J|A|C|S
COMMUNICATIONS

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

Moran Feller, Amir Karton, Gregory Leitus, Jan M. L. Martin,* and David Milstein*

Departments of Organic Chemistry and Chemical Services, The Weizmann Institute of Science, Rehovot, 76100, Israel

Received June 12, 2006; E-mail: david.milstein@weizmann.ac.il

Selective activation of C−H bonds by transition metal complexes has important synthetic applications.[1] Murai[2] 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)][BF_4] (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.

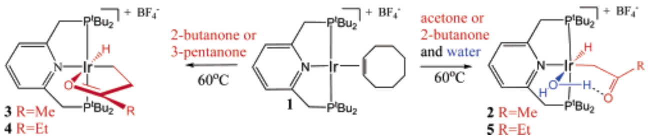
In this communication we report the *selective sp^3 C−H activation* of alkyl ketones at the β position. To our knowledge, the only example[6] of β activation of a sp^3 C−H in a ketone involves a sequence of double β C−H and α C−H activation by $OsH_6(P^iPr_3)_2$.[7] An unexpected effect of water on regioselectivity 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 ^{31}P NMR spectrum of **2** in CD_2Cl_2 exhibits a doublet at 44 ppm owing to coupling to a hydride (^{1}H NMR: δ −28.54, t, $^2J_{HP}$ = 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 ^{31}P and ^{1}H 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 $P(^tBu)_2$ 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 indices[11] 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.

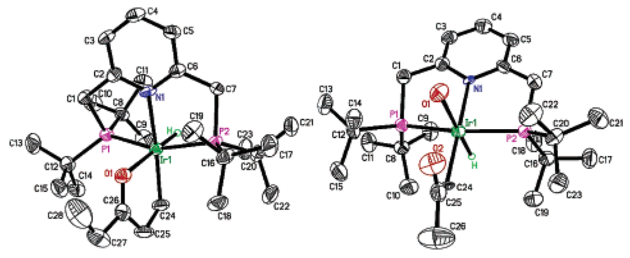


Figure 1. ORTEP drawings of **4** (left) and **2** at 80% probability level. Hydrogen atoms (except hydride) and BF_4 were omitted for clarity.

10.1021/ja0641352 CCC: $33.50

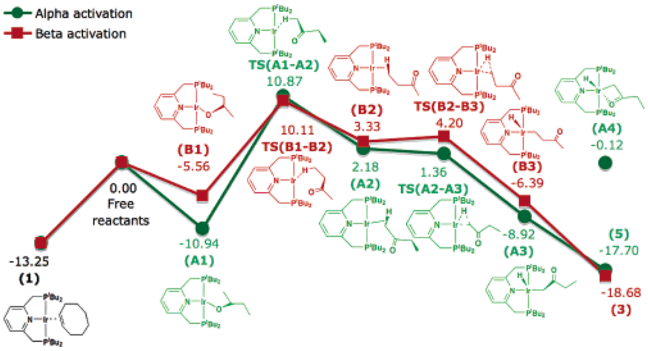


Figure 2. Profile of the reaction of **1** with 2-butanone (ΔG_{298} kcal/mol, COSMO−PBE0/SDB-cc-pVDZ//PBE0/SDD).

$\Delta G^{\#}_{298}$ 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(^{t}Bu)$_2$ 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 ($r_{\mathrm{HOH-O}} = 1.47$ 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 ^{1}H 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.

Acknowledgment. This research was supported by the Minerva Foundation, the Israel Science Foundation (Grant 412/04), the Kimmel Center for Molecular Design, and the Lise Meitner Center for Computational Quantum Chemistry. O.M. is the Israel Matz Professor of Organic Chemistry and J.M.L.M. is the Lady Thatcher Professor of Chemistry.

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.

References

(1) (a) Shilov, A. E.; Shul'pin, G. B. *Chem. Rev.* **1997**, *97*, 2879. (b) Guari Y.; Sabo-Etienne, S.; Chaudret, B. *Eur. J. Inorg. Chem.* **1999**, 1047. (c) Dyker, G. *Angew. Chem., Int. Ed.* **1999**, *38*, 1698.
(2) Kakiuchi, F.; Murai, S. *Acc. Chem. Res.* **2002**, *35*, 826.
(3) Matsubara, T.; Koga, N.; Musaev, G. D.; Morokuma, K. *J. Am. Chem. Soc.* **1998**, *120*, 12692.
(4) Zhang, X.; Kanzelberger, M.; Emge, T. J.; Goldman, A. S. *J. Am. Chem. Soc.* **2004**, *126*, 13192.
(5) (a) Ben-Ari, E.; Gandelman, M.; Rozenberg, H.; Shimon, L. J. W.; Milstein, D. *J. Am. Chem. Soc.* **2003**, *125*, 4714. (b) Ben-Ari, E.; Cohen, R.; Gandelman, M.; Shimon, L. J. W.; Martin J. M. L.; Milstein, D. *Organometallics* **2006**, *25*, 3190.
(6) Vinylic β C−H activation of α,β unsaturated ketones is known, for example: (a) Trost, B. M.; Imi, K.; Davies, I. W. *J. Am. Chem. Soc.* **1995**, *117*, 5371. (b) Kakiuchi, F.; Sato, T.; Chatani, N.; Murai, S. *Chem. Lett.* **1995**, 679. (c) Edwards, A. J.; Elipe, S.; Esteruelas, M. A.; Lahoz, F. J.; Oro, L. A.; Valero, C. *Organometallics* **1997**, *16*, 3828. (d) Jun, C.; Moon, C. W.; Kim, Y.; Lee, H.; Lee, J. H. *Tetrahedron Lett.* **2002**, *43*, 4233. (e) Li, X.; Chen, P.; Faller, J. W.; Crabtree, R. H. *Organometallics* **2005**, *24*, 4810. (f) Esteruelas, M. A.; Hernandez, Y. A.; Lopez, A. M.; Olivan, M.; Onate, E. *Organometallics* **2005**, *24*, 5989. (g) Eguillor, B.; Esteruelas, M. A.; Olivan, M.; Onate, E. *Organometallics* **2005**, *24*, 1428.
(7) Barrio, P.; Castarlenas, R.; Esteruelas, M. A.; Onate, E. *Organometallics* **2001**, *20*, 2635.
(8) (a) Moulton, C. J.; Shaw, B. L. *J. Chem. Soc., Dalton Trans.* **1976**, 1020. (b) Renkema, K. B.; Bosque, R.; Streib, W.; Maseras, F.; Eisenstein, O.; Caulton, K. G. *J. Am. Chem. Soc.* **1999**, *121*, 10895. (c) Hermann, D.; Gandelman, M.; Rozenberg, H.; Shimon, L. J. W.; Milstein, D. *Organometallics* **2002**, *21*, 812.
(9) Since the reaction was preformed in dry acetone, water may be formed by an aldol condensation, perhaps catalyzed by the Ir complex.
(10) See Supporting Information for a full assignment.
(11) Wiberg, K. B. *Tetrahedron* **1968**, *24*, 1083.
(12) The negative barrier is a result of using a PBE0/SDD geometry for the PBE0/SDB-cc-pVDZ single point energy calculations. The PBE0/SDD//PBE0/SDD barrier is 2.3 and 2.9 kcal/mol for the α and β C−H activations, respectively.

JA0641352