Cleavage of sp³ C−O Bonds via Oxidative Addition of C−H Bonds

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The ability of transition-metal complexes to undergo oxidative addition of strong bonds is one of their most characteristic and important traits. In organic chemistry, such reactions are obviously of particular interest in the context of bonds to carbon. The addition of C−Hal bonds has been studied extensively and is a critical step in numerous important catalytic reactions. The oxidative addition of unactivated C−H bonds, first reported in the early 1980s, is now the subject of widespread study and interest. This interest is largely based on the potential value of "functionalizing the C−H bond", for example, by oxidizing it or adding it across an organic unsaturated group such as a C=C double bond.[1]

In contrast to C−Hal and C−H bonds, there is very little precedent for the oxidative addition of unactivated C−O bonds. A few noteworthy intramolecular examples have been reported, involving prior coordination by "directing groups" or ligands.[2] To our knowledge, however, there is only one example of intermolecular addition of an unactivated C(sp³)−O ether bond,[3] eq 1 reported by Tolman and Ittel:[4]

$$Fe(dmpe)_2 + CH_3OPh \rightarrow trans\text{-}(CH_3)(OPh)Fe(dmpe)_2$$

(1)
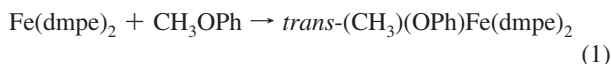
The microscopic reverse of C−O addition, C−O reductive elimination, has been studied.[5−10] Goldberg and Williams[10] have reported that for Pt(IV) complexes, the mechanism involves dissociation of hydroxide or aryl oxide and nucleophilic attack on the alkyl group. In view of the high nucleophilicity of Fe(dmpe)₂, it seems likely that eq 1 proceeds via initial S_N2 attack on the anisole methyl group [i.e., the microscopic reverse of the reaction elucidated for elimination from Pt(IV)[10]].

Pincer-ligated iridium complexes have been investigated extensively in the context of C−H addition, in part because of their ability to generate three-coordinate d⁸ species, which often do not undergo deactivating intramolecular additions or dimerizations. Such species are reactive toward other bonds as well and indeed have been found to oxidatively add to O−H, C−Hal, and N−H bonds, for example. Our preliminary density functional theory (DFT) calculations indicated that C−O addition would also be thermodynamically quite favorable.

We have previously shown that (PCP)Ir(*tert*-butylvinyl)(H) (**1**) (PCP = κ^3-C₆H₃-2,6-[CH₂P(*t*-Bu)₂]₂) acts as a precursor of the active fragment (PCP)Ir.[11] The reaction of **1** with 1.05 equiv of anisole in *p*-xylene-d_{10} at room temperature immediately results in addition of the anisole ortho C−H bond to give **2**, which shows a sharp hydridic resonance at −45.03 ppm (t, ²J_{PH} = 14.4 Hz, 1H, Ir−H) in the ¹H NMR spectrum.[12,13] This complex is spectroscopically very similar to the previously reported[11] complex (PCP)Ir-(Ph)(H), but in that case, the hydride resonance is too broad to observe at room temperature as a result of rapid and reversible C−H elimination. DFT calculations indicate that the formation of complex
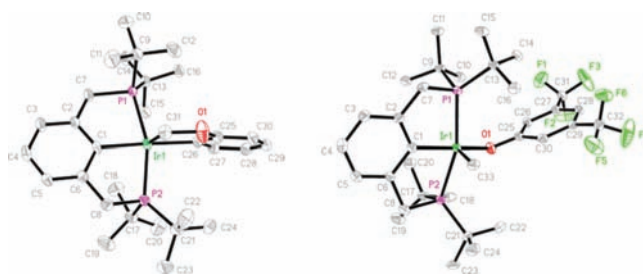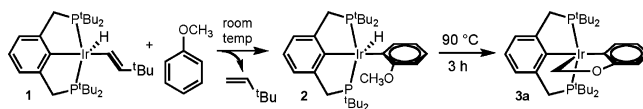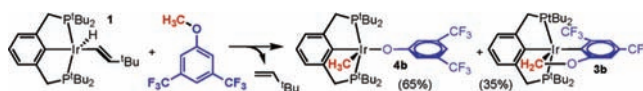

Figure 1. ORTEP diagrams of **3a** (left) and **4b** (right).

Scheme 1. Reaction of **1** with Anisole

Scheme 2. Reaction of **1** with 3,5-Bis(trifluoromethyl)anisole

2 is 2.0 kcal/mol more exergonic than is benzene C−H addition, presumably because of a weak interaction between the methoxy group and the iridium center (Ir−O distance = 3.14 Å).[12]

Heating a solution of **2** for 3 h at 90 °C gave cyclometalated product **3a** (characterized by NMR spectroscopy and X-ray crystallography; Figure 1) in quantitative yield (Scheme 1).[12] Thus, not only (PCP)Ir(I) but also the Ir(III) product of C−H activation, **2**, have the ability to activate C−H bonds.

(PCP)Ir does not add aryl C−H bonds ortho to a methyl group.[11] Accordingly, the addition of either 2,6-dimethylanisole or 3,5-dimethylanisole to a solution of **1**, rather than unsubstituted anisole, did not afford the analogues of products **2** or **3a**; heating to 100 °C gave a complex mixture of products that has not yet been characterized.

To enhance the reactivity of the C−O bond while blocking the ortho C−H bond, we investigated the reactivity of 3,5-bis(trifluoromethyl)anisole. To our satisfaction, we observed the formation of (PCP)Ir(CH₃)(3,5-bis(trifluoromethyl)phenoxide) (**4b**) in 65% yield along with 35% cyclometalated product **3b** (Scheme 2). Diagnostic of the presence of an iridium methyl group in **4b**, resonances appear at 1.75 ppm (t, 3H, J_{PH} = 4.8 Hz) in the ¹H NMR spectrum[12] and −28.67 ppm (t, J_{PC} = 4.4 Hz) in the ¹³C NMR spectrum. The structure of **4b** was also confirmed crystallographically (Figure 1). To our knowledge, this is only the second example, after that of eq 1, of an intermolecular (i.e., without prior coordination or ligation) oxidative addition of an ether (or alcohol)

Table 1. Calculated Gibbs Free Energies (kcal/mol) for C−O Bond Cleavage Reaction Pathways

| C-H activation/ -OAr migration Ar-O-Me [a]	ΔG	C-H activation/ -OPh migration Ph-O-Me	ΔG
(PCP)Ir + Ar-O-Me	0.0	(PCP)Ir + Ph-O-Me	0.0
(PCP)Ir(Ar-O-Me) C-H σ-complex	8.8	(PCP)Ir(Ph-O-Me) C-H -complex	7.8
TS: C-H addition	11.2	TS: C-H addition	11.8
(PCP)Ir(H)(CH₂OAr)	1.1	(PCP)Ir(H)(CH₂OPh)	1.9
TS: ArO α-migration	22.4	TS: PhO -migration	29.9
(PCP)Ir(H)(CH₂)(OAr)	15.1	(PCP)Ir(H)(CH₂)(OPh)	23.1
TS: H migration to CH₂	**29.0**	**TS: H migration to CH₂**	**32.3**
(PCP)Ir(CH₃)(OAr)	-8.7	(PCP)Ir(CH₃)(OPh)	-5.8
Direct C-O activation Ar-O-Me	**ΔG**	**Direct C-O activation Ph-O-Me**	**ΔG**
TS: C-O addition	**39.6**	**TS: C-O addition**	**41.2**
(PCP)Ir(CH₃)(OAr)	-8.7	(PCP)Ir(CH₃)(OPh)	-7.4
C-H activation/ -OAr migration Ar-O-Et	**ΔG**	**C-H activation/ -OPh migration Ph-O-Et**	**ΔG**
(PCP)Ir + Ar-O-Et	0.0	(PCP)Ir + Ph-O-Et	0.0
TS: C-H addition	18.4	TS: C-H addition	17.3
(PCP)Ir(H)(C₂H₄OAr)	8.5	(PCP)Ir(H)(C₂H₄OPh)	10.1
TS: ArO β−migration	**20.5**	**TS: PhO β-migration**	**22.6**
(PCP)Ir(H)(C₂H₄)(OAr)	-1.7	(PCP)Ir(H)(C₂H₄)(OPh)	4.5
(PCP)Ir(H)(OAr) + C₂H₄	-16.4	(PCP)Ir(H)(OPh) + C₂H₄	-9.3
Direct C-O activation Ar-O-Et	**ΔG**	**Direct C-O activation Ph-O-Et**	**ΔG**
TS: C-O activation	**44.4**	**TS: C-O activation**	**46.3**

[a] Ar = p-C₆F₄Me

C−O bond involving a simple alkyl group (probably the most important examples with "activated" carbon centers are allylic[14]).

To fully block the formation of ortho C−H activation products, pentafluoroanisole was investigated. Treatment of **1** with 1.05 equiv of pentafluoroanisole at room temperature resulted in an immediate color change from dark-red to red. NMR spectroscopy revealed quantitative formation of (PCP)Ir(CH₃)(OC₆F₅) (**4c**), whose structure was confirmed crystallographically.[12]

In contrast with the Ittel−Tolman system, a simple S$_N$2 mechanism seems unlikely in the present case. Evidence against such a mechanism, and against a direct C−O oxidative addition pathway, was obtained from isotope effect experiments wherein addition of mixtures containing an excess of 4-methoxy-2,3,5,6-tetrafluorotoluene and its deuteromethoxy analogue were added to a p-xylene solution of **1**; the observed kinetic isotope effect (KIE) was $k_{OCH_3}/k_{OCD_3} = 4.3(3)$ at room temperature.[12,15,16]

DFT calculations (Table 1) predict that direct oxidative addition (three-centered transition state) of (PCP)Ir to the Me−O bond of MeO(p-C₆F₄Me) has a barrier of $\Delta G^\ddagger = 39.6$ kcal/mol [relative to (PCP)Ir and the free aryl ether]. A pathway calculated to be significantly more favorable ($\Delta G^\ddagger = 29.0$ kcal/mol) is that shown in Scheme 3. Methoxy C−H addition is followed by α-aryloxy elimination[17] to give a methylidene complex. A subsequent 1,2-migration of H from Ir to the carbene gives the observed product. Importantly, the mechanism in Scheme 3 accounts for the large isotope effect. The calculated overall KIE is 7.0, which can be expressed as the product of the equilibrium isotope effect (EIE) calculated for formation of the methylidene complex (3.9) and KIE$_{M-CH_2}$ for the metal-to-carbene H migration (1.8). The calculated KIE$_{M-CH_2}$ is in good agreement with the experimental KIE of 2.0(6)

Scheme 3. Proposed Mechanism for the Oxidative Addition of the C−O Bond of Methyl Aryl Ethers by (PCP)Ir
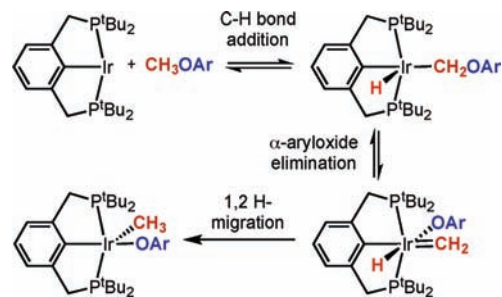
Scheme 4. Reaction of **1** with Ethoxybenzene
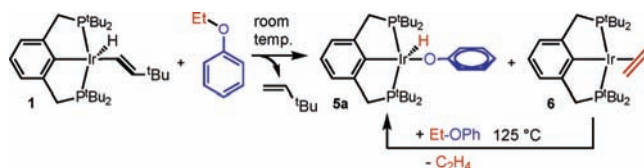
for metal-to-methylidene H migration reported by Bercaw and co-workers.[18] However, for reasons that are not clear, the calculated EIE of 3.9 is greater than experimental values reported for C−H/D addition to metal centers ($\sim$2);[19] this could account for the discrepancy between our calculated (7.0) and experimental [4.3(3)] KIEs for the overall reaction.

During the course of this work, Grubbs and Whited reported a rich body of chemistry involving the reactions of pincer-ligated iridium complexes with ethers.[20] This work was focused mostly on Ozerov's "PNP" pincer but also explored the anthraphos-based PCP-type ligand. Remarkably, the use of different ligands and (perhaps more importantly) different ethers afforded completely different chemistry than is reported in this paper. As in the present work, the Grubbs−Whited chemistry is based on addition of a C−H bond adjacent to oxygen followed by α-elimination, but in marked contrast to this work, it is α-*elimination of H rather than OR* of the CH₂OR group that is the key step responsible for their observations.[21] The resulting alkoxycarbene can undergo elimination of olefin to give a metal carbonyl dihydride. Interestingly, in that case, the net reaction involves cleavage of four of the five bonds of the H₃C−O−R unit, i.e., all of the bonds *except* the C−O bond, which is the *only* bond that is broken in the net reaction of Scheme 3.

We also investigated the chemistry of ethyl aryl ethers with (PCP)Ir precursors. The resulting reaction is quite distinct from, but not unrelated to, that of the methyl aryl ethers. Ethoxybenzene reacts with **1** at room temperature in p-xylene to give a 1:1 ratio of (PCP)Ir(H)(OC₆H₅) (**5a**; crystallographically characterized)[12] and (PCP)Ir(ethylene) (**6**)[12,22] (Scheme 4).[23] Further heating at 125 °C gives complete conversion to **5a**.

Thus, unlike the methylaryloxy C−O oxidative additions, the presence of substituents on the aryl ring (ortho or otherwise) is not required in order to permit the C−O cleavage reaction of Scheme 4. However, the initial reaction of 4-ethoxy-2,3,5,6-tetrafluorotoluene (**7**) with **1** at room temperature is faster (giving the analogous aryl oxide **5d** and **6**), and the subsequent reaction to give full conversion to **5d** proceeds at 80 °C instead of 125 °C.

Direct C−O oxidative addition followed by β-H elimination from the ethyl group would lead to the products shown in Scheme 4. However, on the basis of the above conclusion that direct C−O addition does not occur with methyl aryl ethers, this would seem unlikely. Accordingly, we calculated that the barriers to C(sp³)−O

Scheme 5. Proposed Mechanism for Cleavage of the C–O Bond (Dehydroaryloxation) of Ethyl Aryl Ethers by (PCP)Ir
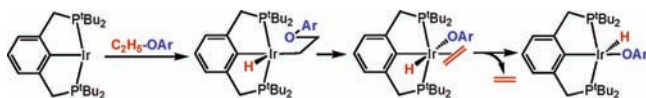
Scheme 6. Competition Experiment To Determine the Relative Rates of Reaction of (PCP)Ir with Methyl versus Ethyl Aryl Ether
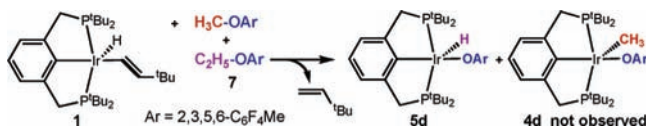
addition are $\Delta G^{\ddagger} = 44.4$ kcal/mol for 4-ethoxy-2,3,5,6-tetrafluorotoluene and 46.3 kcal/mol for ethoxybenzene (Table 1). In contrast, we calculated barriers that are far lower for a pathway involving addition of the terminal C–H bond followed by β-aryloxy elimination and loss of ethylene (Scheme 5): $\Delta G^{\ddagger} = 20.5$ and 22.6 kcal/mol for 4-ethoxy-2,3,5,6-tetrafluorotoluene and ethoxybenzene, respectively.

In accord with the much lower calculated barriers for the β-aryloxy eliminations (Scheme 5; Table 1) than for the α-aryloxy elimination pathway (Scheme 3), when a mixture of 4-methoxy-2,3,5,6-tetrafluorotoluene and **7** was reacted with **1**, complexes **5d** and **6** (the same products that are obtained from pure **7**) were formed exclusively (Scheme 6); i.e., there was no evidence of any reaction with 4-methoxy-2,3,5,6-tetrafluorotoluene.[12]

In conclusion, we have presented two classes of reactions in which the C–O bond of alkyl aryl ethers is cleaved. In the first case, the net reaction is an unusual oxidative addition of the alkyl (methyl) C–O bond. The second is a dehydroaryloxation reaction. In both cases, the initial step is C(sp^3)–H activation at the CH$_3$ of the methoxy and ethyl groups, respectively. It is noteworthy that whereas the C–H bond has historically been characterized by its inertness in contrast to "functional" groups, the results herein suggest that C–H oxidative addition may provide an entry point toward breaking bonds in a molecule that are significantly weaker[24] than the C–H bond itself but kinetically less reactive toward transition metals. In particular, this seems surprising in the case of the C–O oxidative addition, wherein the C–H bond is re-formed following the C–O bond cleavage step. Perhaps even less intuitive is the conclusion, based on microscopic reversibility, that C–O reductive elimination from complexes **4** would proceed via an initial α-H migration. We are currently exploring ways to exploit both of these reactions catalytically in either the direction observed in this study or the reverse.

Supporting Information Available: Experimental details and procedures, details of DFT calculations, spectral data, and crystallographic data for complexes **3a**, **4b**–**d**, **5a**, and **5d** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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