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C−H Bond Activation Reactions of Ethers That Generate Iridium Carbenes

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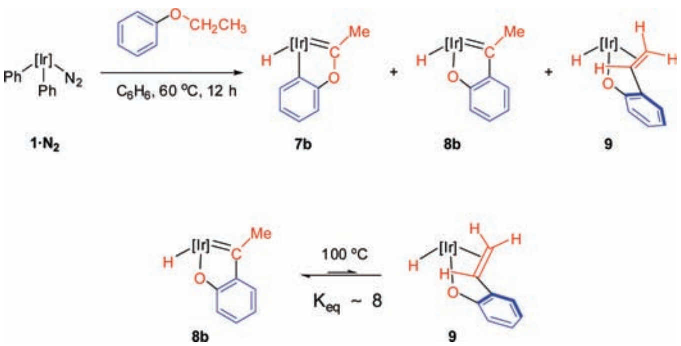

Two important objectives in organometallic chemistry are to understand C−H bond activation reactions mediated by transition metal compounds and then to develop efficient ways of functionalizing the resulting products. A particularly ambitious goal is the generation of metal carbenes from simple organic molecules; the synthetic chemist can then take advantage of the almost unlimited reactivity of this metal−organic functionality. This goal remains very difficult indeed with saturated hydrocarbons, but it is considerably more facile for molecules that possess a heteroatom (such as ethers), because coordination of the heteroatom to the metal renders the ensuing C−H activation an intramolecular reaction.

In this Account, we focus on the activation reaction of different types of unstrained ethers, both aliphatic and hemiaromatic, by (mostly) iridium compounds. We emphasize our recent results with the $Tp^{Me2}Ir(C_6H_5)_2(N_2)$ (**$1 \cdot N_2$**) complex (where Tp^{Me2} denotes hydrotris(3,5-dimethylpyrazolyl)borate). Most of the reactivity observed with this system, and with related electronically unsaturated iridium species, starts with a C−H activation reaction, which is then followed by reversible α-hydrogen elimination. An α-C−H bond is, in every instance, broken first; when there is a choice, cleavage of the stronger terminal C_{sp^3}−H bonds is always preferred over the weaker internal C_{sp^3}−H (methylene) bonds of the ether. Nevertheless, competitive reactions of the unsaturated $[Tp^{Me2}Ir(C_6H_5)_2]$ iridium intermediate with ethers that contain C_{sp^3}−H and C_{sp^2}−H bonds are also discussed. We present theoretical evidence for a σ-complex-assisted metathesis mechanism (σ-CAM), although for other systems oxidative addition and reductive elimination events can be effective reaction pathways. We also show that additional unusual chemical transformations may occur, depending on the nature of the ether, and can result in C−O and C−C bond-breaking and bond-forming reactions, leading to the formation of more elaborate molecules.

Although the possibility of extending these results to saturated hydrocarbons appears to be limited for this iridium system, the findings described in this Account are of fundamental importance for various facets of C−H bond activation chemistry, and with suitable modifications of the ancillary ligands, they could be even broader in scope. We further discuss experimental and theoretical studies on unusual alkene-to-alkylidene equilibria for some of the products obtained in the reactions of iridium complex **$1 \cdot N_2$** with alkyl aryl ethers. The rearrangement involves reversible α- and β-hydrogen eliminations, with a rate-determining metal inversion step (supported by theoretical calculations); the alkylidene is always favored thermodynamically over the alkene. This startling result contrasts with the energetically unfavorable isomerization of free ethene to ethylidene (by about 80 kcal mol^{-1}), showing that the tautomerism equilibrium can be directed toward one product or the other by a judicious choice of the transition metal complex.

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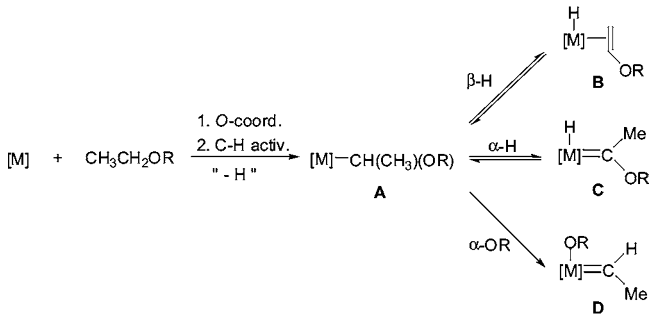
Introduction

The efficient activation and functionalization of the C−H bonds of hydrocarbons by transition metal compounds is one of the most important, but at the same time difficult, challenges in chemistry.[1] In the late 1960s and 1970s some remarkable discoveries pointed toward the possibility of using transition metals to cleave the C−H bonds of hydrocarbons, that is, the previous step needed for further functionalization.[2] In 1982 Bergman[3a] and Graham[3b] observed for the first time the intermolecular activation of saturated hydrocarbons by iridium complexes, and these results encouraged numerous efforts that have culminated in some instances in the catalytic functionalization of these molecules.[4]

The almost unlimited reactivity of metal carbenes disclosed in the last decades, which has led to an explosive growth of this field of chemistry,[5] makes highly desirable direct conversion of alkanes into metal alkylidenes, because these molecules could then offer a manifold of useful reactivity pathways. Nonetheless, generation of a metal alkylidene, M═C(H)R, from a saturated hydrocarbon, RCH_3, is in general a highly endothermic process, since the formation of dihydrogen does not compensate for the cleavage of two strong C_{sp^3}−H bonds.[6] Moreover, approaching the C−H bonds to be broken to the reactive metal is enthropically unfavorable and suffers from the undesirable energetics of donating electron density from a strong, highly directional C_{sp^3}−H bond. Indeed, for mononuclear M−alkane σ-complexes,[7a] binding energies are on the order of 40−50 kJ mol^{-1} or may have even lower values.[7b,c] Despite these difficulties, many transition metal compounds are known to activate the C−H bonds of hydrocarbons.[1,7,8]

An alternative strategy to investigate C−H bond activation reactions makes use of organic molecules that possess a heteroatom (O, N, etc.), whose coordination to the metal center converts C−H activation in an intramolecular process. In order to facilitate subsequent formation of the required C−H σ-complex,[1c] the M−heteroatom bond must be relatively weak, and this makes ethers, a family of relatively poor Lewis bases, ideal molecules for these model studies.[9] The need for oxygen precoordination leads invariably to initial C−H activation at one of the adjacent carbon atoms. Thus, for an ethyl ether, an alkoxyalkyl intermediate would first form (**A** in Scheme 1). This step could be facilitated by the presence in the starting complex of a sacrificial hydride or hydrocarbyl group (not represented in the scheme) that would form a strong H−H or R−H bond. Common β-H elimination[10] can then lead to a hydride alkene (π vinyl ether complex, **B**), whereas the alternative α-H elimination provides the target metal carbene (**C**).

SCHEME 1. Possible Products of C−H Bond Activation of an Ethyl Ether



A third, also attractive, reaction pathway, namely, α-OR elimination, produces a carbene too. With a suitable choice of the metal and ancillary ligands, these reaction routes may be viable, and the ether double C−H activation results in a complex of either of these types or a derivative thereof. In particular, the potential utility of the α-H elimination path has been demonstrated recently by Grubbs and co-workers[11] and also by ourselves.[9,12]

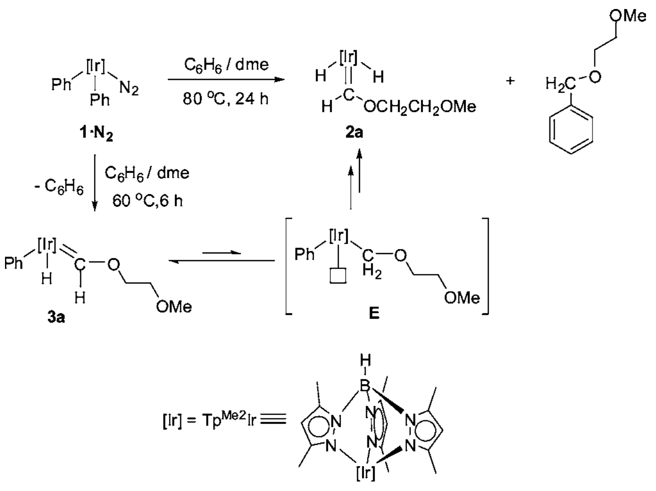
In 1992, we observed the formation of a ca. 1:1 mixture of an iridium hydride allyl and an iridium hydride cyclic alkoxy-carbene during the reaction of $Tp^{Me2}Ir(C_2H_4)_2$ (Tp^{Me2} denotes hydrotris(3,5-dimethylpyrazolyl)borate) with tetrahydrofuran.[13] Following a previous perspective article,[9] in this Account, we focus on recent results regarding the C−H activation reactions of unstrained ethers (aliphatic and hemiaromatic ethers) by iridium(III) complexes stabilized by the hydrotris(3,5-dimethylpyrazolyl)borate ligand. The reaction pathways observed can involve not only multiple C−H bond activation but also cleavage of C−O bonds along with generation of new C−C bonds. In the activation of alkyl aryl ethers, a tautomeric alkylidene-to-alkene equilibrium is often detected. Theoretical calculations have provided valuable information with regard not only to the mechanism of the C−H activation steps but also to the thermodynamics that govern formation of the carbene tautomers.

Activation of Aliphatic Ethers

When a solution of $Tp^{Me2}Ir(C_6H_5)_2(N_2)$ (**1·N$_2$**) was heated at 80 °C in benzene in the presence of 1,2-dimethoxyethane (dme), two products were formed, an iridium carbene complex (**2a**) and $C_6H_5CH_2OCH_2CH_2OCH_3$.[14] Obviously, the benzyl ether derived formally from a dehydrogenative coupling of one molecule of benzene and one of dme (Scheme 2).

Important mechanistic information was obtained carrying out the reaction under milder conditions (60 °C, 6 h) or at 80

SCHEME 2. Activation of $MeOCH_2CH_2OMe$ by $\mathbf{1 \cdot N_2}$



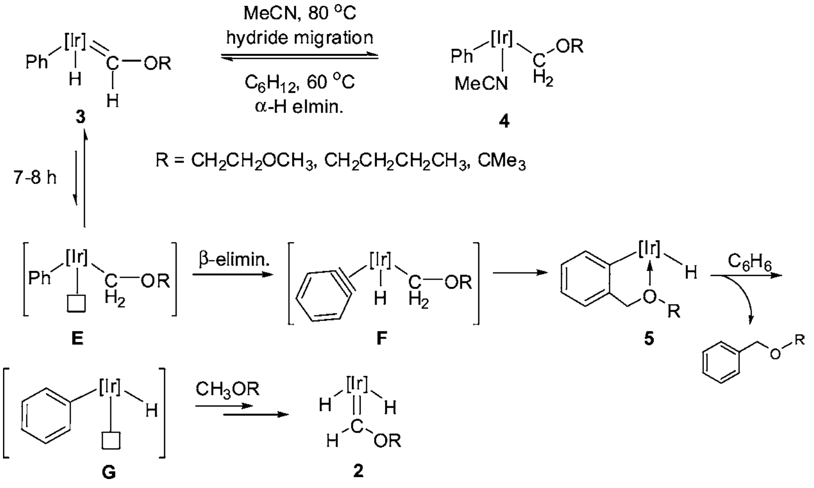
°C for a shorter period of time (30 min). In this case, quantitative formation of carbene **3a** is achieved by double C−H bond activation of a CH_3O− fragment of dme. To confirm the generality of the double C−H bond activation, two other methyl ethers were studied, namely, $MeOBu^n$ and $MeOBu^t$.[14] Corresponding carbene complexes **3b** and **3c**, respectively, were obtained, once more as a result of the selective cleavage of two C−H bonds of the MeO− group of the ether. Schemes 2 and 3 depict the mechanism of formation of these complexes, which involves generation of an alkoxyalkyl intermediate **E**, which undergoes reversible α-H elimination to form compounds **3**. Experimental evidence for this intermediate was obtained by isolation for the three ethers of corresponding NCMe adducts, which form, also reversibly, upon treatment of **3** with NCMe at 80 °C (Scheme 3). The need for O-coordination of the ether was shown by failure to isolate a carbene derived from activation at the $-OCMe_3$ terminus of $MeOBu^t$. For both dme and $MeOBu^n$, cleavage of the somewhat weaker $-OCH_2-$ bonds did not take place.[14] The same selectivity has been reported by Grubbs, Ozerov, and co-workers in the activation of *sec*- and *n*-butyl ether by an Ir(I) unsaturated fragment stabilized by amidobis(phosphine), PNP, pincer ligand.[15] This is in line with well-established trends in C−H bond activation chemistry, where C−H activation of the stronger primary bonds is preferred over the weaker secondary or tertiary C−H bonds, due to the higher strength of the resulting $M-CH_2R$ bond.[16]

In contrast with the simplicity of the α,α-dehydrogenation of methyl ethers, activation of Et_2O by $\mathbf{1 \cdot N_2}$ gives a complex mixture of products that are still under investigation. It is remarkable that a simple modification of the ligand environment by use of a complex that contains a phenyl-substituted hydrotris(pyrazolyl)borate ligand gives cleanly the ethoxycarbene complex resulting from α,α-C−H activation of Et_2O.[17a] A similar type of product was obtained by Bercaw with a platinum system,[17b] while Templeton (also with Pt),[18a] Bergman,[18b] and Grubbs[15] (both with the use of Ir(I) precursors) obtained vinyl ethers derived from α,β-C−H bond activation. Clearly, for intermediate **A** in Scheme 1, α- and β-elimination are competitive, and as pointed out earlier,[9] subtle factors, therefore hard to discover, may determine prevalence of one over the other fundamental reaction.

C−C Bond Formation Ensuing from C−H Activation

Formation of a C−C bond following C−H activation is an attractive methodology for the synthesis of elaborate molecules from common starting materials.[19] As shown in Scheme 2 activation of dme by $\mathbf{1 \cdot N_2}$ gives a bis(hydride) carbene **2a** accompanied by the benzyl ether $C_6H_5CH_2OCH_2CH_2OMe$, which results from dehydrogenative coupling of a molecule of C_6H_6 (the reaction solvent) and another of dme. The reaction

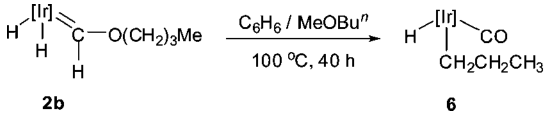
SCHEME 3. C−C Bond Formation Following C−H Activation of Methyl Ethers



is general and related carbenes (**2b**, **2c**) and benzyl ethers ($C_6H_5CH_2OR$) were obtained in the analogous activation of $MeOBu^n$ and $MeOBu^t$. Evidently, carbenes **3** are active participants in these reactions.[14]

Another mechanistic insight was made when complex **3a** was heated in cyclohexane for a few hours. This reaction allowed the isolation of hydride aryl derivative **5a**, which probably forms through the mechanism shown in Scheme 3. In a first step, migration of the hydride to the carbene in complexes **3** generates unsaturated 16-electron Ir(III) species that, as already stated, were trapped in the form of acetonitrile adducts **4**. These species can evolve through β-H elimination, leading to hydride benzyne complex intermediates **F**, which finally experience a C–C coupling reaction. Subsequently, a molecule of benzene reacts with complexes **5** releasing the benzyl ether and the unsaturated iridium phenyl hydrides **G**. Double C–H bond activation of the methyl group of a second molecule of the aliphatic ether by intermediates **G** will eventually generate the dihydride carbene complexes **2**. It is worth mentioning that the reactions were carried out in the presence of an excess of the aliphatic ether; hence no side reactions with the released benzyl ether were observed. It is also worth stating that when heated in benzene, carbenes **2** did not release H_2 to form compounds **3**. This prevented development of a catalytic cycle for the production of benzyl ethers, $C_6H_5CH_2OR$, from benzene and methyl ethers, MeOR.[14]

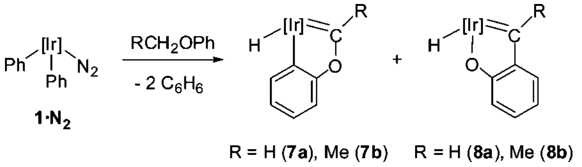
Before closing this section, it is pertinent to note that, in addition to products already analyzed, the thermal activation of $MeOBu^n$ provided *n*-propyl complex **6**, as shown in eq 1. Although mechanistic studies were not performed, it was suggested that the α-alkoxide elimination route of Scheme 1 plays a key role in the generation of this compound, through the intermediacy of a transient hydride alkoxide methylene species.[14a] The latter would convert into product by well-established reaction steps: 1,2-H shift, β-H elimination, aldehyde C–H activation with elimination of CH_4, and carbon monoxide deinsertion.[14a]



(1)

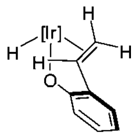
Activation of Alkyl Aryl Ethers

So far, we have discussed the activation of aliphatic ethers and analyzed which of the possible C_{sp^3}–H bonds (terminal or internal) are cleaved by the iridium complex $\mathbf{1 \cdot N_2}$. If alkyl aryl ethers $RCH_2OC_6H_5$ (R = H, Me) are employed instead, two competitive reactions might take place at first glance, leading to cleavage of either C_{sp^3}–H or C_{sp^2}–H bonds. Indeed, our results show that both activations take place, although the reaction is not as simple as one might anticipate in view of the results described in the previous section. Thus, when complex $\mathbf{1 \cdot N_2}$ was reacted with anisole ($CH_3OC_6H_5$) or phenetole ($CH_3CH_2OC_6H_5$) two isomeric iridium hydride carbene compounds, **7a**,**b** and **8a**,**b**, formed in different ratios (eq 2).[20] While complexes **7a**,**b** are clearly related to the products obtained in the reaction of $\mathbf{1 \cdot N_2}$ with alkyl ethers (see, for example, compounds **3**) and resulted from C–H activation of the alkyl terminus of the ether accompanied by C_{sp^2}–H cyclometalation, compounds **8a**,**b** were completely unexpected. The structure of these compounds could not be established unmistakably by NMR spectroscopy. Furthermore, crystals suitable for X-ray diffraction studies proved unattainable, and these facts, along with their high reactivity toward oxygen and moisture (in contrast with derivatives **7**, which can be handled with no special care), made characterization difficult. Nevertheless, they were trapped in the form of different adducts[20b] by addition of NCMe or PMe_3, and characterization of the latter by NMR and X-ray methods demonstrated the true nature of compounds **8**, as containing a chelating alkylidene aryloxide ligand (eq 2). Evidently, formation of these species requires rupture of the RCH_2–O bond of the ether and concomitant C–C bond formation.



(2)

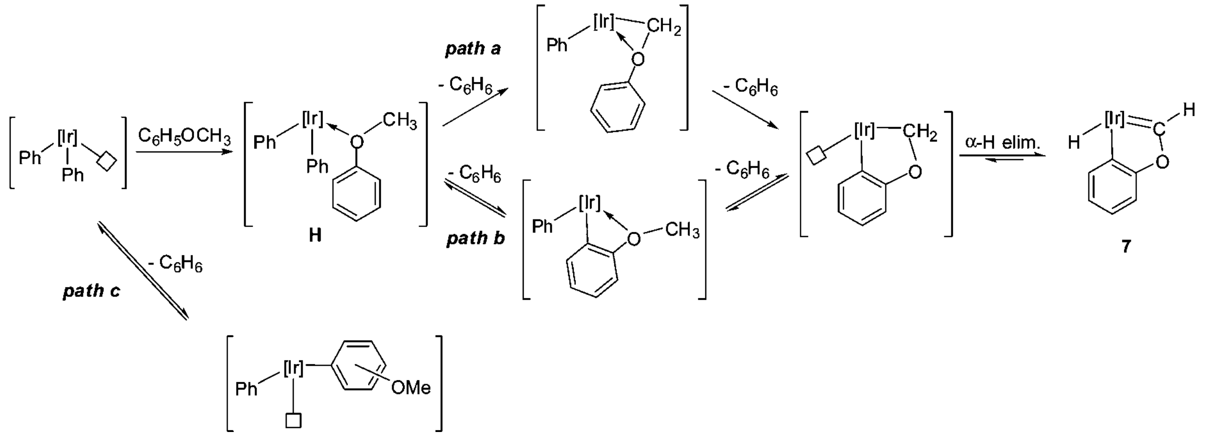
In the reaction of $\mathbf{1 \cdot N_2}$ with phenetole, an additional minor complex was formed in very low yield (<5%) and was identified as the iridium hydride–alkene **9**, that is, the alkene tautomer of alkylidene **8b**. As discussed later on, this compound is indeed in equilibrium with complex **8b**.



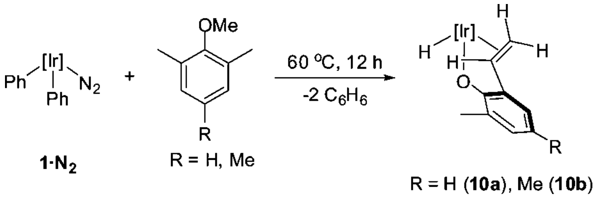
9

A different outcome resulted when solutions of 2,6-dimethylanisole or 2,4,6-trimethylanisole were heated with complex $\mathbf{1 \cdot N_2}$. In this case, complexes **10a**,**b** were the only observable products of the reaction in high spectroscopic yields (eq 3).[21] The complexity of this reaction is apparent in view of the number of bonds that need be cleaved (C–H and C–O) and formed (C–C) in a single reaction. Clearly, com-

SCHEME 4. Mechanistic Pathways in the C−H Bond Activation of Anisole



pounds **10a**,**b** are related to **9**, with which they share the ability to equilibrate with their carbene tautomers at higher temperatures (see below).



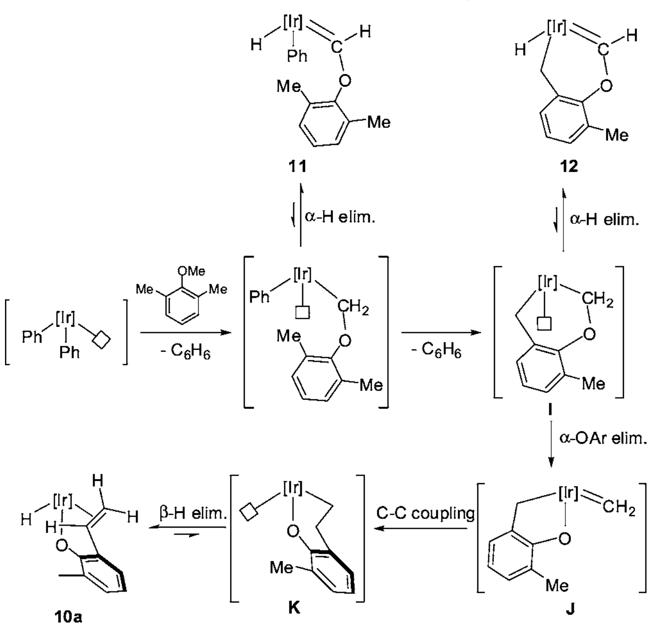
Mechanistic Considerations in the Activation of Alkyl Aryl Ethers

The mechanism for the activation reaction of the alkyl aryl ethers is not trivial and involves several reversible and irreversible steps. As will be discussed, anisole, phenetole, 2,6-dimethylanisole, and 2,4,6-trimethylanisole probably share akin reaction intermediates through a σ-complex-assisted metathesis mechanism (σ-CAM). Regarding the formation of iridium hydride alkoxy-carbenes **7**, at first sight three possible mechanisms may be operative. The first two possibilities (paths a and b in Scheme 4) have in common that the activation reaction is assisted by coordination of the oxygen atom to the metal center. Path c implies instead a direct activation of a C_{sp^2}−H bond of the phenyl ring, assisted either by π-coordination or by formation of a σ-complex. Pertinent to this possibility, Martin, Milstein, et al. observed that the activation of anisole by an unsaturated Ir(I) complex resulted in preferential *ortho* activation by a factor of 14 over the sum of the *meta* and *para* possibilities.[22] Theoretical calculations from our laboratories[20b] led us to conclude that paths a and b have similar energy barriers and hence that both mechanisms may be competent in the formation of the heteroatom-substituted carbene complexes. The most stable among the different possible intermediates at an initial stage is that coordinated to the ether through the oxygen atom (**H**), while other possible coordination modes, including π-aromatic coordination, or the formation of σ-complexes are higher in energy. Very recently, in the reaction between pincer complex (PNP)IrH_2 and $MeOBu^t$, Grubbs and co-workers have found fast formation of an O-adduct which then undergoes double C−H activation, to yield carbene complex (PNP)Ir=C(H)(OBu^t).[23] Theoretical calculations by Yates et al. have disclosed an interesting and complex autocatalytic mechanism for this reaction that may in fact proceed through a σ-C−H ether complex generated in a barrierless mechanism following dehydrogenation of (PNP)IrH_2 by norbornene.[24]

In our [$Tp^{Me2}Ir(C_6H_5)_2$] system, once the ether is coordinated to the metal center, aliphatic $H-CH_2O$ or aromatic OC_6H_4-H activations are energetically indiscernible and involve, very likely, a σ-CAM mechanism.[25] For the two pathways, the highest point in the corresponding potential-energy profiles correspond actually to the first activation. Also for the two paths, the last C−H cleavage is a reversible α-hydrogen elimination that yields the final iridium hydride−carbene complex.

To gain insight into the mechanism of the activation of 2,6-dimethylanisole and 2,4,6-trimethylanisole, monitoring of the reaction by NMR spectroscopy (^1H and $^{13}C\{^1H\}$), with ^{13}C labeling at the methoxy group of 2,6-dimethylanisole was undertaken. At 60 °C, two iridium hydride carbenes, spectroscopically characterized as **11** and **12**, were observed (Scheme 5). Prolonged heating led ^1H NMR signals for **12** to increase at the expense of those of compound **11,** until complete disappearance of the latter. At the same time, signals for the main product of the reaction, namely, **10a**, started to appear while **12** was consumed. The mechanism for the conversion of **11** into **12** necessitates, once again, a reversible α-H elimination, followed by C−H bond activation of one of the *ortho* methyl groups of the ether and concomitant elimination of a molecule of benzene. It is worth noting that α-H elimination from intermediate **I** has com-

SCHEME 5. C–H Bond Activation of 2,6-Dimethylanisole



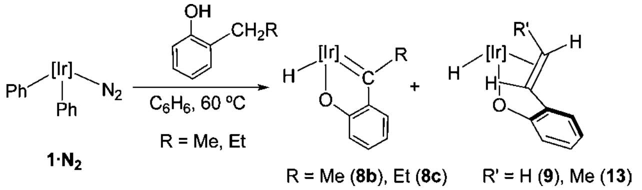
plete chemoselectivity toward the Ir–CH_2O moiety; no products derived from C–H activation reaction of the Ir–CH_2Ar fragment were observed. No other intermediates were detected but it seems probable that conversion of **I** into product **10a** occurs through the elementary reactions depicted in Scheme 5.[21]

The labeling experiments with $ArO^{13}CH_3$ led to a somewhat surprising result, because the ^{13}C label was unexpectedly found to distribute unevenly across the two olefinic sites, with preference for the terminal carbon atom (70% in **10a** and 55% in **10b**) (Scheme 6). A possible, albeit speculative, explanation for this observation is that intermediate **I** is in an otherwise unproductive equilibrium with a cyclohexadienone species **L**.

Equilibria between Hydride Alkene and Hydride Alkylidene Tautomers

The conversion of an alkylidene complex into the corresponding alkene isomer is a well-known transformation, characteristic of electrophilic alkylidenes.[26] The isomerization involves a 1,2-H migration from an adjacent carbon to the carbene carbon, and it is so favorable that occurs even when there are no α hydrogen atoms, that is, with a carbon (alkyl or aryl) shift.[27]

SCHEME 7. Generation of Isomeric Hydride–Alkylidene and Hydride–Alkene Structures by Activation of 2-Alkyl Substituted Phenols

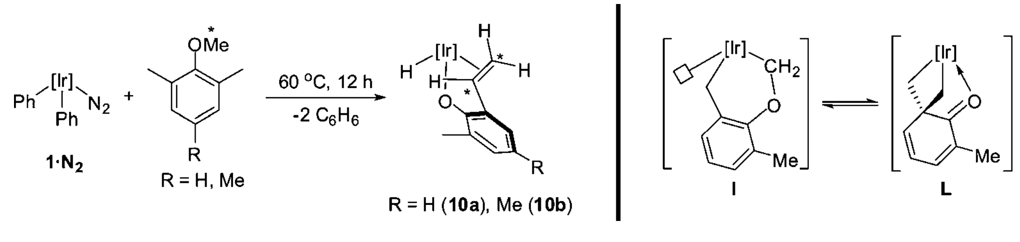


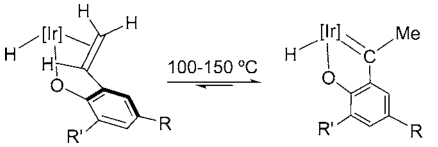
The reverse process, namely, the alkene-to-alkylidene rearrangement, is a very unusual transformation but a few examples have been reported for transition metal complexes with low d electron counts.[28] Equilibration of metal–alkene and metal–alkylidene structures is an example of prototropic tautomerism in organometallic compounds that finds scarce literature precedent too.[29] Prior to our own work,[30] there was only one example[29b] of an equilibrium between species of these types, but additional examples have been reported recently.[31,32]

As pointed out in the previous section, during studies on the reactions of the unsaturated $[Tp^{Me2}Ir(C_6H_5)_2]$ fragment with alkyl aryl ethers, equilibria between isomeric hydride alkylidene and hydride alkene structures were detected[30,33] (eq 4). Equilibrium constants of between ca. 9 and 24, always in favor of the alkylidene isomer, were measured for various combinations of R (H, Me, or Br) and R′ (H, Me) groups. As an alternative route to complexes of this kind, the activation of appropriate phenols (2-ethyl or 2-propylphenol) was considered. Thus, it was found that 2-ethylphenol and 2-propylphenol reacted similarly with $\mathbf{1{\cdot}N_2}$ to give the corresponding hydride alkylidenes, **8b** and **8c**, respectively, in very high yields (~95%), accompanied by minor amounts of corresponding hydride alkene isomers **9** and **13** (Scheme 7). O–H and C–H bond activations are the only steps involved in this case, in contrast with multiple C–H and C–O bond breaking and C–C forming reactions that occur with the *ortho* disubstituted ethers mentioned in the preceding section.

During the reactions of 2,6-dimethylanisole, 2,4,6-trimethylanisole, and 4-bromo-2,6-dimethylanisole with the unsaturated species **1**, the corresponding iridium alkene compounds **10a–c** analogous to **9** and **13** were obtained. The structure

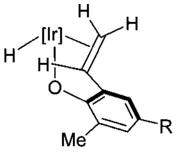
SCHEME 6. Reaction of $\mathbf{1{\cdot}N_2}$ with ^{13}C-Labeled 2,6-Dimethyl-Substituted Anisoles





(4)

proposed for these compounds finds support in the observation of a strong correlation signal between the olefinic HC= resonance and the hydride signal in their NOESY spectra[20b] and by an X-ray diffraction study performed with compound **10b**.[33]

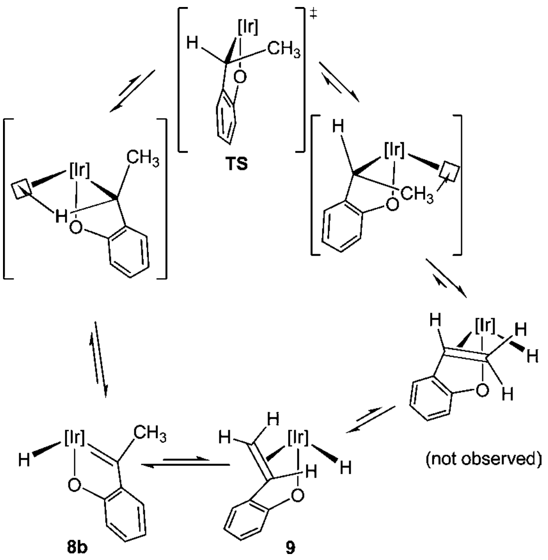


R = H (**10a**), Me (**10b**), Br (**10c**)

Theoretical calculations by Lledós and co-workers reveal that equilibration between hydride alkene and hydride alkylidene structures (see eq 4) cannot occur by a direct reversible 1,2-H migration from the carbene methyl substituent to the carbene carbon atom (energy barrier of ca. 205 kJ mol^{-1}).[33] The alternative, metal-mediated rearrangement of Scheme 8 occurs in four elementary steps: α- and β-H eliminations and their microscopically reverse migratory insertions.[30,33] However, due to the rigid nature of the chelating unit that provides the basis for both the alkene and the alkylidene termini, metal inversion is also needed. The latter was computed to proceed through a five-coordinate transition state (**TS** in Scheme 8) with a barrier of ca. 148 kJ mol^{-1}. Theoretical support for the two isomeric agostic alkyl intermediates and for the unobserved hydride alkene structure was also obtained.

A final comment that is worthy of note is concerned with the reasons that justify the somewhat superior thermodynamic stability of hydride alkylidene over hydride alkene isomers in this system. As expected, the free aryloxide alkene ligand in **9** is more stable than the isomeric aryloxide alkylidene in **8b** by almost 242 kJ mol^{-1} (Figure 1). Nonetheless, theoretical calculations reveal that the electronic interaction between the cationic metal fragment [Tp^{Me2}Ir(H)]$^{+}$ and the two anionic ligand moieties in Figure 1 favors the alkylidene by about 225 kJ mol^{-1}. This, along with steric factors, which also lean on the carbene side, more than compensates the unfavorable energetics that exist between the free ligands and supports the carbene over the alkylidene by a calculated difference of ca. 12 kJ mol^{-1}. Therefore, it is mostly the strong Ir–carbene electronic interaction present in these compounds that stabilizes the alkylidene over the alkene structure.[33]

SCHEME 8. Proposed Mechanism for Interconversion of Hydride–Alkene and –Alkylidene Structures



Summary and Prospects

Study of the C–H bond activation reactions of ethers by different researchers,[34] including ourselves, has demonstrated that, in addition to intrinsic interest, characteristic reactivity and specific applications, these reactions serve as models for the elementary steps involved in alkane C–H activation. In fact, coordination of the oxygen atom facilitates C–H activation and converts it into an intramolecular process. Taking advantage of the knowledge gained, some efficient synthetic procedures have been developed. Thus, Grubbs and co-workers have achieved[15] catalytic functionalization of the C–H bonds of ethers, with high selectivity toward terminal CH_3O– bonds, whereas we have developed efficient synthesis for benzyl ethers from benzene and methyl ethers[14b] and of 2-ethyl phenols from 2,6-dimethyl substituted anisoles.[21]

An obvious conclusion from our work is that five-coordinate iridium fragments [(κ^3-Tp′)Ir(R)(R′)], [Tp′ stands for any type of hydrotris(pyrazolyl)borate ligand; R and R′ represent hydride or hydrocarbyl groups] have a remarkable affinity for carbene ligands. Thus, not only Fischer-type carbenes are common, stable products of the reactions of these fragments with various ethers and amines,[9,12–14] but moreover when iridium alkylidenes like **8** (i.e., non-heteroatom-stabilized carbenes) are

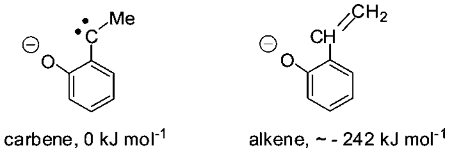


FIGURE 1. Calculated relative energies of isomeric aryloxide–alkylidene and –alkene ligands of complexes **8b** and **9**, respectively.

generated in some of these reactions, they equilibrate with, and prevail over, their alkene tautomers.[33] The somewhat less common α-H elimination (in comparison with β-H elimination) is ubiquitous in these systems and occurs reversibly.

While at first sight activation of ethers should simply involve a double C—H bond activation, in practice other transformations like C—O bond breaking and C—C bond formation are commonly observed. For the aliphatic ethers MeOR, activation occurs invariably at an α position, showing that O-coordination is a prerequisite and involves the stronger of the C—H bonds available. Although some of the reactivity we have disclosed is related to recent findings from Grubbs and co-workers, in their case Ir(I) carbenes of unusual Roper-type reactivity[35] that are nucleophilic at the metal are involved, whereas we have dealt with Tp′Ir(III) centers that activate C—H bonds by a σ-CAM mechanism. This may be due, at least in part, to the well-known propensity of Tp′ ligands to enforce octahedral coordination.

Some important objectives remain open for future research in this field. A question of fundamental importance, key to directing activation of ethers toward selective formation of metal—carbenes, concerns with the reasons that favor α-H elimination in intermediate **A** of Scheme 1 versus more common β-H elimination. A detailed investigation of these factors is clearly needed. Of more practical importance and relevant to chemical synthesis would be developing new methodologies for the catalytic selective functionalization of simple, common ethers with participation of metal—carbenes. Finally, one wonders whether novel transition metal systems could be found where C—H activation of ethers like Et_2O, dme, etc., commonly employed as reaction solvents, may occur reversibly, hence unnoticed. And, if so, what would be the implication of this "side reaction" in the synthesis being pursued?

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FOOTNOTES

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