism.

Scheme 2. Ir^I-Ir^{III} and Ir^{III}-Ir^V pathways of Ir-catalyzed C-H functionalization

79

80 Recently, calculations using density functional theory (DFT) have been widely
81 used to investigate the mechanisms of Ir-catalyzed reactions.^{13,22,23} Brookhart found a
82 methane complex intermediate in the hydrogenolysis of the Ir-methyl bond combining
83 experiments and DFT calculations.²⁴ Heinekey studied the mechanism of C-H
84 activation by cationic Ir^{III} N-heterocyclic carbene (NHC) complexes.²⁵ Gorelsky and
85 Woo conducted a mechanistic analysis of Ir^{III} catalyzed direct C-H arylation
86 reactions.²⁶ Eisenstein and Crabtree elucidated the mechanism of Ir-catalyzed
87 hydrogenation of N-heterocyclic compounds.²⁷ Nowadays DFT calculations can
88 provide structures and energies of transient intermediates and transition states that are
89 difficult to be observed by experiments.²⁸⁻³⁰

90 In this work, the detailed mechanism of Ir-catalyzed intramolecular C-H
91 functionalization of alcohols was studied by DFT calculations. Based on the
92 calculated Gibbs energies in THF solution for every intermediate and transition state,
93 a new Ir^{III}-Ir^V catalytic pathway was compared with the reported Ir^I-Ir^{III} pathway. The
94 regioselectivity is also discussed.

95

96 2. Computational Methodologies

97 All calculations were performed with Gaussian 09 package.³¹ Geometries of
98 all species were fully optimized in the gas phase with the B3LYP density
99 functional^{32,33} using a combination basis set (BS1): the LANL2DZ basis set³⁴⁻³⁶ with
100 added f functions ($\xi_f = 0.938$)³⁷ was used for Ir, and the 6-31G(d) basis set³⁸ was used
101 for the other atoms. The application of B3LYP method to calculations of Ir mediated
102 reactions has been validated by previous theoretical reports.^{17,25,26,39-43} Transition
103 states were located using the default Berny algorithm⁴⁴ in Gaussian 09. For species

that have multiple conformations, several different starting geometries were subjected to optimization to find the conformation with the lowest energy. Harmonic vibrational frequencies were calculated to confirm minima (no imaginary frequency) and transition states (only one imaginary frequency). Transition states were verified by calculating the intrinsic reaction coordinate (IRC) to ensure that they connect the relevant reactant and product.⁴⁵ The thermodynamic correction for the gas-phase Gibbs energy (TCG) was obtained in the frequency calculation. Single point calculations were calculated using the M06 functional⁴⁶ with a combination basis set (BS2): SDD basis set⁴⁷ for Ir, and the 6-311+G(2d,p) basis set⁴⁸ for the other atoms. The solvation Gibbs energy was calculated by the conductor polarizable continuum model (CPCM)⁴⁹ at the same geometries optimized in the gas phase using B3LYP/BS1 method. Here, THF was chosen as the solvent because it was used in the experiments. The Gibbs energy was calculated by adding TCG and solvation Gibbs energy to the single point energy. Geometry optimizations in THF solution were performed for key species (**11a**, **11b**, **TS₉₋₁₀**, and **TS_{13b-14}**) using polarizable continuum model (PCM)⁵⁰ at the level of B3LYP/BS1 (see supporting information for details). All the solution-phase Gibbs energies reported in the paper correspond to the reference state of 1 mol/L, 298 K.

3. Results and discussion

3.1 Generation of the Active Catalyst

The catalyst precursor used in the experiments were $[\text{Ir}(\text{cod})\text{OMe}]_2$ (**1**, cod=1,5-cyclooctadiene) and the ligand was Me₄phen, and **1** should be transformed to the active catalyst first. In a recent theoretical report,¹⁰ monomeric complexes **2** or **3** were determined to be produced in the initiation of the reaction. Their Gibbs energies

are at least 18.7 kcal/mol higher than that of **1**. Here a more favored pathway was found using a model system using the phen ligand and HSi(OMe)Me₂ (Scheme 3). This pathway was inspired by the report that [Ir(coe)₂Cl]₂ (coe = cyclooctene) catalyzes Et₃SiH to produce [(Et₃Si)₂IrH₂(Cl)]₂ and the free coe ligand at room temperature.⁵¹ Analogously, we envisioned that **1** could react with HSi(OMe)Me₂ to produce **4**. The Gibbs energy of **4** was calculated to be -0.7 kcal/mol (Fig. 1). The following ligand substitution of coe by the phen ligand is exergonic by -10.9 kcal/mol to produce **5** (Fig. 2). The decomposition of **5** into the monomer **6** is slightly endergonic, and **6** undergoes Si-O reductive elimination via TS_{6-7a} with a Gibbs energy barrier of +14.2 kcal/mol to produce **7**. The overall reaction Gibbs energy to produce **7a** is -2.6 kcal/mol. If the more realistic model compound **7b** is used in the calculation, the Gibbs energy change is -9.6 kcal/mol (Fig. 3). According to the computed Gibbs energies, this pathway is more feasible than pathways leading to **2** or **3**.

Scheme 3. Generation of the active catalyst **7a**

3.2 The catalytic cycle of Ir^I-Ir^{III} mechanism

From this section on, the full ligand Me₄phen (3,4,7,8-tetramethyl-1,10-phenanthroline) and HSi(OR)Et₂ (R=CH(C₂H₅)C₃H₇) are used to study the reaction pathways. First, the same Ir^I-Ir^{III} catalytic pathway as in the recent report¹⁰ (Scheme 2, cycle 1) was examined. The Gibbs energy profile was calculated only as far as the Si-C reductive elimination step because this step has the highest barrier that determines the feasibility of this pathway compared to other mechanistic proposals (Fig. 3). In **7b**, the terminal hydrogen atoms coordinate with the Ir center, with Ir-H bond lengths of 1.94 Å and 2.22 Å (**Fig. 4**). A norbornene can loosely coordinate to **7b** to generate **8** with an energy increase of +5.0 kcal/mol. The next C-H oxidative addition step has a barrier of +10.7 kcal/mol relative to **7b** through **TS_{8,9}** leading to the formation of **9**. The Si-C reductive elimination of **9** proceeds via **TS_{9,10}** and has a barrier of +36.5 kcal/mol relative to **9**. This barrier is close to the reported barrier, +34.4 kcal/mol.¹⁰ This is expected because the density functional method (M06) for single point calculations is the same as that of the previous report. The product of the Si-C reductive elimination is **10a**. The substitution of the norbornene ligand of **10a** by the THF solvent to produce **10b** is highly endergonic with a Gibbs energy increase of 25.0 kcal/mol. As a result, the concentration of **10b** is negligible in the reaction system.

Fig. 1. Gibbs energy profile of the formation of active catalyst (kcal/mol).

Fig. 2. Structures of **5**, **6** and TS_{6-7a} (Unit: Å)

Fig. 3. C-H activation from **7b** via the Ir^I-Ir^{III} pathway

3.3 The catalytic cycle of Ir^{III}-Ir^V mechanism

The Ir^{III}-Ir^V catalytic pathway also begins with **7b** (Scheme 4), but it undergoes the Si-H oxidative insertion with HSi(OMe)Et₂ to produce the Ir^{III} complex **11a** rather than the intramolecular C-H activation. The barrier of TS_{7b-11a} is 11.4 kcal/mol relative to **7b** (Fig. 5). The Gibbs energy of **11a** is 24.1 kcal/mol lower than that of **7b**. The binding of norbornene to **11a** only slightly increases the Gibbs energy by 0.2 kcal/mol to form the hexacoordinate **12**. The distances between the two carbons of the norbornene and the Ir center are 2.81 Å and 2.87 Å (Fig. 6). A subsequent β-migratory insertion transfers the hydride ligand to one of the unsaturated carbon atoms in the norbornene ligand to produce **13a**. The transition state of this step is TS₁₂₋₁₃ with a barrier of 15.5 kcal/mol relative to **11a**.

If **11a** and TS_{7b-11a} are put together with the Gibbs energy profile of the Ir^I-Ir^{III} pathway (Fig. 3), it is clear that the rate of the transformation from **9** to **10** is slower

than that from **9** to **11a** because **TS**₉₋₁₀ has a higher barrier than those of both **TS**₈₋₉ and **TS**_{7b-11a}. **11a** is the resting state of the catalyst according to the energetic span model developed by Kozuch and Shaik.⁵² As a result, the overall barrier of **TS**₉₋₁₀ is 45.1 kcal/mol relative to **11a**. This is much higher than the previously reported barrier of the Ir^I-Ir^{III} catalytic cycle because the formation of **11a** was not considered.¹⁰ As we will show later, this barrier is much higher than the highest barrier in the Ir^{III}-Ir^V pathway.

Fig. 4. Structures of **7b**, **TS**₈₋₉, **9** and **TS**₉₋₁₀ (Unit: Å)

From **13**, two pathways were investigated (Scheme 4). The first one consists of the oxidative addition of another Et₂Si(OR)H to produce the Ir^V complex **14**, the C-

H reductive elimination to release the norbornane to produce **15**, the intramolecular C-H oxidative addition to form **16**, and the C-Si reductive elimination to furnish the final product and regenerate catalyst **11a**. This pathway is inspired by the report that Ir^{V} complexes can be synthesized by the oxidative addition of two equivalents of HSiPh_3 .⁵³ The second pathway involves the intramolecular C-H oxidative addition to produce **17**, the C-H reductive elimination to produce norbornane and **18**, and the C-Si reductive elimination to afford the final product and regenerate **7**.

Scheme 4. Proposed pathways of the Ir^{III} - Ir^{V} mechanism

In order to save computational cost, **11a** ($\text{R} = \text{CH}_2(\text{C}_2\text{H}_5)\text{C}_3\text{H}_7$) was replaced by **11b** ($\text{R} = \text{Me}$) in pathway I in Scheme 4, and the relative energy of **11b** is set to be the same as **11a** (Fig. 7). Subsequently, the relative Gibbs energy of **13b** is -29.0 kcal/mol, which is close to **13a** (-27.8 kcal/mol), and then **13b** undergoes oxidative

addition with another molecule of $\text{Et}_2\text{Si}(\text{OR})\text{H}$ to produce **14**. The geometry of **TS**_{13b-14} indicates that it is an early transition state with a long Ir-H distance (Fig. 8). The barrier of **TS**_{13b-14} (37.8 kcal/mol relative to **11b**) is much higher than that of the Si-H oxidative addition of **7b**, presumably because the oxidation state of **13** is higher and the steric hindrance is larger due to the 7 ligands around the Ir center. Heptacoordinate Ir complexes have been reported before.^{54,55}

Fig. 5. Gibbs energy profile of the first part of Ir^{III}-Ir^V (kcal/mol).

Fig. 6. Structures of **TS**_{7b-11a}, **12** and **TS**₁₂₋₁₃ (Unit: Å)

Fig. 7. Gibbs energy profile of pathway I in the Ir^{III}-Ir^V mechanism (kcal/mol).

The subsequent C-H reductive elimination of norbornane takes place via **TS₁₄₋₁₅** with a barrier of only 2.5 kcal/mol to provide **15**. The transition state of the intramolecular C-H oxidative addition of **15** is **TS₁₅₋₁₆**. The C-H bond approaches the Ir center vertically to the Me₄phen ligand plane (Fig. 8), whereas the C-H activation occurs almost in the Me₄phen plane in **TS₈₋₉** in the Ir^I-Ir^{III} mechanism (Fig. 4). **TS₁₅₋₁₆** is also a late transition state with the H atom closer to the Ir, which is contrary to the case of **TS₈₋₉**. The immediate product is **16a** with the hydride ligand in the axial position. The hydride rearranges to the equatorial position through isomerization via **TS_{16a-b}** with a small barrier of 3.8 kcal/mol. The C-H activation step is endergonic from **15** to **16b**. The C-Si reductive elimination of **16b** is 8.5 kcal/mol, and this produces the final product and **11b**.

Fig. 8. Structures of **TS_{13b-14}**, **14**, **TS₁₅₋₁₆** and **16a** (Unit: Å)

In pathway II, the first step is the intramolecular C-H oxidative addition through TS_{13-17} with a barrier of 23.2 kcal/mol to provide **17** (Fig. 9). Similar to pathway I, the C-H activation step is also endergonic. The C-H activation occurs in the Me₄phen ligand plane, which is similar to that of the Ir^I-Ir^{III} mechanism (Fig. 10). After the C-H activation step, either C-H or Si-C reductive elimination may occur from **17**. The transition state of the former, i.e., TS_{17-18} , is much lower than that of the latter, TS_{17-21} . Therefore, the formation of **18** is favored. After the binding of a norbornene ligand to form **20**, the Si-C reductive elimination proceeds via TS_{20-8b} to produce **8b** and the final product **19**. The barrier is 47.8 kcal/mol relative to **18**, which is the highest one among all transition states in pathway II. This barrier is much

higher than the highest barrier of pathway I (37.8 kcal/mol). Thus path II is not feasible.

261

262 **Fig. 9.** Gibbs energy profile of pathway II in the Ir^{III}-Ir^V mechanism (kcal/mol).

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264

265 **Fig. 10.** Structures of TS_{13a-17} and 17 (Unit: Å).

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267

268 In order to know the favored mechanism, pathway I of the Ir^{III}-Ir^V mechanism
 269 should be compared with the Ir^I-Ir^{III} mechanism. **11a** (**11b**) is the common resting
 270 state of both the Ir^I-Ir^{III} and Ir^{III}-Ir^V mechanisms. The overall barrier of **TS**_{13b-14} is the
 271 highest among all the steps in pathway I (Fig. 7). This barrier is 7.3 kcal/mol lower
 272 than that of the Ir^I-Ir^{III} pathway (Fig. 3, **TS**₉₋₁₀). We also calculated these barriers at the
 273 geometries optimized in THF solution (see supporting information for details). The
 274 barriers are 44.3 kcal/mol and 46.0 kcal/mol for **TS**_{13b-14} and **TS**₉₋₁₀, respectively. As a
 275 result, the Ir^I-Ir^{III} catalytic cycle is not favored.

276

277 3.4 Regioselectivity in the C-H activation step

278 The barriers of the C-H activation step with various substrates have been
 279 calculated to explain the observed regioselectivity (Fig. 11). The secondary γ -H (Fig.
 280 11, b) of **15** has a barrier that is 23.5 kcal/mol, which is 1.3 kcal/mol higher than that
 281 of the primary γ -H (Fig. 11, a). This is in consistent with the experimental report that
 282 the reaction rate of the secondary C-H bond is about 50 times slower than that of the
 283 primary C-H bond.¹¹ The barrier of the primary δ -H is even higher, 27.5 kcal/mol (Fig.
 284 11, c). The primary β -H (Fig. 11, d), tertiary γ -H (Fig. 11, e) and aromatic-H (Fig. 11,

f) all have higher barriers than that of the primary γ -H. The fact that the primary γ -H has the lowest activation barrier is consistent with the experimental regioselectivity and explains the strong directing ability of the (hydrido)silyl group. When there are two primary γ -H available to the oxidative addition, the one in the threo position relative to the siloxyl group has the lower barrier (Fig. 11, g and h). Indeed, the product resulting from the oxidation of the H in the threo position is the major diastereomer. The intermolecular C-H oxidative addition has a relatively high barrier of 37.7 kcal/mol. This explains why the intermolecular reaction has not been achieved.

Fig. 11. Activation barriers for the C-H oxidative addition step of various substrates

([Ir] = (Me₄phen)Ir[Si(OMe)Et₂]₂, Unit: kcal/mol)

4. Conclusion

The mechanism of the Ir-catalyzed γ -functionalization of a primary C(sp^3)-H bond was investigated by DFT calculations augmented with CPCM solvation model.

By careful comparison of the Gibbs energy profiles of different pathways, a new Ir^{III}-Ir^V mechanism was found to be more feasible than a previously reported Ir^I-Ir^{III} mechanism. The formation of (Me₄phen)Ir^I[Si(OR)Et₂] as the catalyst precursor was found to be more probable than the formation of (Me₄phen)Ir^IH(norbornene), which was proposed in a previous theoretical report. This new mechanism consists of five major steps after the initial formation of the active catalyst (Me₄phen)Ir^{III}H[Si(OR)Et₂]₂: 1) the β -migratory insertion of norbornene into the Ir-H bond to afford (Me₄phen)Ir^{III}(norbornyl)[Si(OR)Et₂]₂; 2) the oxidative addition of one more HSi(OR)Et₂ to provide (Me₄phen)Ir^VH(norbornyl)[Si(OR)Et₂]₃; 3) the C-H reductive elimination that produces norbornane and (Me₄phen)Ir^{III}[Si(OR)Et₂]₃; 4) the intramolecular C-H oxidative addition of the primary γ -C-H bond; and 5) the Si-C reductive elimination to produce the final product and regenerate the catalyst. The Si-H oxidative addition step 2) has the highest barrier of all the steps. This barrier is 7.3 kcal/mol less than the highest barrier in the Ir^I-Ir^{III} mechanism. In addition, the calculated barriers of the intramolecular C-H oxidative addition step are in accordance with the regioselectivity of the functionalization of corresponding substrates.

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Supporting Information Available: Cartesian coordinates of optimized structures and detailed thermodynamic data.

324

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