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Formation and Cleavage of C−H, C−C, and C−O Bonds of *ortho*-Methyl-Substituted Anisoles by Late Transition Metals

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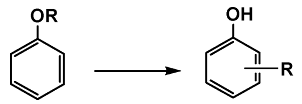
Rearrangement of alkyl aryl ethers, ROAr, to alkyl phenols (eq 1) is an important reaction that occurs with (or without) various Lewis acid catalysts.[1] *ortho*-Substituted phenols are commonly obtained (as in the Claisen rearrangement for R = allyl[1]), but blocking the *o*-positions with aliphatic groups (e.g., CH_3) yields usually the corresponding *p*-R-substituted phenols instead of those resulting from aliphatic C−C coupling of the R group with one of the *o*-substituents.[2] Herein we wish to report the conversion of the anisoles of Scheme 1 into the corresponding 2-ethyl-6-methylphenols **2**, through the intermediacy of the hydride aryloxide iridium compounds **1**. The use of the ^{13}C-enriched anisoles, $ArO^{13}CH_3$, demonstrates that the ^{13}C label distributes across the two olefinic sites of compounds **1** and thereby across the two ethyl positions of the phenols **2**. Hence the irreversible cleavage of the unstrained R−OAr bond[3−6] is accompanied by multiple C−H bond activations and by reversible and irreversible C−C and C−O bond forming and breaking reactions.[7−9]

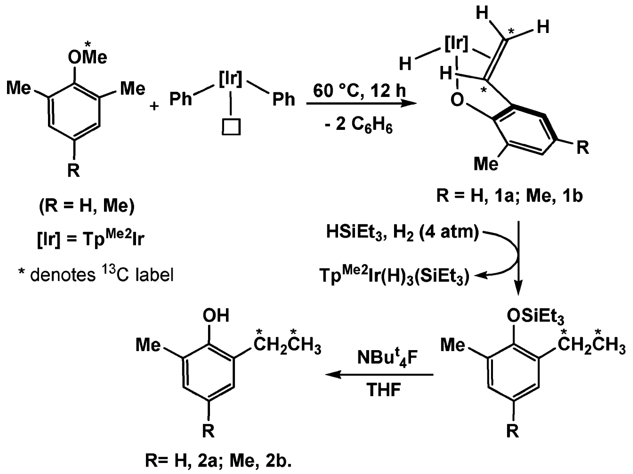


(1)

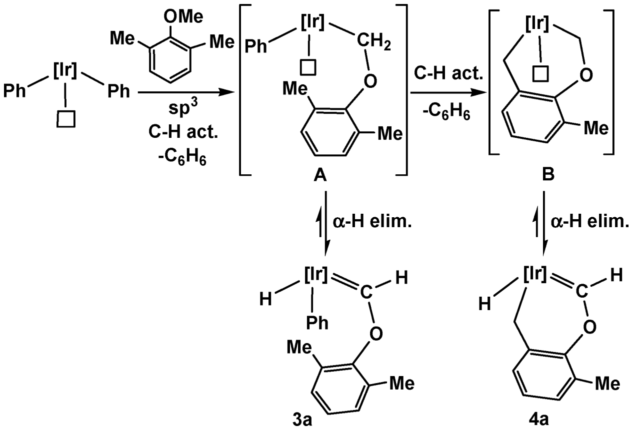
Heating the anisoles $2,6\text{-}Me_2C_6H_3OMe$ and $2,4,6\text{-}Me_3C_6H_2OMe$ in the presence of the unsaturated species $[Tp^{Me_2}Ir(C_6H_5)_2]$[10] gives compounds **1a** and **1b**, respectively, in spectroscopic yields close to 90%. These compounds feature a characteristic high-field ^{1}H NMR resonance around δ −17.5 ppm, whereas the ^{1}H and ^{13}C{^{1}H} NMR data for their olefinic ligands are very similar to those found for an analogous complex generated in the reaction of 2-ethylphenol with the same Ir(III) precursor.[11a] Obtention of phenols **2a** and **2b** from **1a** and **1b**, respectively, can be achieved by treatment with $SiHEt_3$ under 4 atm of H_2 to yield $Tp^{Me_2}(H)_3(SiEt_3)$[11b] along with the corresponding silyl ethers, which are then easily hydrolyzed to the phenols **2**. The reaction steps of Scheme 1 can be effected sequentially without isolating the intermediate products.

To gain mechanistic insight into this complex transformation, the reaction of $Tp^{Me_2}Ir(C_6H_5)_2(N_2)$ and 2,6-dimethylanisole has been monitored by ^{1}H NMR spectroscopy (60 °C, C_6D_{12}, Ar atmosphere). Two hydride carbene intermediates can be detected (Scheme 2) and are characterized by ^{1}H carbene and hydride resonances, respectively, at 15.49 and −15.06 ppm (**3a**) and 15.75 and −17.03 ppm (**4a**). Further heating results in the progressive disappearance of the signals due to **3a** and the emergence of resonances corresponding to the reaction product **1a**. The NMR monitoring reveals conclusively that **3a** converts into **4a** which then rearranges to **1a** without any other observable intermediate. 2,4,6-Trimethylanisole exhibits an almost identical behavior.

Scheme 1



Scheme 2



Even though analytically pure samples of **3a** and **4a** have not been obtained (contamination by minor amounts of the other carbene intermediate and the hydride alkene product was unavoidable), the structural characterization of the two compounds by 1D and 2D NMR techniques is unambiguous (see Supporting Information). Their formation can be proposed to take place as depicted in Scheme 2 for the 2,6-dimethylanisole reaction. Following initial sp^3 C−H bond activation within the −OMe unit, reversible α-H elimination would give the hydride carbene **3a**,[12] whereas a second sp^3 C−H bond activation, this time involving one of the *ortho*-Me groups of the anisole, along with another reversible α-H elimination step would account for the formation of the second intermediate **4a**.[13] The isomeric hydride alkylidene resulting from α-H elimination from the other Ir−CH_2 unit of **B** has not been detected. Similar

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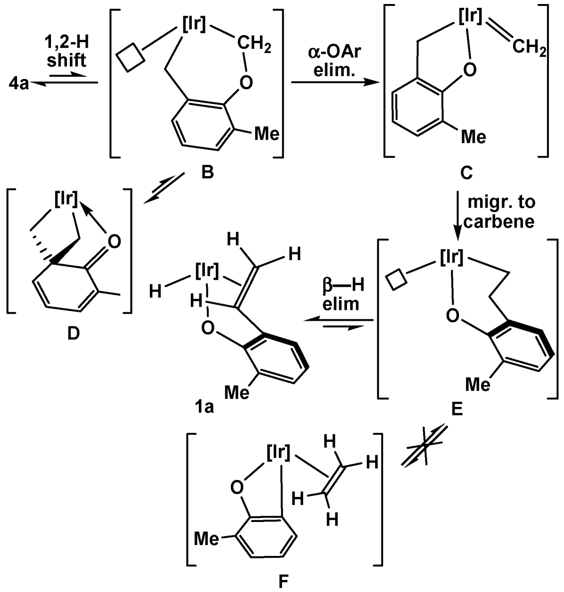
10.1021/ja0586790 CCC: $33.50

Scheme 3



studies employing the ^{13}C-enriched (ca. 45%) anisoles ArO^{13}CH$_3$ reveal that the label appears exclusively at the carbene carbon of **3a** and **4a** ($^1J_{CH}$ values of 154 (**3a**) and 159 Hz (**4a**) for their Ir═CH− functionalities).

A definite mechanistic proposal for the conversion of **4a** into product **1a** cannot be made at this stage. Scheme 3 shows a plausible reaction pathway that implies an irreversible α-OAr elimination[14] to yield a transient methylene species **C** that progresses by migratory insertion and β-H elimination. However, by this direct route, the use of the ^{13}C-enriched anisoles, ArO^{13}CH$_3$, would give complexes **1** labeled exclusively at the terminal alkene carbon atoms, instead of the experimentally observed ^{13}C distribution across the two olefinic sites (favoring the terminal alkene carbon, regardless of the reaction time, by ca. 70 and 55% for **1a** and **1b**, respectively). To account for this fact, partial equilibration of **B** with a cyclohexadienone intermediate **D**[15] may be suggested. As indicated by a reviewer, **4a** could also evolve by migration of the benzylic carbon onto the carbene carbon, followed by α-OAr elimination within the resulting benzodihydrofuran intermediate, so that the distribution of the ^{13}C label would occur by rearrangement of a carbenium zwitterion. Theoretical calculations, presently underway, could help to clarify these mechanistic aspects. It is worth pointing out that an alternative explanation for the ^{13}C scrambling implying reversible β-aryl elimination[9a,c,d,17,18] from **E** to **F** as the only cause of the ^{13}C scrambling in **1** can also be discarded, as fast rotation[19] in the putative ethylene species **F** would result in the even distribution of the ^{13}C label in the alkene sites of **1**.

In summary, this work demonstrates that late transition metals are able to induce unprecedented reactivity in methyl aromatic ethers that have their *ortho* positions blocked by Me substituents. Multiple C−H bond activations[12] as well as reversible and irreversible C−O and C−C bond cleavage and forming reactions have been ascertained. Extension of these studies to other alkyl (and allyl) aryl ethers, with and without *ortho* substituents, appears feasible and is presently being pursued.

Acknowledgment. Dedicated to Prof. Victor Riera on the occasion of his retirement. Financial support from the DGI (Project CTQ 2004-00409/BQU, FEDER support), the Junta de Andalucía, and cooperation project CSIC-CONACyT are gratefully acknowledged. L.L.S. and P.L. thank the MEC for research grants.

Supporting Information Available: Synthetic procedures and spectroscopic and analytical data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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JA0586790