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Selective sp^3 C–H Activation of Ketones at the β Position by Ir(I). Origin of Regioselectivity and Water Effect

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Selective activation of C–H bonds by transition metal complexes has important synthetic applications.¹ Murai² demonstrated Ru(0) catalyzed functionalization of aromatic ketones and imines at the ortho position. The regioselectivity in this case was suggested to be due to precoordination of the functional group.³ On the other hand, Goldman reported the selective ortho C–H activation of acetophenone and nitrobenzene by a (PCP)Ir(I) complex in which precoordination of the functional group was not involved: it occurs after the oxidative addition step, trapping the ortho C–H activation product to form a stable chelated complex.⁴ We reported the selective ortho C–H activation of haloarenes by the cationic [(PNP)Ir(COE)][BF₄] (PNP = 2,6-bis(di-*tert*-butylphosphinomethyl)pyridine, COE = cyclooctene) **1**,⁵ in which the observed selectivity is both kinetic and thermodynamic: it involves precoordination of the halogen atom to the metal center, as well as product stabilization. All of these cases involve arene sp^2 C–H activation.

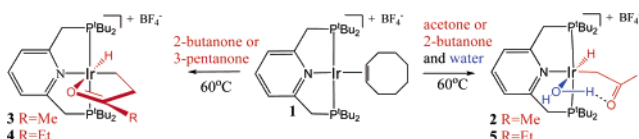
In this communication we report the *selective sp^3 C–H activation* of alkyl ketones at the β position. To our knowledge, the only example⁶ of β activation of a sp^3 C–H in a ketone involves a sequence of double β C–H and α C–H activation by OsH₆(P(*i*-Pr)₃)₂.⁷ An unexpected effect of water on regioselectivity is also presented here.

Complex **1** reacts with acetone at 60 °C to give the acetonyl hydride complex **2** (Scheme 1) in 70% isolated yield. The ³¹P NMR spectrum of **2** in CD₂Cl₂ exhibits a doublet at 44 ppm owing to coupling to a hydride (¹H NMR: δ –28.54, t, ²*J*_{HP} = 14.3 Hz). The high field chemical shift of the hydride indicates that this ligand is located trans to an occupied coordination site,^{5,8} while the chemical shift of the carbonyl carbon at 209 ppm suggests that no chelation through the carbonyl group exists. A single-crystal X-ray analysis of complex **2** (Figure 1) reveals a distorted octahedral structure with a molecule of water coordinated trans to the hydride ligand.⁹ The P–Ir–P angle of 160.44(7)° is typical for PNP complexes.^{5,8c} The distance between the carbonyl oxygen and the oxygen of the aqua ligand, 2.68 Å, is in the hydrogen bonding range.

Surprisingly, when complex **1** was dissolved in 2-butanone, quantitative activation of a β C–H bond took place, rather than activation of the more acidic and more abundant α C–H bonds, quantitatively yielding complex **3** after 3 h at 60 °C (Scheme 1). Similarly, 3-pentanone reacts with the Ir(I) complex **1** to quantitatively yield the β C–H activated complex **4** after 2 h at 60 °C. Complexes **3** and **4** were fully characterized by NMR experiments.¹⁰ The chemical shift of the carbonyl carbon is significantly shifted downfield compared to the corresponding free ketone ($\Delta\delta$ P = 24.8 and 24.2 ppm for **3** and **4**, respectively), indicating that the carbonyl is coordinated to the metal.

X-ray analysis of complex **4** confirmed the existence of a five-membered ring chelate, the carbonyl oxygen being located trans to the hydride with an Ir–O distance of 2.230(3) Å (Figure 1).

Scheme 1



Complex **4** has a slightly distorted octahedral structure with a P–Ir–P bond angle of 158.86(4). The five-membered ring formed by 3-pentanone is almost planar (maximum deviation 0.067 Å (C25)). Complexes **3** and **4** were also obtained at ambient temperature after 3 days. No other products were detected upon following the reaction at room temperature by ³¹P and ¹H NMR spectroscopy. Unexpectedly, when **1** was heated in a solution of acetone and 2-butanone (1:1 molar) for 3 h, complex **3** was quantitatively obtained, with not even traces of **2**. Complexes **3** and **4** were also obtained by heating complex **2** in solutions of equimolar amounts of acetone and 2-butanone (or acetone and 3-pentanone, respectively) for 3 h at 60 °C or after 3 days at room temperature. Thus, the oxidative addition of acetone to **1** is reversible, and the chelated complexes **3** and **4** are thermodynamically more stable than the acetonyl complex **2**.

DFT calculations were performed in order to gain more insight into the mechanism of the selective β C–H activation of 2-butanone by complex **1**, using the actual experimental system with the bulky P(*t*Bu)₂ groups. The potential energy surface (PES) in a simulated acetone solvent is shown in Figure 2 along with a schematic illustration of the local minima and transition states that were located. Following COE dissociation, intermediates **A1** and **B1**, in which the carbonyl oxygen is coordinated to the Ir(I) center, are formed. These local minima are the entry channel complexes for the α and β C–H activation routes, respectively. The rate determining step (RDS) for both pathways is the conversion of **A1** and **B1** to the η^2 -C,H complexes, **A2** and **B2** (Figure 2). Wiberg bond indices¹¹ for the Ir–C bond of 0.19 and 0.17 in **A2** and **B2**, respectively, and for the Ir–H bond (0.12 and 0.13), are clear evidence of the interaction of the C–H bond with the metal center. Furthermore, the coordinated C–H bond (whether α or β) is lengthened by 0.07 Å compared to the free 2-butanone.

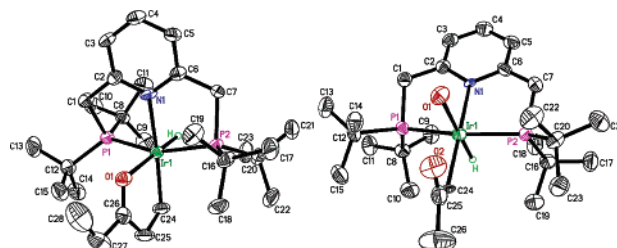


Figure 1. ORTEP drawings of **4** (left) and **2** at 80% probability level. Hydrogen atoms (except hydride) and BF₄ were omitted for clarity.

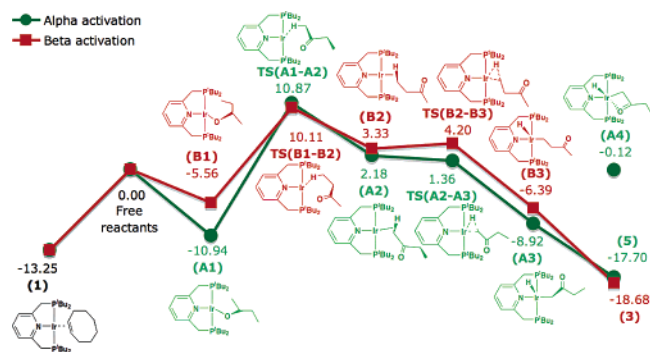


Figure 2. Profile of the reaction of **1** with 2-butanone ($\Delta G_{298}^{\ddagger}$ kcal/mol, COSMO-PBE0/SDB-cc-pVDZ//PBE0/SDD).

$\Delta G_{298}^{\ddagger}$ of the RDS is 5.38 kcal/mol lower for the activation of the β C–H bond. Most of this difference is due to the fact that complex **A1** is lower in energy by 5.4 kcal/mol than **B1**. This stabilization is due mainly to steric effects that are more pronounced in **B1**. Note that in **A1** a methyl group is directed toward the bulky $P(tBu)_2$ groups, as compared with an ethyl group in **B1**. Since the intermediates **A1** and **B1** are expected to be in rapid equilibrium (much lower barrier for the back reaction than for the RDS), the reaction proceeds via the β route, although no metal–oxygen interaction in the transition state was detected.

The transition state for the oxidative addition of the β C–H bond **TS(B2–B3)** has a barrier of 0.9 kcal/mol while that for the α C–H bond **TS(A2–A3)** is practically zero.¹² Activation of the α and β C–H bonds first results in the formation of the intermediates **A3** and **B3**, respectively, in which the carbonyl oxygen does not interact with the Ir(III) center. Coordination of the carbonyl oxygen to the metal center results in the formation of a four-membered ring in **A4** (Figure 2) and a five-membered ring in complex **3** (Scheme 1). As expected, closure of a four-membered ring is highly unfavorable and **A4** is 8.8 kcal/mol higher in energy than **A3**. Overall the β C–H activated product **3** is thermodynamically more stable by 9.8 kcal/mol over the α C–H activated product **A3**. Significantly, if water is present it will coordinate to the Ir(III) center of **A3** forming **5** (Scheme 1) which is energetically on par with **3**. One of the driving forces for this water coordination is a hydrogen bond formed between the water proton and the carbonyl oxygen ($r_{HOH-O} = 1.47$ Å and Wiberg bond index of 0.16) such that a six-membered ring is formed.

The reaction of **1** with 3-pentanone was also considered. The species located on the PES (Figure S1, Supporting Information) are very similar to those located for the oxidative addition of the 2-butanone ligand. In contrast to the 2-butanone case, where there is practically no thermodynamic preference for the activation of the α or β hydrogen in the presence of water, here activation of the β hydrogen in the presence of water is thermodynamically favored by 5.2 kcal/mol. This difference between the 2-butanone and 3-pentanone systems is due to the fact that the α -hydrogen is less sterically hindered in 2-butanone (CH_3 vs CH_2), resulting in the destabilization of the α -route compared to the β -route in the 3-pentanone case.

Inspired by the coordination of water to the vacant coordination site in complex **2** and by the DFT calculations, we followed the reaction of **1** with 2-butanone and 3-pentanone in the presence of a large excess of water by ^{31}P NMR and 1H NMR. As predicted

by the calculations, in the 3-pentanone case only complex **4** was found, while in the 2-butanone case we obtained a 3:2 mixture of complex **3** and the terminal α C–H activation product **5**. (**5** was characterized spectroscopically). Evaporation of the 2-butanone reaction mixture to dryness and redissolving in methylene chloride yielded complex **3** exclusively.

In conclusion, a (PNP)Ir(I) cationic complex exhibits highly selective C–H activation of the β C–H bonds of 2-butanone and 3-pentanone, giving the thermodynamically favored chelated products **3** and **4**, respectively. Calculations show that the selectivity is both kinetically (because of steric effects in the RDS) and thermodynamically controlled, the latter as a result of carbonyl oxygen coordination in the product. In the case of 2-pentanone, steric thermodynamic preference for β C–H activation also plays a role. Water has a strong influence on the regioselectivity and in its presence α C–H activation of 2-butanone takes place as well. Experimental and computational studies show that water can stabilize the terminal α C–H activation product **5** by hydrogen bonding, forming a six-membered ring with the ketone. Utilization of water as a tool in C–H activation selectivity is being explored.

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Supporting Information Available: Experimental procedures and characterization of complexes **2**–**5**, computational details (PDF), and X-ray data for **2** and **4** (CIF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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