C–H Activation

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Reversible Insertion of Aldehydes and Ketones into C_{sp^3}–H Bonds of Chiral Bis(oxazoline)/Iridium Complexes**

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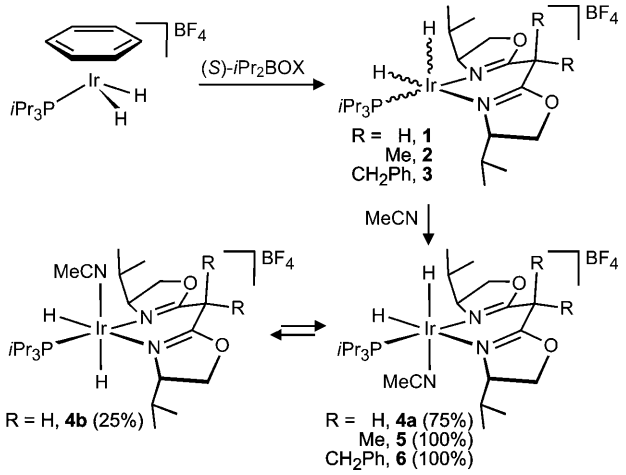
The discovery of new procedures for the direct functionalization of C–H bonds may inspire alternative "greener" synthetic strategies. So far, the intense research in this field has led to several methods for C–H functionalization using transition-metal complexes.[1] For transformations such as oxidations,[2] dehydrogenations,[3] borylations,[4] and some C–C formations,[5] the metal accomplishes the difficult cleavage of C–H bonds at its coordination sphere, often with the help of non-innocent ligands[6] or external bases.[7] In other cases, the metal complex is limited to generating highly reactive ligands such as oxo radicals,[8] carbenes, and nitrenes,[9] which are thereafter able to attack the virtually intact C–H bonds.[10] This work describes C–H activation reactions within bis(oxazoline)/iridium complexes that include the classic oxidative additions together with those that lead to rare aldehyde and ketone insertions into C_{sp^3}–H bonds. For the aldehyde and ketone insertions, rather than breaking the C–H bond or generating reactive ligands, the metal just holds the reactants close enough to favor nucleophilic additions to the carbonyl functions. The nucleophile, in this case, can be as unconventional as a methylene group.

The versatile iridium precursor $[IrH_2(\eta^6\text{-}C_6H_6)(P\mathit{i}Pr_3)]BF_4$[11] was found to react with C_2-symmetric bis(oxazoline) ligands derived from the bis[(4*S*)-4-isopropyl-4,5-dihydro-oxazole] [(*S*)-*i*Pr$_2$BOX], to form the five-coordinate cationic dihydride complexes **1**, **2**, and **3** (Scheme 1). The ^{1}H and $^{13}C\{^1H\}$ NMR spectra of these compounds in solution at low temperature indicate the loss of the C_2 symmetry of the (*S*)-*i*Pr$_2$BOX ligand upon coordination, as well as the non-equivalence of the two hydride ligands. For each of the complexes **1**–**3**, the ^{1}H NMR signal corresponding to one of the hydrides appears at a chemical shift as low as $\delta = -32$ ppm, which suggests that, as expected from the usual trends of structural *trans* effects,[12] the empty coordination site is located in the *trans* position to the hydride. At room temperature, the ^{1}H and $^{13}C\{^1H\}$ NMR signals for the (*S*)-*i*Pr$_2$BOX ligand indicate a recovery in the symmetry of the free ligand, whilst the hydrides remain non-equivalent. This data suggests a fast concerted rotation of the face of the complex that is defined by the hydrides and the phosphane; that is a rotation that can average the positions that are *trans* to the (*S*)-*i*Pr$_2$BOX ligand without any hydride exchange. The activation parameters for this fluxional process in complex **3** were estimated from the line widths of the ^{1}H NMR signals in $CDCl_3$ as $\Delta H^{\neq} = (12.8 \pm 0.5)$ kcal mol^{-1} and $\Delta S^{\neq} = (2 \pm 1)$ cal K^{-1} mol^{-1}. The slow exchange between the non-equivalent hydrides of this complex was detected by ^{1}H NMR spin-saturation transfer methods only above 323 K.



Scheme 1. Synthesis of cationic bis(oxazoline)/iridium dihydrides.

In agreement with the proposed structures and dynamics, the addition of potential ligands to solutions of **1**–**3** was observed to stop the fast fluxional process to give, in the general case, two six-coordinate isomeric adducts. The slow conversion between isomers remains possible for adducts of weakly coordinating ligands such as acetonitrile (**4**–**6**; Scheme 1), hence these isomeric adducts are in equilibrium. The equilibrium position is sensitive to the size of the R groups on the bridge connecting the oxazoline rings. The X-ray crystal structure[13] of the only observable isomer of adduct **6** (R = CH_2Ph, Figure 1) shows that in order to minimize the steric repulsions between the phosphane and the closest isopropyl group of the (*S*)-*i*Pr$_2$BOX ligand, the (*S*)-*i*Pr$_2$BOX ligand bends away from the compound's coordination plane and towards one of the axial ligands. This subtle distortion seems to be enough to discourage the more encumbered isomers that could result (**b** in Scheme 1), as

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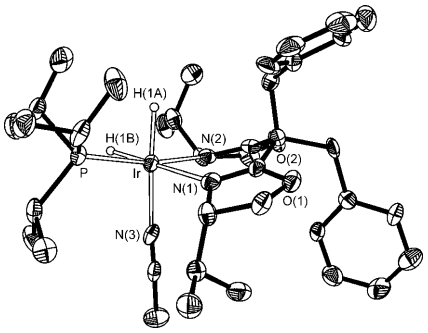
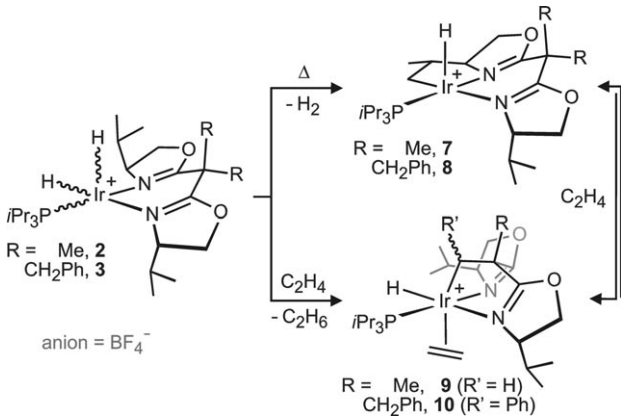


Figure 1. The X-ray crystal structure of the cation of complex **6**. For the ORTEP diagram the thermal ellipsoids are shown at 50% probability. Selected bond distances [Å] and angles [°]: Ir–P 2.247(3), Ir–N(1) 2.204(9), Ir–N(2) 2.086(6), Ir–N(3) 2.091(6); P-Ir-N(1) 107.13(17), P-Ir-N(2) 166.47(17), P-Ir-N(3) 103.8(3), N(1)-Ir-N(2) 83.1(3), N(1)-Ir-N(3) 88.8(3).

only **4b** (R = H) was observed. The major isomers were readily identified by ^{1}H NMR spectroscopy through the NOE effect between the axial hydride and hydrogen atoms of the CR_2 bridge.

During the dehydrogenation of their iridium centers, complexes **2** and **3** were found to undergo intramolecular oxidative additions of the C–H bonds of the (*S*)-*i*Pr$_2$BOX ligand. Interestingly, the target C–H bond changed depending on the method used to achieve dehydrogenation; namely, the thermally induced H_2 reductive elimination or the use of a hydrogen acceptor such as ethylene (Scheme 2).



Scheme 2. Competitive oxidative additions of (*S*)-*i*Pr$_2$BOX C–H bonds to Ir.

The five-coordinate hydrides **7** and **8** (Scheme 2), which contain *mer*-coordinating (*S*)-*i*Pr$_2$BOX ligands metalated at one isopropyl group, were prepared by heating toluene suspensions of **2** and **3**, respectively, at 383 K. In both syntheses, the crude residues obtained after 48 hours were found to contain the isomer shown in Scheme 2 as the main reaction product (> 80%), together with several unidentified minor products. The ^{1}H NMR values (δ) that correspond to the hydride ligands in complexes **7** and **8** are upfield from $\delta = -33$ ppm, which suggests that these complexes display coordination vacancies in the position *trans* to the hydride. The various cross-peaks in the ^{1}H NOESY spectra confirm that the metalated (*S*)-*i*Pr$_2$BOX ligands are bent towards the position of the hydride, and indicate that the new stereogenic carbon centers generated by the C–H oxidative addition have an *R* configuration. In such a seemingly sterically preferred configuration, the methyl substituent is equatorial and points outwards from the iridium coordination sphere.

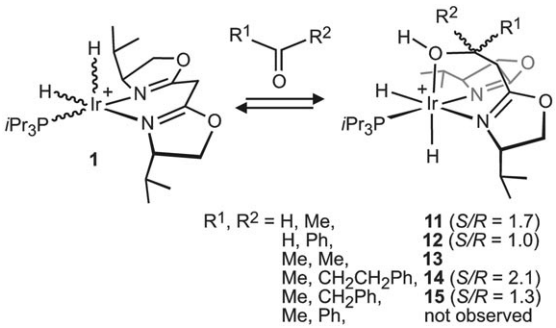
The treatment of **2** and **3** with an excess of ethylene at 323 K was found to afford six-coordinate complexes that display *fac*-tridentate (*S*)-*i*Pr$_2$BOX ligands metalated at the CR_2 bridge (**9** and **10**; Scheme 2). The coupling constants in the ^{1}H and ^{13}C{^{1}H} NMR spectra of these compounds indicate that the hydride and ethylene ligands, as well as the metalated carbon atom, occupy coordination positions that are *cis* to phosphorous. In agreement with the proposed structures, the ^{1}H NOESY spectra confirm the spatial proximity of the hydrogen atom (or atoms) at the metalated carbon center and both the hydride and phosphane ligands. Derivative **10** was obtained as a 2:1 (*S*/*R*) mixture of diastereomers that differ in the configuration of the metalated carbon center (from ^{1}H NOE spectrum). In the major isomer, the phenyl substituent is located further away from the closest (*S*)-*i*Pr$_2$BOX isopropyl group.

Upon additional heating in solution, the isomers of **10** were observed to partially transform into the five-coordinate complex **8** with release of ethylene (Scheme 2). The presence of ethylene in solution minimally modified the ^{1}H NMR signals of **8** at room temperature, thus indicating that although the coordination of ethylene to this unsaturated complex is likely it only occurs to a modest extent. Yet, the removal of dissolved ethylene was found to accelerate the transformation and also resulted in the complete disappearance of **10**. In turn, the prolonged treatment of **7** with an excess of ethylene yielded complex **9**.

Competitive metalations such as those shown in Scheme 2 have been studied in depth within the context of palladacycle chemistry.[14] For oxazolines and other imines, the *endo* metallacycles (C=N bond inside the cycle) are commonly favored for thermodynamic reasons.[15] In contrast, for our iridium derivatives the selectivity seems to rely on the coordination number of the unsaturated Ir^{I} species that precedes the oxidative addition step. Thus, isopropyl activations are likely to occur via three-coordinate intermediates generated by H_2 (or CH) reductive eliminations.[16] Metalations at the (*S*)-*i*Pr$_2$BOX CR_2 bridges however, only seem feasible in the presence of ethylene or other ligands,[17] that is metalation occurs via four-coordinate intermediates. Rather than changing the relative stability of the Ir^{III} reaction products, the additional ligands seem to determine the selectivity of the C–H oxidative addition in a previous step, by modifying the position of equilibrium between the three- and four-coordinate Ir^{I} reaction intermediates.

The methylene-bridged (*S*)-*i*Pr$_2$BOX ligand of complex **1** did not undergo any of the oxidative additions shown in Scheme 2. Indeed, the metalation of the CH_2 bridge seems unlikely because of geometric constraints, but isopropyl activation should not be more difficult than in its analogues. In spite of this, under all the reaction conditions shown in

Scheme 2, **1** led to a complex mixture of products in which only species that contain two *trans*-phosphane ligands were recognized using ^{1}H and $^{13}P\{^{1}H\}$ NMR spectroscopy, thus indicating extensive disproportionation. Nevertheless, complex **1** was found to undergo facile insertions of aldehydes and ketones into one of the methylene C–H bonds. These insertions did not need the previous dehydrogenation of the iridium and yielded six-coordinate complexes that contain (*S*)-*i*Pr$_2$BOX ligands functionalized with an additional alcohol arm (**11**–**15**, Scheme 3). The X-ray crystal structure of complex **13** (Figure 2) confirmed the *fac* κ-*N*,*N*,*O* coordination mode of the new ligand generated by the insertion of acetone. All other insertion products displayed very similar ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra, which is in agreement with a common structure.



Scheme 3. Reversible diastereoselective aldehyde and ketone insertions into a bis(oxazoline) C_{sp^3}–H bond. Anion is BF_4.

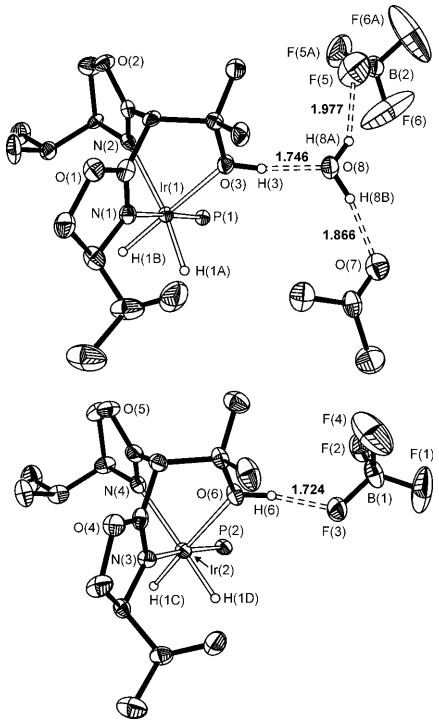


Figure 2. The X-ray crystal structures of the two independent molecules found in the asymmetric unit of **13**. For the ORTEP diagram the thermal ellipsoids are shown at 50% probability. The various hydrogen-bonding interactions are highlighted. The phosphane substituents have been omitted for clarity. Selected bond distances [Å] and angles [°] for **13a** (above): Ir(1)–P(1) 2.2504(14), Ir(1)–O(3) 2.296(4), Ir(1)–N(1) 2.116(4), Ir(1)–N(2) 2.164(4); P(1)-Ir(1)-O(3) 99.73(10), P(1)-Ir(1)-N(1) 178.02(13), P(1)-Ir(1)-N(2) 100.40(12), O(3)-Ir(1)-N(1) 80.92(15), O(3)-Ir(1)-N(2) 80.85(14), N(1)-Ir(1)-N(2) 81.54(16).

The insertion products **11**–**15** were found to be involved in slow equilibrium with complex **1** (Scheme 3). Therefore, the cleavage of not only a C–H bond in the precursor complex occurs, but also that of a C–C bond in the product, and both occur under remarkably mild reaction conditions. The reversible character of these insertions was substantiated in [D$_6$]acetone solutions of complex **13**, in which the quantitative replacement of the inserted acetone after 24 hours at room temperature was seen. The quantitative deuteration of the OH under the same reaction conditions was found to take less than 1 hour. The position of the equilibria depicted in Scheme 3 depends on the steric and electronic features of the carbonyl reagent. The stability of the insertion products was found to decrease going from compounds **11** to **15**. Acetaldehyde was the only reagent that led to stoichiometric quantitative insertion, whereas the insertion of acetophenone was not detected even when heating at 213 K in the presence of excess reagent. Under such reaction conditions, however, the species observed by ^{1}H, $^{13}P\{^{1}H\}$ and $^{13}C\{^{1}H\}$ NMR spectroscopy was not the precursor **1** but its acetophenone adduct [IrH$_2${κ^2-*N*-((S)-*i*Pr$_2$BOX)-CH$_2$}{OC(Me)Ph}-(P*i*Pr$_3$)]BF$_4$ (**16**), which is an analogue of the acetonitrile complex **4a**.

The data in Scheme 3 also shows that the chirality of the (*S*)-*i*Pr$_2$BOX ligand can be transmitted to the stereogenic centers that are generated by the insertion. The reaction with benzaldehyde seems to be an exception, as it yielded a 1:1 mixture of the two possible diastereomers. For all the other insertions, as for the oxidative addition product **10**, the *S* configured diastereomer is favored because the bulkiest group of the carbonyl reagent (R^2) is further away from the closest (*S*)-*i*Pr$_2$BOX isopropyl substituent. Nevertheless, the diastereoselectivity achieved with this particular (*S*)-*i*Pr$_2$BOX ligand and the present set of R^2 groups is modest.

These insertion reactions are precedented for tungsten complexes, which were observed to insert aldehydes and ketones into the C_{sp^2}–H bonds at the *ortho* positions of pyridine, to form five-membered azaoxymetallacycles.[18] Although the experimental evidence collected for these reactions did not lead to a single mechanistic interpretation, it suggested that elementary steps such as the direct C–C bond formations involving mutually *cis* ligands with subsequent hydrogen shifts, were preferred over pathways initiated by C–H bond activations at the metal. Such preferred reaction steps also seem to be the most likely explanation in our case, since the possibility of methylene metalation appears remote.

Formally at least, these insertions are nucleophilic additions of the methylene C–H bond to the carbonyl reagents, which could benefit from the close proximity of the reacting sites if the insertion occurs in the aldehyde or ketone adducts of **1** that are analogous to the acetonitrile isomer **4b** (see

Scheme 1). Such spatial proximity might render an effective mechanism involving the deprotonation of methylene even in the absence of strong bases; a possibility already suggested by the network of hydrogen-bonding interactions exhibited by **13** in the solid state (Figure 2). Any of the participants in this network, that is the anion and the water and acetone solvent molecules, seem capable of assisting a proton shift from the oxygen atom to the former methylene carbon atom and vice versa, via a short-lived protonated species or transition state.[19] More durable deprotonations, such as those caused by excess potassium *tert*-butoxide or triethylamine, have been found to provoke the release of the ketone to give the neutral five-coordinate bis(oxazolinate) complex [IrH_2\{κ^2-*N*-((*S*)-*i*Pr_2BOX)-CH\}(P*i*Pr_3)] (**17**).[20] This result suggests that the more conventional stepwise mechanisms that involve long-lived deprotonated intermediates are less likely.

In summary, it has been shown that C–H bonds can be reversibly and diastereoselectively functionalized into alcohols by the insertion of aldehydes or ketones. Such reactions have been observed in octahedral iridium complexes and require the coordination of the reagents, although they do not seem to involve the coordination of the C–H bond or its activation at the iridium coordination sphere. On the basis of these observations further mechanistic details of such reactions, their scope, and possible applications are currently under investigation.

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