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Review

Iridium carboxycarbene complexes by C–H bond activation of aliphatic ethers and of alkyl aryl ethers

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Contents

Abstract

The double C–H bond activation of ethers that have an alkyl terminus, RCH_2OR' (R′ = alkyl, aryl), is a useful route to heteroatom-stabilized iridium carbenes, $Ir = C(R)OR'$. An overview of our recent work in this field, using Ir(III) fragments stabilized by hydrotris(pyrazolyl)borate ligands, is presented concentrating on some aliphatic, non-cyclic ethers and on anisole, the latter taken as a representative example of alkyl aryl ethers.

Keywords: Iridium; Carbenes; C–H activation; Hydrotris(pyrazolyl)borate; Coordination chemistry

1. Introduction

Early work on transition metal carbenes demonstrated that the abstraction of an atom or group bonded to the α-carbon of a transition metal alkyl is a useful, versatile method for the synthesis of this kind of compound. For instance, the reaction of the α-functionalized molybdenum alkyl, $Cp(CO)_2(PPh_3)MoCH_2OCH_3$ with trimethylsilyl trifluoromethanesulfonate, Me_3SiOTf, gives a cationic methylene compound, contaminated with small amounts of a heteroatom stabilized carbene (Scheme 1). The use of trityl hexafluoroarsenate as the abstracting reagent produces only the heteroatom carbene (together with equimolar amounts of the related [Mo]–CH_3 compound) [1].

Although this synthetic methodology has been widely employed [2–4] it has the limitations of: (i) an abstracting reagent is required; and (ii) a convenient synthesis of the α-functionalized metal alkyl must be available. During the last decade we have prepared a number of $Ir = C(R)X$ complexes by means of double C–H bond activation of ethers ($X = OR'$) and amines ($X = NR'_2$). X-coordination to an unsaturated Ir(III) centre facilitates metal attack to the adjacent C–H bonds, whereas the formation of sufficiently strong C–H

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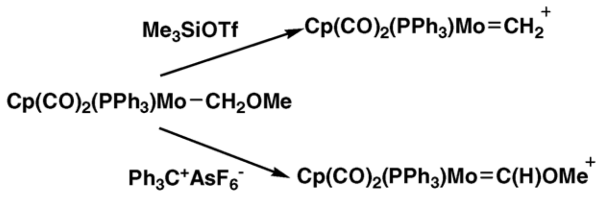


Scheme 1.

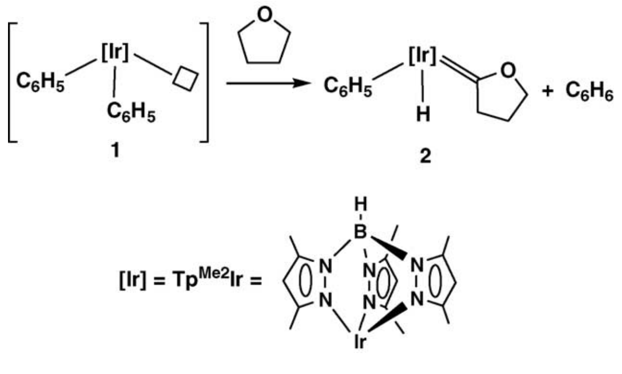
bonds with sacrificial alkyl or aryl leaving groups provides the thermodynamic driving force needed for the formation of the metal–carbene linkage. For example, the unsaturated $[Tp^{Me2}Ir(C_6H_5)_2]$ fragment, **1** (Tp^{Me2} = hydrotris(3,5-dimethylpyrazolyl)borate), generated in situ either from the N_2 complex $Tp^{Me2}Ir(C_6H_5)_2(N_2)$ or from the mild heating of $Tp^{Me2}Ir(C_2H_4)_2$ in C_6H_6, under argon, effects the double α-C–H bond activation of tetrahydrofuran (and other cyclic ethers) with formation of the corresponding cyclic carbene **2** (Scheme 2). The strength of the Ir–H, and above all of the C_6H_5–H bonds generated in the reaction, make this conversion thermodynamically allowed [5,6].

This reaction proved to be quite general for other Tp′Ir(III) precursors and a variety of related cyclic ethers. As an illustration of its applicability, Scheme 3 collects the carbenes generated from each of the ethers depicted when reacted with the Ir(III) derivative $Tp^{Me2}Ir(H)(C_2H_3)(C_2H_4)$.

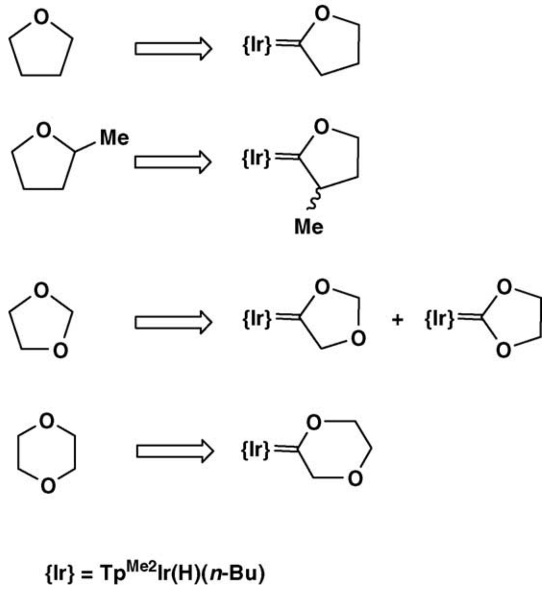
Simultaneous but independent work from Werner et al. yielded osmium carbenes derived from the double metalation of the methyl group of $MeOCH_2CH_2PPr^i_2$ and related ligands [7]. Scheme 4 shows the formation of a structurally characterized (X-ray crystallography) osmium carbene generated in high yields from the reaction of $OsCl_3{\cdot}xH_2O$ with $MeOCH_2CH_2PPr^i_2$.

Interestingly, a different carbene isomer was formed when $OsCl_2(PPh_3)_3$ was employed as the metal precursor. An osmium hydride was postulated as a key intermediate and the reaction thought to proceed with insertion of the metal into the C–H bond of the OCH_3 group [7].

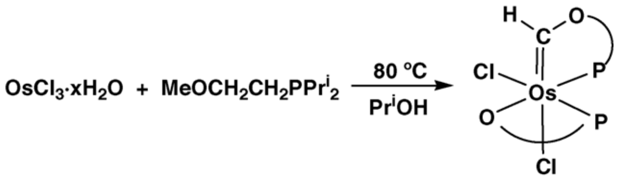
Subsequent work by others [8–16] provided additional examples of double C–H bond activation reactions. Schemes 5 and 6 show some selected reactions [8,10].



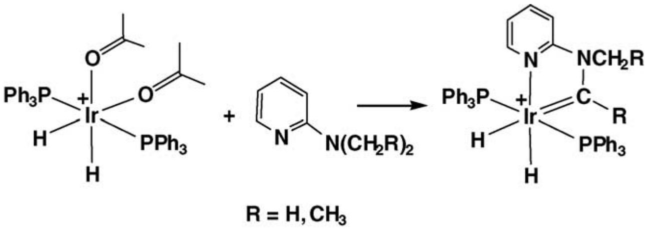
Scheme 2.



Scheme 3.

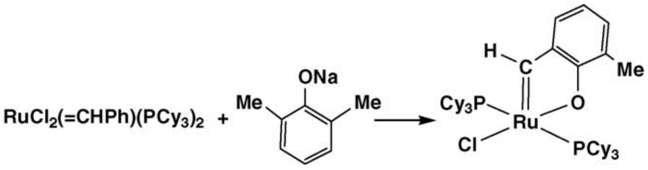


Scheme 4.

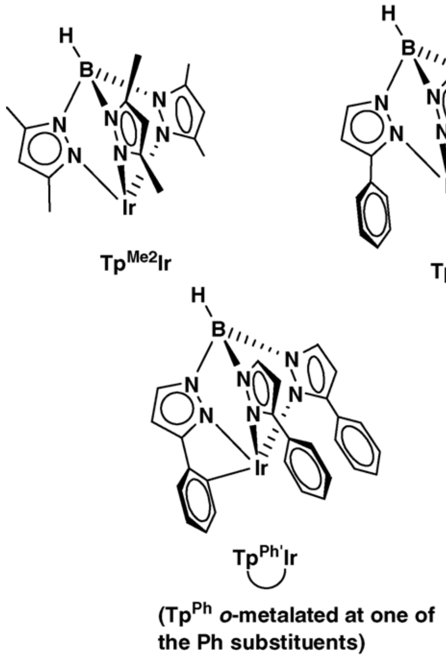


Scheme 5.

Work carried out in our laboratory in recent years has expanded considerably the scope of this C–H bond activation chemistry [17–22]. Tp′Ir fragments based on different auxiliary tris(pyrazolyl)borate ligands (Tp′: see Scheme 7) have been employed with the result that even ethers like Et_2O, $MeOCH_2CH_2OMe$, $MeOBu^n$, and others of low Lewis basicity, that very seldom participate in rearrangements of this



Scheme 6.



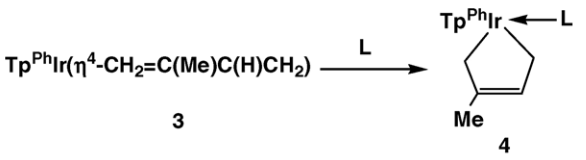
Scheme 7.

type can be activated under mild conditions. In this contribution we present an overview of this work, concentrating on the activation of aliphatic ethers and of anisole (as a representative example of alkyl aryl ethers) by Tp′Ir(III) complexes.

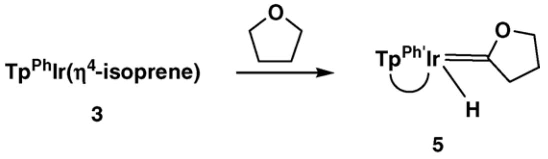
2. Compounds of the $Tp^{Ph}Ir(III)$ fragment

Similarly to Ir(I) diene complexes of the type $Tp^{Me2}Ir(\eta^4$-diene), the isoprene derivative $Tp^{Ph}Ir(\eta^4$-isoprene) (isoprene = 2-methyl-1,3-butadiene; Tp^{Ph} = hydrotris(3-phenylpyrazolyl)borate) reacts with different Lewis bases with formation of Ir(III) adducts, $Tp^{Ph}Ir(\sigma^2\text{-}CH_2C(Me)=C(H)CH_2)L$ (Scheme 8). It can therefore be expected that when L = THF, subsequent C–H bond activation may take place, with formation of the corresponding carbene complex.

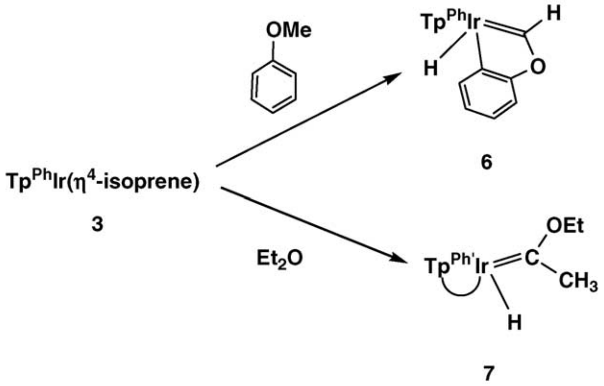
The H atoms from the two cleaved C–H bonds would add in a 1,4-fashion to the alkyl termini of the chelating hydrocarbyl ligand of **4** (Scheme 8), so that the original η^4-diene ligand of **3** acts as a sacrificial hydrogen acceptor, being liberated as 2-methyl-2-butene. However, as shown in Scheme 9 the activation of THF by compound **3** is somewhat more complex than indicated, for one of the phenyl substituents of the Tp^{Ph} ligand undergoes cyclometalation [17].



Scheme 8.



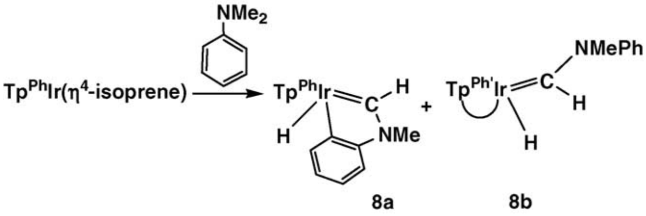
Scheme 9.



Scheme 10.

Note that, as depicted in Scheme 7, $Tp^{Ph'}$ represents the Tp^{Ph} group acting as a tetradentate ligand by means of the *ortho*-metalation of one of the Ph pyrazolyl substituents. Non-cyclic ethers like anisole, and also Et_2O, are activated by **3** under mild conditions (60–80 °C). For anisole, *ortho*-metalation of its own phenyl group occurs preferentially (Scheme 10), whereas the activation of Et_2O involves, once more, the *o*-metalation of one of the phenyl Tp^{Ph} substituents [17]. It is worth noting that despite the flexibility of the molecules of Et_2O, as compared with the more rigid, cyclic molecules of THF, α-H elimination (to give the hydride carbene **7**) competes favourably with β-H elimination. A comparable result was found for platinum [13], but the somewhat related unsaturated, cationic $[Cp^*Ir(Me)(PMe_3)]^+$ unit, whilst activating THF to give a cyclic carbene, reacts with Et_2O with generation of the vinyl ether complex $[Cp^*Ir(H)(PMe_3)(\eta^2\text{-}CH_2=C(H)OEt)]^+$ [15,16].

Aromatic amines are also activated by the $Tp^{Ph}Ir(\eta^4$-isoprene) complex. As shown in Scheme 11 the reaction with *N*,*N*-dimethylaniline gives a mixture of two N-substituted



Scheme 11.

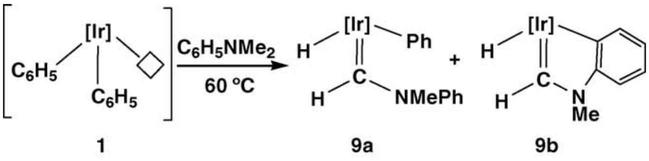
carbene derivatives in a ca. 2:1 ratio (^{1}H NMR monitoring). The major product, **8a**, contains the aromatic ring of the aniline metalated at one of the *ortho* positions, whereas the minor isomer, **8b**, features a κ^4-$Tp^{Ph'}$ ligand and a nonmetalated =C(H)NMePh terminus. The observed **8a**:**8b** ratio is probably a reflection of steric factors, the less-strained metalation of the ring attached to the carbene prevailing over that of the Tp^{Ph} phenyl substituent.

3. Activation of aliphatic ethers by Tp^{Me2}Ir(III) compounds

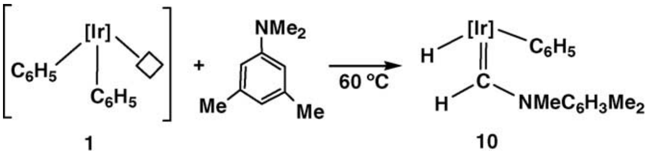
Extension of the above results to related compounds of the ancillary Tp^{Me2} ligand is feasible. As a matter of fact, and further extending the discussion of aromatic amines activation mentioned in the preceding paragraph, the reaction of the unsaturated bis(phenyl) fragment **1** with $C_6H_5NMe_2$ also provides a mixture of two N-substituted Fischer carbenes, **9a** and **9b** in a ratio that does not vary with time (Scheme 12). Since isolated samples of **9a** do not rearrange upon prolonged heating (12 h) in cyclohexane at 120 °C, it is evident that **9a** is not an intermediate for the formation of the *ortho*-metalated complex **9b**.

Instead, the two carbenes must form through different, competitive reaction pathways. A reasonable working hypothesis is that the activation of an *ortho*-hydrogen atom of $C_6H_5NMe_2$ is the first activation step in the reaction leading to **9b**, whereas exclusive sp^3 C–H activation at one of the methyl groups of the aniline, anchimerically assisted by metal coordination to the heteroatom, is responsible for the generation of **9a**. In accord with this assumption the activation of *N*,*N*,3,5-tetramethylaniline (Scheme 13) gives a single carbene compound **10**, with structure related to that of **9a**. Thus the two methyl substituents at the 3 and 5 ring positions hinder *ortho*-metalation making the reaction to progress through the alternative sp^3 C–H methyl activation pathway.

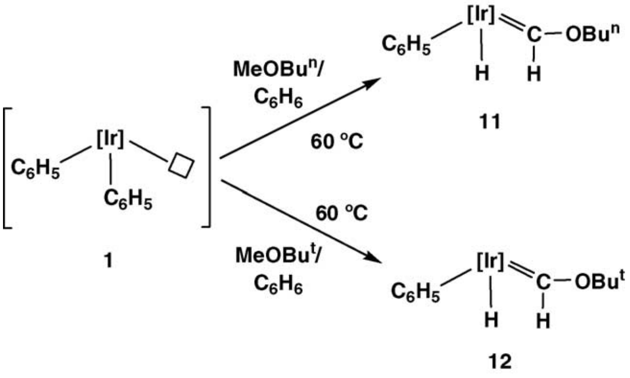
Aliphatic ethers are also appropriate substrates for double C–H bond activation reactions by the Tp^{Me2}Ir(III) fragment. Thus, **1** reacts at 60 °C with $MeOCH_2CH_2CH_2CH_3$ (MeOBu^n) and $MeOCMe_3$ (MeOBu^t) with exclusive activation of the C–H bonds of the –OMe group (Scheme 14). This strongly suggests that metal coordination of the ether through its oxygen atom is needed in order for the C–H bond activation reaction to take place under mild conditions. Note that on the basis of this assumption, **12** is the only reaction product for the activation of MeOBu^t. As for MeOBu^n, cleavage of the somewhat weaker $-OCH_2-$ bonds, although possible, is not detected. As found previously for other C–H bond activation reactions, it is probable that the activation of the stronger primary C–H bonds is thermodynamically more favourable than that of the secondary C–H bonds, due to the greater strength of the resulting Ir-primary carbon bond [23].



Scheme 12.



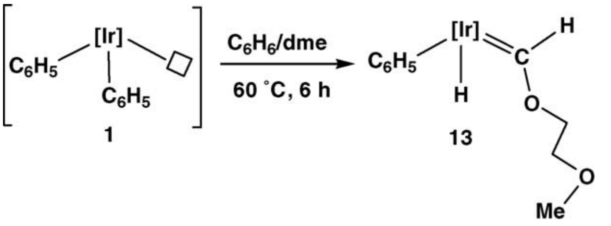
Scheme 13.



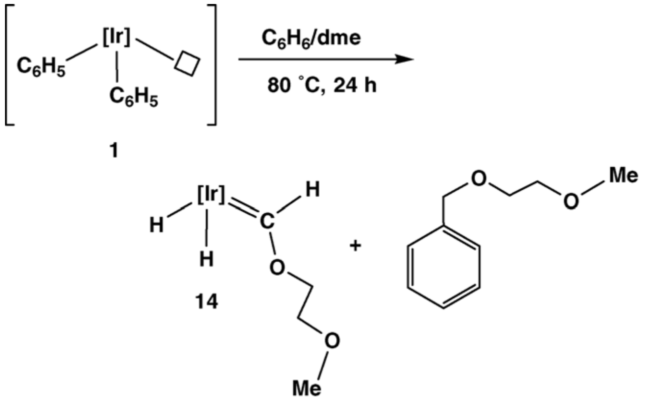
Scheme 14.

1,2-Dimethoxyethane (dme), a commonly used solvent, also undergoes the regioselective cleavage of two C–H bonds of one of the Me groups, giving rise to the related hydride carbene **13** (Scheme 15). Metalation of the intact Me substituent within the carbene ligand of **13** by reaction with an additional equivalent of **1** does not take place under the reaction conditions [22].

The carbene complexes **11**–**13** of Schemes 14 and 15 constitute only the initial products of the corresponding activation reactions. Prolonged heating of the respective reaction mixtures at higher temperatures (24 h, 80 °C) gives rise to bis(hydride) carbene derivatives, as illustrated in Scheme 16 for the dme/C_6H_6 reaction, taken as a representative example [22]. In addition, an organic product resulting from C–C coupling between one molecule of C_6H_6 and one of the ether,



Scheme 15.

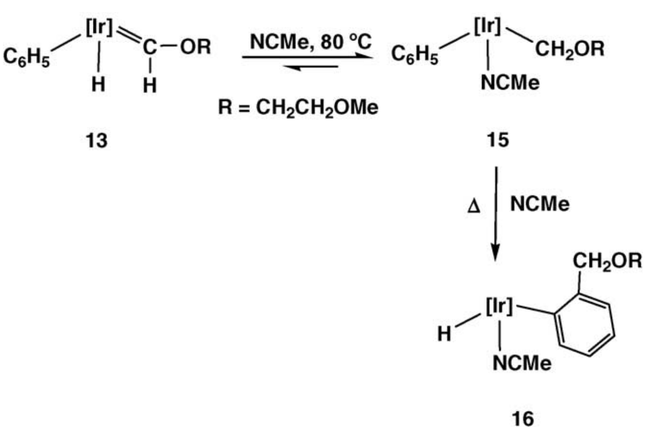


Scheme 16.

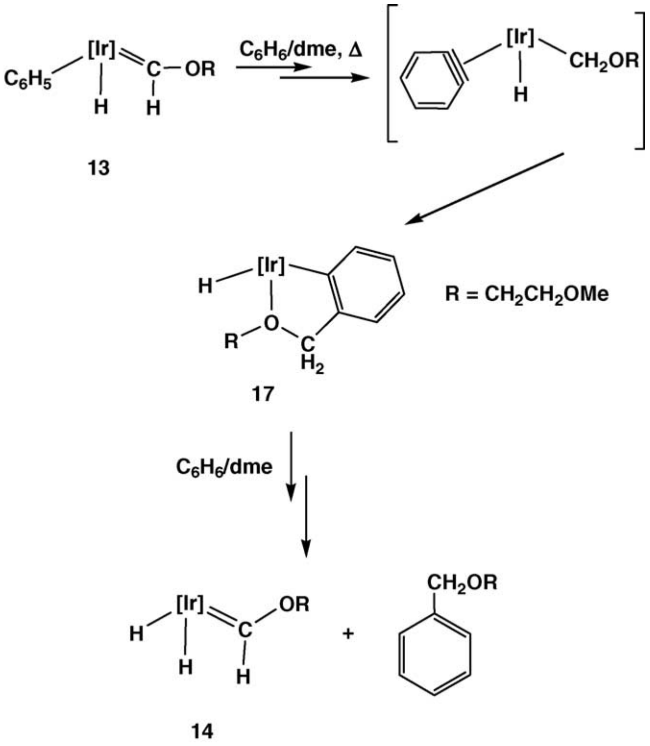
following their respective, prior C–H activation, is also generated.

Heteroatom-stabilized iridium carbenes like **13** or **14** are, in general, reluctant to undergo migratory insertion chemistry. However, heating **13** in neat acetonitrile at 80 °C allows isolation of the expected α-functionalized alkyl in the form of the acetonitrile adduct **15** (Scheme 10). Prolonged heating (12 h) of **13** in the presence of 1–2 equiv. of NCMe, affords the hydride aryl **16** (Scheme 17). This compound contains a hydrocarbyl unit that derives from a carbon–carbon bond forming reaction between the hydrocarbyl ligands of the putative intermediate resulting from a 1,2-H shift from iridium to the carbene carbon of **13**.

In the absence of NCMe, compound **13** rearranges into a hydride aryl **17** related to **16** (Scheme 18). Presumably, the C–C coupling involves an undetected benzyne species (Scheme 18). Compound **17** has been isolated and shown to convert into the final reaction products (see Scheme 16) when heated in the presence of C_6H_6 and dme. Therefore complexes **13** and **17** are active intermediates in the overall transformation represented in Scheme 16.



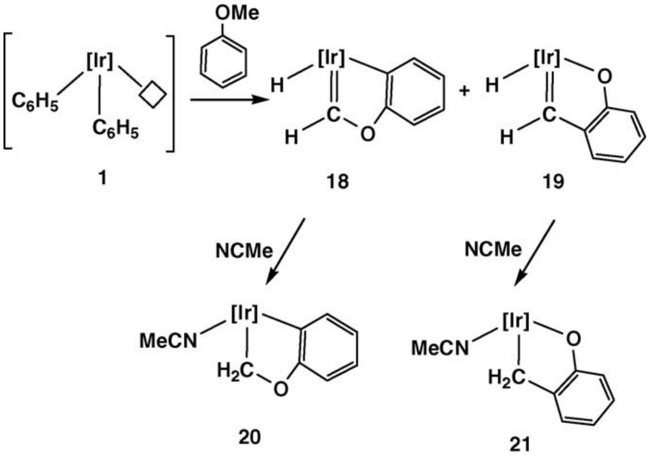
Scheme 17.



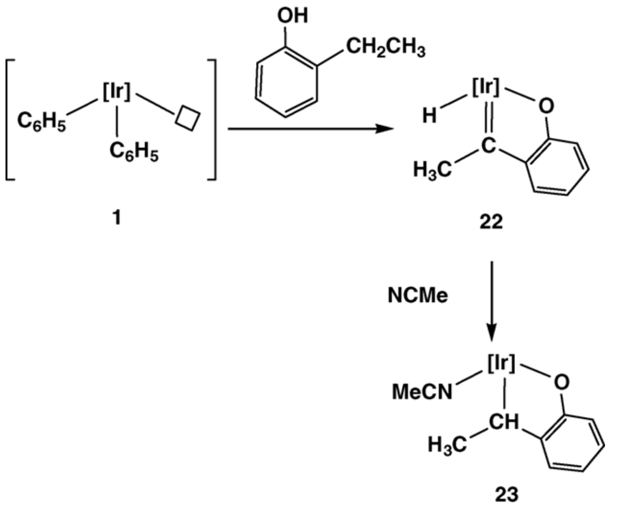
Scheme 18.

4. Activation of alkyl aryl ethers by Tp^{Me2}Ir(III) derivatives

Under reaction conditions similar to those needed for the activation of the aliphatic ethers described in the previous section, the unsaturated bis(phenyl) fragment **1** reacts with anisole to give a mixture of two hydride carbenes, **18** and **19**. Compound **18** is a yellow crystalline solid, readily characterized by spectroscopy [20] as the heteroatom stabilized carbene depicted in Scheme 19. Additional experimental evidence in favour of this proposal comes from its facile conversion into adduct **20** upon treatment with NCMe.



Scheme 19.

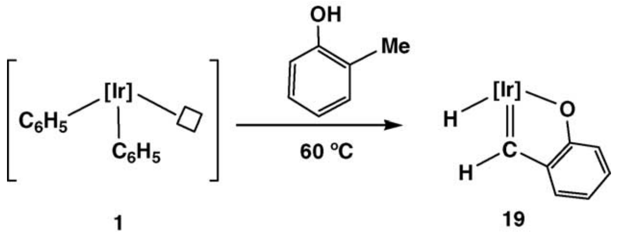


Scheme 20.

At the outset of this work, identification of the green complex **19** was not straightforward. At variance with **18** that exhibits moderate stability toward oxygen and water, compound **19** is very reactive toward atmospheric reagents and undergoes extensive decomposition during attempted chromatographic separation from **18**. Moreover, 1D and 2D, ^{1}H and ^{13}C NMR studies do not allow an unequivocal structural proposal to be made. Although **19** also reacts with NCMe to give **21**, i.e. an acetonitrile adduct isomer of **20**, NMR structural characterization of **21** also proves elusive.

Recent work from our group on related systems has revealed that **1** reacts with 2-ethylphenol (Scheme 20) with formation of a green product, **22**, of spectroscopic properties strikingly similar to those of **19** [24]. In particular, $^{13}C\{^{1}H\}$ NMR data for the six aromatic carbon and the carbene carbon nuclei are almost identical to corresponding data for **19**.

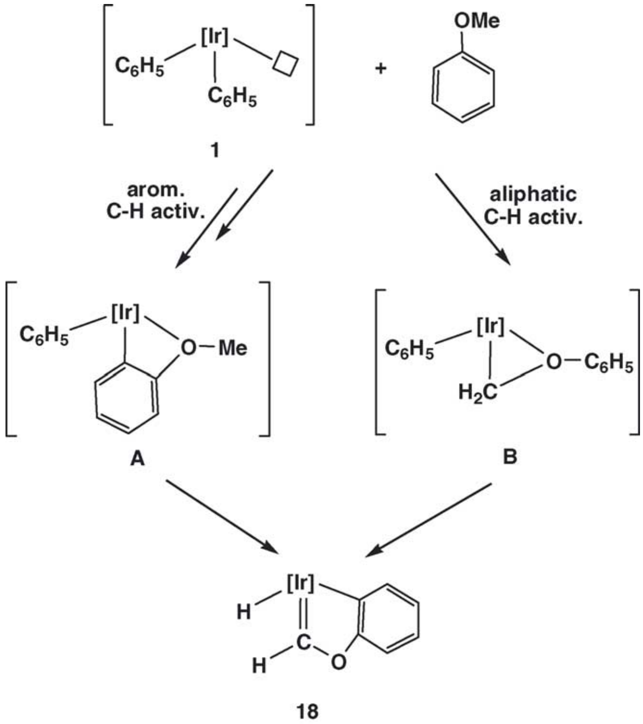
Moreover the reaction of **22** with different Lewis bases (NCMe, PMe_3, NC_5H_5) generates the expected adducts that show spectroscopic properties similar to those of **21**. Of these adducts (see Scheme 20 for the NCMe compound) the PMe_3 derivative has been characterized by X-ray crystallography [24], thereby providing unequivocal evidence about the existence of a direct Ir–O bond in the molecules of this compound and by extension in those of **19** and **21** (Scheme 19). It becomes in this way evident that **1** reacts with anisole through two independent pathways (interconversion of **18** and **19**, Scheme 19, does not occur under the conditions employed for their formation) and whereas the route leading to **18** requires only C–H bond activation, the formation of **19** involves more complex reactivity. In the latter case the selective cleavage of the O–CH_3 bond of anisole and the formation of a new carbon–carbon bond must be additionally postulated. As a final confirmation of the identity of **19**, its independent, high-yield synthesis has been achieved by the reaction of **1** and *ortho*-cresol (Scheme 21). This has allowed full characterization of **19** by spectroscopic and chemical procedures [25].



Scheme 21.

By similarity with the activation of aliphatic ethers discussed in the preceding section, it appears reasonable that the multiple C–H bond activation process that ultimately leads to **18**, may start with coordination of the ether to **1**. However, since arene C–H bond activation by this iridium fragment is very fast [6], it is also plausible that the first reaction step is an aromatic C–H bond activation. This could occur at any of the ring positions and remain undetected until eventually an *ortho*-metalated intermediate **A** (Scheme 22) is formed [20], rendering the product **18**, following the cleavage of two sp^3 OMe carbon–hydrogen bonds. In an alternative pathway (that could in fact operate simultaneously with the above) an aliphatic C–H bond is cleaved first to give **B**. *Ortho*-metalation and α-H elimination then explain the generation of **18**.

Mechanistic studies on the unusual C–O bond cleavage reaction that gives rise to the green carbene **19** are presently underway and will be discussed in a future publication [25]. A plausible mechanistic assumption at this, still very preliminary, stage could involve α-aryloxide elimination from an intermediate like **B**. Nevertheless a more elaborated proposal



Scheme 22.

must await until sufficient mechanistic information becomes available.

5. Conclusions

Reactive Ir(III) coordination units of composition [Tp′ $Ir(R)_2$], where R represents a phenyl group or another sigma-bonded hydrocarbyl ligand, can be generated under mild conditions from suitable Ir(I)-olefin precursors. Fragments of this kind that contain a sterically demanding hydrotris(pyrazolyl)borate ligand, for instance Tp^{Me2} or Tp^{Ph}, are capable of generating Fischer-type carbenes when reacted with a variety of ethers (and amines). The reactions are complex and proceed with multiple C–H bond activation, the last step being the α-H elimination that renders the hydride carbene products. For many of the systems studied α-H elimination is reversible and occurs in all cases even in the presence of β-hydrogens.

Aliphatic ethers like $MeOBu^n$, $MeOBu^t$ and $MeOCH_2CH_2OMe$, that are often used as reaction solvents, experience exclusive activation of the C–H bonds of the –OMe unit, suggesting the importance of oxygen coordination to the metal for the C–H bond cleavage to occur. When the activation of these molecules is performed in the presence of C_6H_6, a more complex reaction pathway manifests, as in addition to the C–H bond activation reactivity, formation of a new carbon–carbon bond between one molecule of the ether and one of the aromatic hydrocarbon is observed.

Alkyl aryl ethers like anisole also exhibit complex reactivity against these $Tp'Ir(R)_2$ fragments. Similarly to aliphatic ethers, C–H bond activation at the $-OCH_3$ end gives rise to related O-substituted carbenes. But an alternative reaction course that brings about O–C(alkyl) bond cleavage and formation of a new carbon–carbon bond becomes competitive for these molecules.

Acknowledgments

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