Taming Reactive Phenol Tautomers and *o*-Quinone Methides with Transition Metals: A Structure−Reactivity Relationship

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ABSTRACT

Quinone methides act as important intermediates in organic syntheses, as well as in chemical and biological processes; however, examples of such isolated species are scarce as a result of their high reactivity. Phenol tautomers (keto form of phenol) are also important intermediates in several organic and organometallic reactions; nevertheless, isolated complexes are rare. This Account reviews the recent progress on the synthesis and reactivity of iridium and rhodium *o*-quinone methide complexes as well as on iridium-mediated ortho functionalization of phenols. This reaction was at the origin of the discovery of a general synthetic procedure to prepare the first metal-stabilized *o*-quinone methide.

Introduction

Friedel−Crafts alkylation is one of the most important methods for the placement of a carbon substituent on an arene ring.[1] Yet this reaction is not without drawbacks. For instance, lack of selectivity: multiple alkylations and carbocation rearrangements result in difficulty of product separation and, consequently, lower yields. Transition metal binding to aromatic systems profoundly modifies the electronic properties of the arene rings and activates the π hydrocarbon to nucleophilic substitutions and addition reactions.[2] Of prime importance, however, is the stabilization of highly reactive species by metal coordination. This approach provides unique opportunities to characterize such elusive organic transients by spectroscopic methods and even to elucidate their structures by X-ray crystallography. Although metal complexes of a variety of inaccessible molecules are discussed in the literature, for instance carbynes, cyclobutadienes, ylides, benzynes, and thiocarbonyls, yet metal complexes of phenol tautomers and quinone methides (QMs) are scarce.

Quinone methides (QMs) have been proposed as intermediates in a large number of chemical and biological processes.[3] QMs exists in three isomeric forms (Scheme 1a): *o*-QM (**1**), *m*-QM, and *p*-QM. The importance of *o*- and *p*-quinone methides in organic synthesis and their role in biochemistry have been reviewed.[4] Unlike benzoquinones, *o*-QM and *p*-QM derivatives are highly polarized compounds, usually observed with difficulty or postulated as reactive intermediates because of facile reactions driven by the formation of aromatized phenol derivatives. *p*-Quinone methides have been discussed as intermediates in the chemistry of lignins[5] and have been used in organic synthesis[6] as electrophiles or electron acceptors.

o-Quinone methides, such as **1**, are versatile reactive intermediates used in organic synthesis,[4b,c,7,8] acting as electrophilic enones toward nucleophiles or as heterodiene[7] cycloaddition partners in inter- and intramolecular Diels−Alder [2 + 4] cycloadditions with alkenes to give various substituted chromans **2** (Scheme 1b). Remarkable demonstrations of the potential of such cycloadditions are the total syntheses of carpanone,[8a,d] hexahydrocannabinols,[8e,g,i] and thielocin-A1.[8j] *o*-Quinone methides are also believed to act as key intermediates in the action of several antitumor and antibiotic drugs. Because of their highly electrophilic character, they can act as alkylating agents of DNA.[4c,9]

However, despite this widening interest, examples of isolated simple quinone methides (i.e., those not bearing substituents on the exocyclic double bond) are scarce, and in fact, in condensed phases, the parent compound **1** has been characterized spectroscopically only at temperatures below −100 °C,[10] because it is extremely reactive. These experimental procedures show how difficult it has been to isolate QMs. Although many highly reactive systems (e.g., cyclobutadienes) have been stabilized by metal complexation, as far as we are aware, prior to our first publication, there were only three known QM complexes. Two alkenyl-substituted *o*-quinone methide complexes **3** are known,[11a] but neither was of a simple QM, and neither was characterized crystallographically. Further, one *p*-

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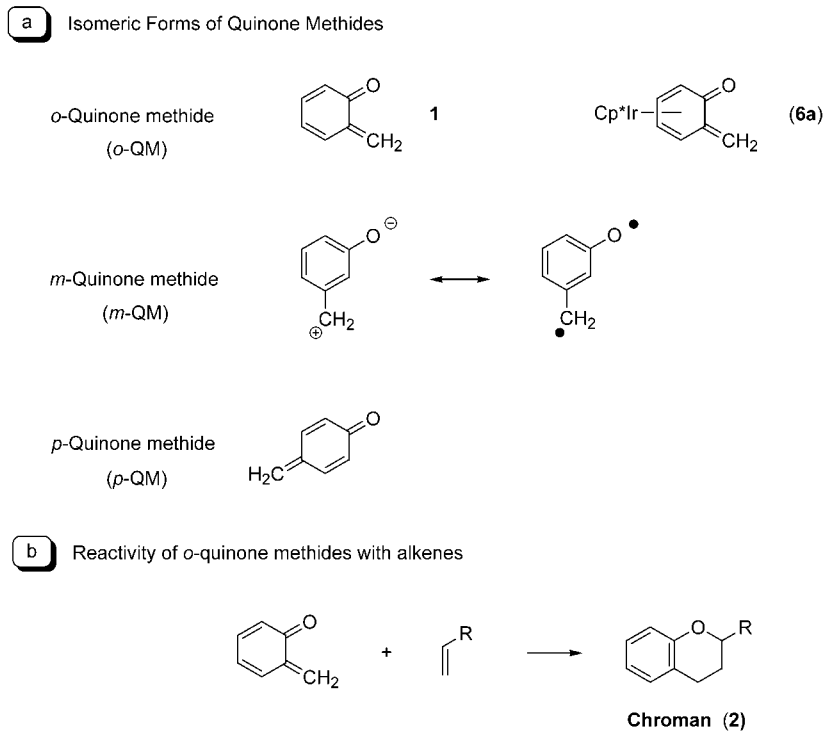
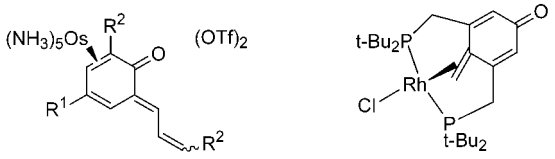
Scheme 1



quinone methide complex **4** features two strongly coordinating tertiary phosphine groups that anchor the metal to the methylene unit (Figure 1).[11b]

In 1998, we communicated[12] a general synthetic procedure to make the first metal complex **6a** of the parent *o*-quinone methides **1** (Scheme 1) as well as complexes of simple alkylated derivatives Cp*Ir-η^4-*o*-quinone methide complexes. In fact, it was during our early work on iridium-mediated ortho functionalization of phenols that we discovered an appropriate route to these *o*-QM complexes. Further, a large number of natural products, in particular, antitumor agents, possess *o*-alkoxyphenol- or *o*-quinone-type structures; hence, organometallic strategies that will provide access to such molecules are of great importance. Interestingly, the key intermediate of iridium-mediated *ortho*-phenol functionalization reaction is a phenol tautomer that is also η^4-coordinated to the metal center.

Phenol tautomers have been postulated as reactive intermediates in organic reactions (Claisen rearrangement, etc.)[13] and in Dötz carbene reaction;[13] however, isolated complexes of such an intermediate were not reported. Thus, in view of the many rapid developments, we felt it is time to present our review on *ortho*-quinone methide and *ortho*-phenol functionalization.



3 4

FIGURE 1. Known *o*-, *p*-quinone methide complexes.

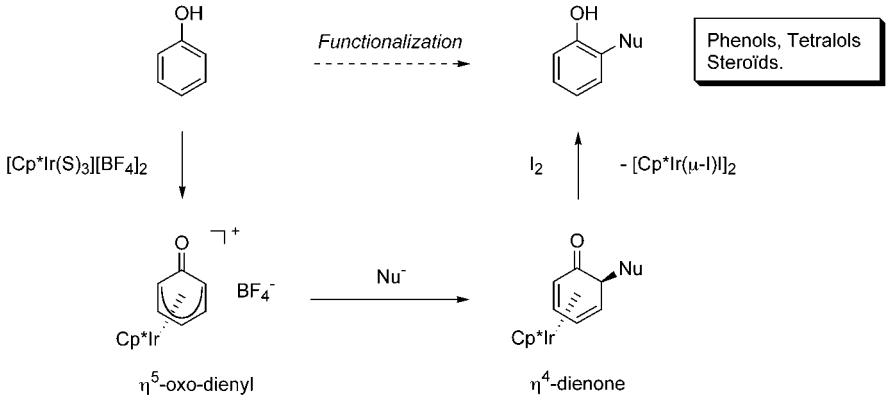
In this Account, we describe the chemistry of iridium-mediated *ortho*-phenol functionalization and its application in organic synthesis as well as the structure of some iridium-stabilized phenol tautomers that are the key reaction of *ortho*-phenol functionalization.[14] The 2-alkyl-oxodienyl-iridium used in the previous reaction served as appropriate precursors to prepare the first stable *ortho*-quinone methides. Then we discuss the structure, spectroscopy, and chemical reactivity of this unusual molecule Cp*Ir-η^4-*o*-quinone methide (**6a)** and compare it to the free intermediate *o*-quinone methide (**1**).

Early Work and Background: Iridium-Mediated *ortho*-Phenol Functionalization. The chemistry of arene−metal complexes has been developed in the past 30 years, and their use in organic synthesis has been the focus of several reviews,[15] yet there is no organometallic procedure that allows *nucleophilic* phenol functionalization. The only known organometallic procedure that allows systematic *electrophilic* phenol functionalization was described by Harman and co-workers.[16]

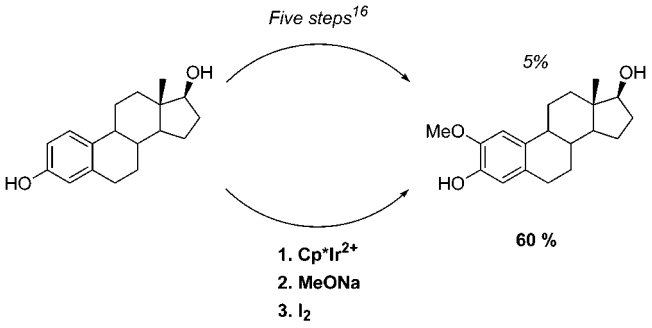
Scheme 2 describes the general procedure of nucleophilic phenol functionalization mediated by the $[Cp^*Ir]^{2+}$ moiety that involves three steps: (a) Placement of the Cp*Ir moiety on the phenolic ring, followed by treatment with a base affords the (oxo-η^5-dienyl)iridium complexes. (b) The latter react with a nucleophile (Nu) to give the stable η^4-dienone compounds. (c) Subsequent oxidative decomplexation by iodine provides the ortho-substituted phenols along with the starting organometallic material recycled in the form $[Cp^*Ir(\mu\text{-}I)I]_2$.[14]

A notable application is the preparation of 2-methoxy estradiol by this method. The latter is obtained from β-estradiol in 60% yield and only in three steps,[14e] as

Scheme 2



Scheme 3



compared to the conventional organic procedure that affords the same compound in 5% overall yield and via five steps (Scheme 3). 2-Methoxyestradiol is an anticancer agent and possesses important physiological properties.[17]

We have found that oxidation of the dienone iridium complexes [Cp*Ir(η^4-exo-2-Nu-C_6H_6O)] depends dramatically on the nature and electron properties of the exo-2-nucleophile. For instance, R_3C-, RO-, and R_3P-centered nucleophiles gave the related ortho functionalized phenol along with the starting material recycled in the form of [Cp*Ir(μ-I)I]$_2$, as shown by Scheme 2. In dramatic contrast N- and S-centered nucleophiles showed a retronucleophilic addition or C−Nu bond cleavage, as shown in Table 1. In the latter case, the proposed mechanism involves a one-electron oxidation process. Therefore, oxidation of Cp*Ir(I) to [Cp*Ir(μ-I)I]$_2$ and formation of the related functionalized phenols does not occur.

Table 1 shows the reactants and products of the nucleophilic phenol functionalization reaction.

The key reaction of the previous chemical transformation is the formation of an η^4-dienone complex in which the nucleophile is now attached at C-2 (Scheme 2). We were able to isolate and characterize by X-ray structure two η^4-dienone complexes: the neutral compound [Cp*Ir(η^4-2-exo-(CH(COMe)$_2$)-C_6H_5O] (**7**)[14d] and the cationic species [Cp*Ir(η^4-exo-2-(PMe_3)-C_6H_5O)][BF_4] (**8**).[14c] In both compounds, the Nu is exo and trans to the organometallic moiety, Cp*Ir. It is noteworthy that the organic ligands in **7** and **8** are phenol tautomers and, hence, highly reactive species that have not been isolated. The powerful stabilizing properties of Cp*Ir were later employed to stabilize and isolate the first *ortho*-quinone methide complexes (*o*-MQs) (vide infra).

X-ray Molecular Structures of Stable η^4-Dienone Iridium Complexes. Figure 2 shows the structures of [Cp*Ir(η^4-exo-2-(PMe_3)-C_6H_5O)]$^+$ and [Cp*Ir(η^4-exo-2-(CH(COMe)$_2$)-C_6H_5O] (**7**) with the atom-numbering system. The structures reveal that the Nu {Nu = PMe_3, CH(COOMe)$_2$} is indeed attached at C-2 with exo stereochemistry relative to the organometallic moiety, Cp*Ir. The distances from the metal to the centers of the p-bonded carbons are 1.68 Å for the dienone fragment in **7** and 1.74 in **8** and 1.82 Å for the η^5-C_5Me_5 ligand in **7** and 1.83 in **8**. Further, the Cp*Ir moiety is coordinated to only four carbons of the dienone unit. Loss of aromaticity is manifested by the irregularity of the C−C bond distances; the length of the uncoordinated bond C(1)−C(2) is 1.50(1) Å in **7** and 1.51(2) Å in **8**, whereas the C(1)−O(1) bond distance is 1.22(1) Å in **7** and 1.23(3) Å in **8**, which is characteristic of a C=O double bond of a ketonic function. The uncoordinated part of the dienone is bent in a distorted fashion. This is due to the presence of linked C1(sp^2)−C2(sp^3) carbons. The dihedral angle "hinge" across C(3)−C(6) is 36.5° for **7** and 39° for **8**.

At this stage, a brief comment on this η^4-phenol tautomer is required. The only known η^4-phenol tautomer complex is the Birch compound Fe(CO)$_3$(η^4-2-4-cyclohexadien-1-one);[18] further, there is no X-ray structure for monocyclic η^4-phenol tautomer compounds.[19] As mentioned in the previous paragraph, free phenol tautomers are unstable and tautomerize rapidly to the related phenols; however, it has been reported that they can be generated by vacuum pyrolysis and were partially characterized.[20] In this example, the Cp*Ir moiety allows the first X-ray structural determination of an organic phenol tautomer through η^4-coordination.

Synthesis of Stable η^4-*o*-Quinone Methide Complexes. Pursuing our research in phenol-iridium chemistry, in the Fall of 1997 we discovered serendipitously that oxo-η^5-dienyl iridium and rhodium complexes **5** with an alkyl group at C-2 provide a convenient synthetic route to the first family of metal-stabilized *o*-quinone complexes **6** (Scheme 4).[12] In particular, we found that treatment of oxo-η^5-dienyl iridium and rhodium complexes **6** undergo regioselective deprotonation at a benzylic position of the

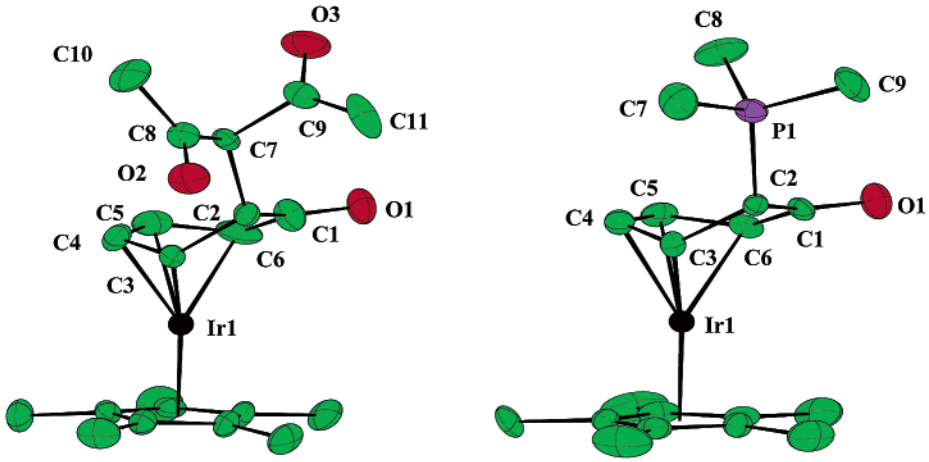


FIGURE 2.

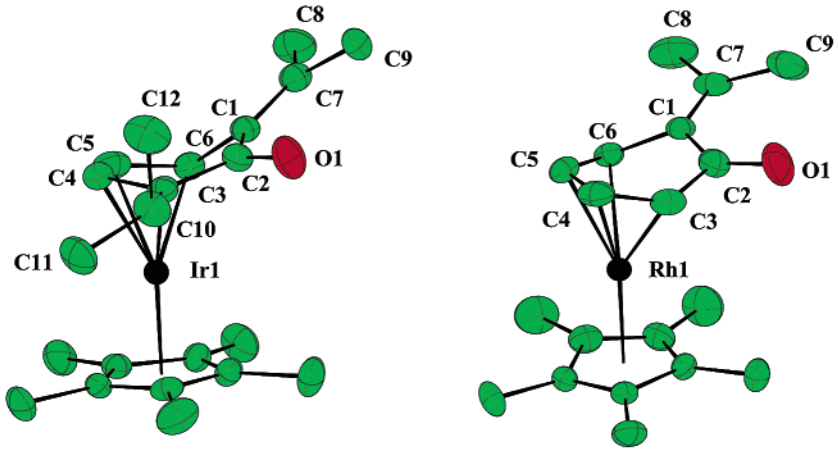


FIGURE 3.

alkyl group to afford the related neutral η^4-*o*-quinone methide complexes. Bases used include NaOMe in methanol or, better, a suspension of t-BuOK in CH_2Cl_2 for several hours at room temperature.

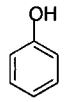
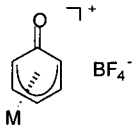
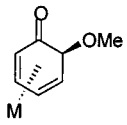
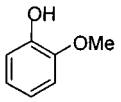
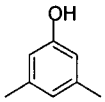
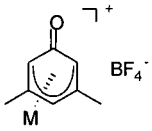
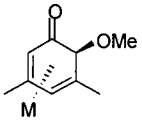
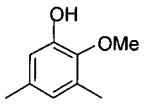
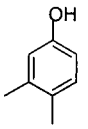
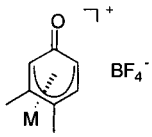
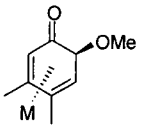
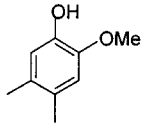
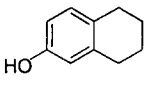
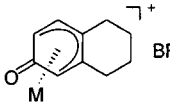
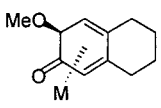
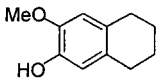
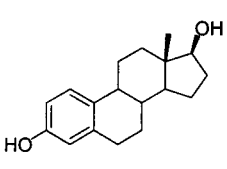
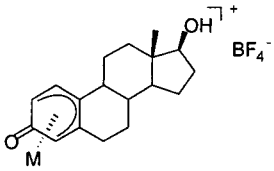
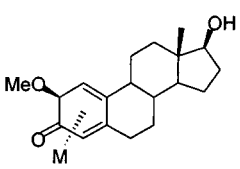
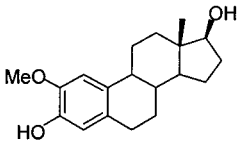
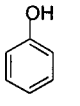
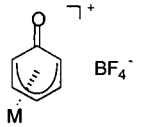
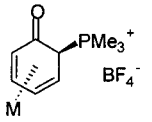
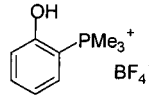
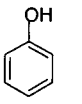
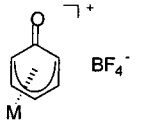
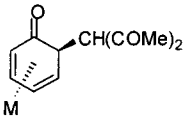
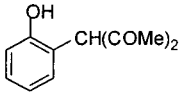
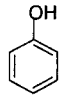
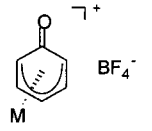
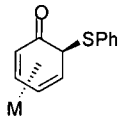
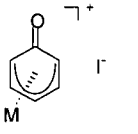
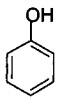
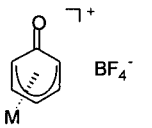
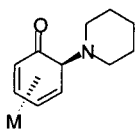
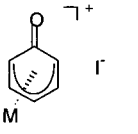
The importance of metal complexation to stabilize related *p*-quinone methides was elegantly illustrated by Milstein and co-workers;[11b] however these *p*-quinone methide complexes show important differences in bonding and reactivity, as compared with *o*-QM complexes. For example, the metal is η^2-coordinated to the exocyclic double bond. In addition, in most cases, the complexed *p*-QM is a part of a bis-chelating PCP-type ligand system, whereas in our case, the metal is η^4-coordinated to the internal diene bonds of the *o*-QM moiety. Further, very recently, a review on the chemistry of *p*-quinone methide was reported by the same group.[21]

The neutral iridium η^4-*o*-quinone methide complexes **6** were obtained as yellow microcrystalline substances in yields of 81−96%. The infrared spectra of these complexes recorded in KBr displayed two bands in the area 1600−1643 cm^{-1} (s) and one band in the area 1457−1510 cm^{-1} (m) attributed to C═O and C═CR_2 {R = H, alkyl} stretching. The literature data for free *o*-QM (**1**) generated by photolysis at 7.6 and 10 K in Ar matrix was reported by two different groups, and three main bands were observed at 1668 (s), 1616 (s), and 1568 (s) cm^{-1} [10e] and at 1668 (s), 1642 (s), and 1569 (s) cm^{-1}. [10f] These bands were attributed to C═O and C═CH_2 stretching modes. In addition, the vibrational frequencies were also calculated and compared to the experimental values.[10e,f] It is clearly from our data that the C═O and C═CH_2 bands of the metalated *o*-QM show the same pattern but are shifted to lower wavenumber, as compared to the free *o*-QM, as a result of metal complexation.

Because the parent *o*-QM molecule C_7H_6O (**1**) is unstable, NMR spectroscopic data are not available. Therefore, we fully examined by 2D NMR techniques the parent *o*-QM complex [Cp*Ir(η^4-C_7H_6O)] (**6a**), to understand its structure and reactivity. Six multiplets in the region 3.6−5.6 ppm that are attributed to the four diene protons and to the geminal protons of the exocyclic double bond are visible; the complete NMR assignment was previously published.[22] Similar trends are seen for the diene protons of the other complexes **6b**−**d**.

We have found that the Rh-η^4-*o*-quinone methide complexes **6ef** are less stable than the iridium congeners; for instance, the parent *o*-QM complex [Cp*Rh(η^4-C_7H_6O)] (**6e**) was characterized spectroscopically but was unstable at room temperature.[23] Such a stability trend has been recently reported by Sheldrick and co-workers in the case of arene π complexes to Cp*M moieties (M = Rh, Ir).[24] These authors have shown that the iridium complexes are

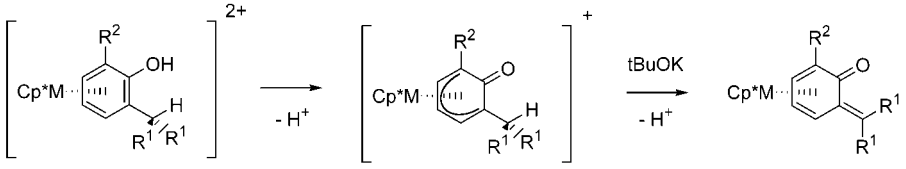
Table 1

Starting material derivatives	Oxo-η^5-cyclohexadienyl-Ir derivatives	η^4-cyclohexadienone-Ir derivatives	I_2 Oxidation / Products	Ref
				14a
				14a
				14a
				14e
				14e
				14c
				14d
				14d
				14d

more stable, a behavior confirmed by their theoretical calculations. We were able to obtain suitable crystals of the first two *o*-QM complexes featuring, respectively, one Cp*Rh and Cp*Ir moieties coordinated in η^4 fashion to the *o*-QM ligand.

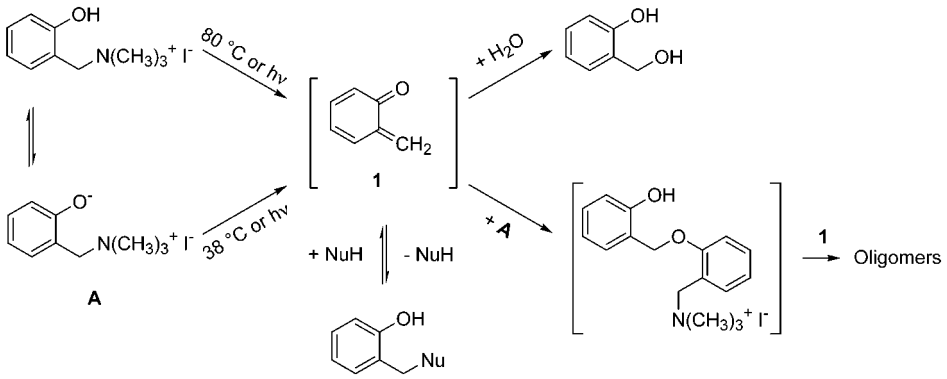
X-ray Molecular Structures of *ortho*-Quinone Methide Complexes Cp*M−η^4-*o*-QM (M = Rh, Ir). The X-ray molecular structures confirmed the spectroscopic studies and provided comparative data on the effects of the Cp*Rh and Cp*Ir fragments on the *o*-QM π system. The bonding and molecular geometry of **6d** and **6f** are shown in an ORTEP diagram in Figure 3. The structures clearly show the lack of aromaticity in the six-membered ring and coordination of Cp*M (M = Rh, Ir) to four ring carbons. In the six-membered ring, the C−C bond distances are irregular; the length of the uncoordinated bond C(1)−C(2)

Scheme 4



a $R^1 = H$, $R^2 = H$, M = Ir
b $R^1 = H$, $R^2 = CH_3$, M = Ir
c $R^1 = CH_3$, $R^2 = H$, M = Ir
d $R^1 = CH_3$, $R^2 = CH(CH_3)_2$, M = Ir
e $R^1 = H$, $R^2 = H$, M = Rh
f $R^1 = CH_3$, $R^2 = H$, M = Rh

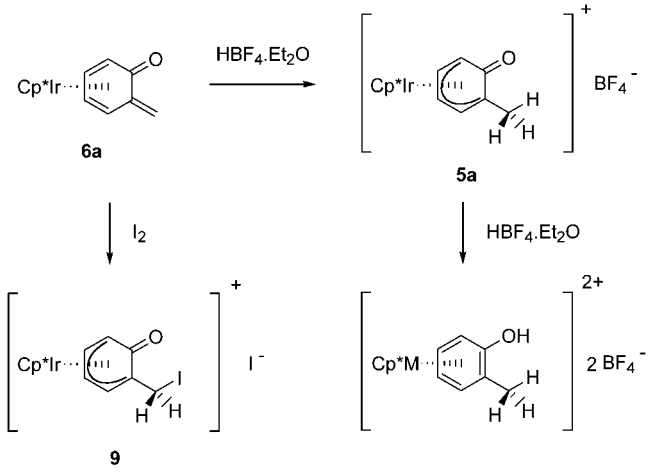
Scheme 5



is 1.48(1) Å in **6f** and 1.49(1) Å in **6d**, whereas the C(2)−O(1) bond distance is 1.24(1) Å in **6f** and 1.23(1) Å in **6d**, which is characteristic of a C═O double bond and in the range expected for substituted quinones. Additionally, the C(1)−C(7) bond distance is 1.35(1) in **6f** and 1.34(1) Å in **6d**, slightly shorter than that reported for the C═C double bond in duroquinone [cf. 1.352(8)].[25] The distances from the metal to the centers of the η^4-bonded carbons is 1.71 Å in **6f**, 1.76 Å in **6d** for the *o*-QM ligand, and 1.83 Å in **6f** and 1.84 Å in **6d** for the η^5-C_5Me_5 ligand. The uncoordinated part of the *o*-QM ligand is bent away from the metal. Shown by the dihedral angle of the "hinge" across C(3)−C(6) of 25° in **6f** and 33° in **6d,** this implies that electronic delocalization within the bonded organic moiety is much more reduced in the iridium case **6d**, as compared to the rhodium complex **6f**. In summary, it is evident that the structural data suggest that the *o*-QM ligand is more stabilized by the iridium moiety than by the rhodium one. This difference is also noted in the reactivities of *o*-QM complexes of the two metals. To our knowledge, these are the only known X-ray structures of *o*-QM complexes reported in the literature. Having elucidated the geometric and electronic structure of such η^4-*o*-quinone methide complexes, we investigated their reactivity.

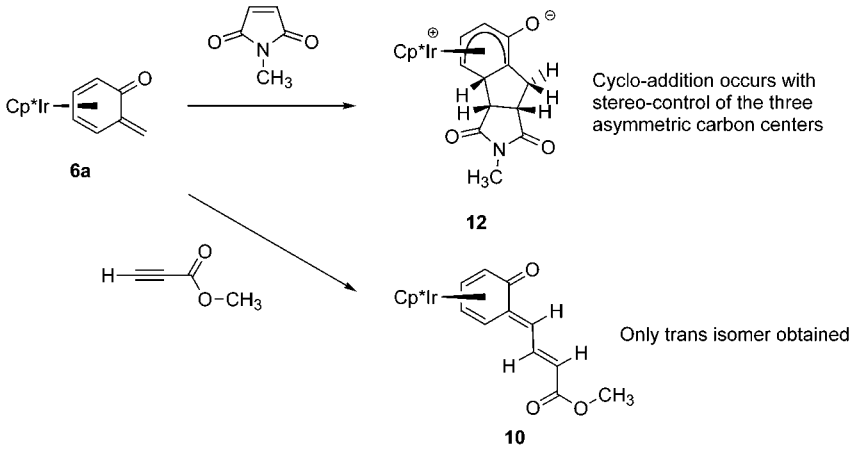
Unusual Chemical Reactivity of the Cp*Ir-Stabilized *o*-QM Complex. The electrophilicity of *o*-QM and its derivatives has been exploited in several synthetic applications.[7] Padwa and co-workers have shown in a series of papers that *o*-quinone methide intermediates generated by photolysis of a pyran can be trapped by nucleophilic

Scheme 6

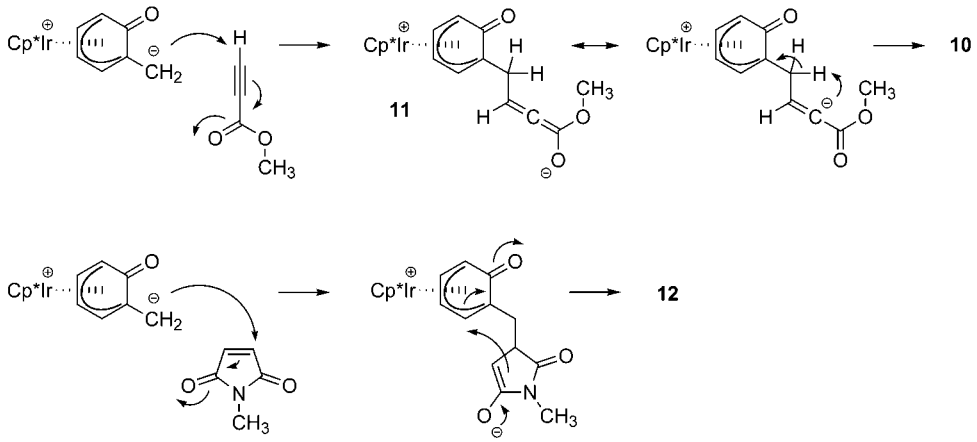


solvents, such as MeOH, to give methyl ether addition products or to return to the original pyran structure.[7a−c] Similarly, Wan and co-workers have generated reactive *o*-quinone methides through flash photolysis[4c,7e,f] and have found products from nucleophilic addition of alcohols or water at the exocyclic carbon. Moore and co-workers have shown that (trimethylsilyl)methyl-1,4-benzoquinone can be converted to reactive electrophilic *o*-quinone methides, which are subsequently trapped by various nucleophiles.[7d] Recently, Freccero and co-workers reported on the alkylation of amino acids by the electrophilic *o*-QM **1** generated from (2-hydroxybenzyl)trimethylammonium iodide by heating or by photolysis (Scheme 5).[26] The same group has also performed a computational study on the elec-

Scheme 7



Scheme 8



trophilic character of the same transient species *o*-QM **1**.[27] In these addition reactions, *the o-quinone methide intermediates are electrophilic species, reacting at the exocyclic carbon*.

In contrast, metal-stabilized *o*-quinone methide **6a** reacts as a base or nucleophile (Scheme 6). Thus, protonation of complex **6a** by $HBF_4 \cdot Et_2O$ afforded primarily the oxo-dienyl compound **5a**; however, in the presence of an excess of $HBF_4 \cdot Et_2O$, the dicationic species was obtained. All subsequent reactions of **6a** described in this account show how the *o*-QM system is activated to reactions with other electrophiles at the exocyclic carbon. Attempted oxidation of **6a** in diethyl ether by iodine did not liberate the free *o*-quinone methide ligand **1**, but rather the novel oxo-dienyl complex **9** was obtained in 88% yield (Scheme 6). Further, carbonylation of **6a** in C_6D_6 solution at 1 atm and room temperature for 2 days did not lead to the displacement of the free *o*-quinone methide, suggesting that complex **6a** is very stable.

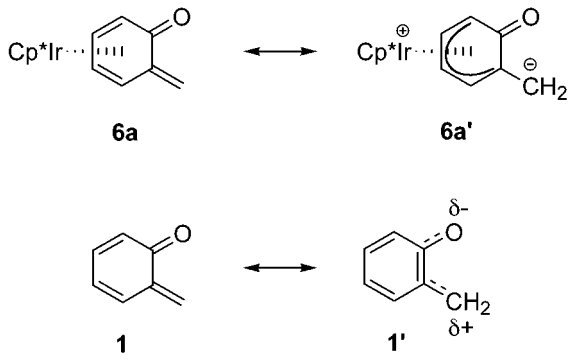
The reactivity of **6a** at the exocyclic carbon of the methylene group (Scheme 6) can be compared with the behavior of enol acetates or enol silyl ethers, which undergo electrophilic iodination[28] or similar reactions at the more electron-rich carbon to the oxygenated substituent.

We reasoned that the nucleophilic reactivity of the exocyclic carbon of **6a** could be used to make carbon−carbon bonds by using electron-poor alkenes and alkynes as electrophiles or cycloaddition partners. With the electron-poor alkyne methyl propynoate, within several hours at room temperature, formation of coupling product **10** (Scheme 7, 46% yield) as a single stereoisomer is observed. The structure of **10** was secured by a combination of NOESY and gradient COSY, HMQC, and HMBC experiments and elemental analysis.

Coupling of the *o*-QM complex **6a** with the electrophilic alkyne may be initiated by nucleophilic attack of the terminal carbon of the exocyclic alkene unit on the terminal carbon of the alkyne, generating zwitterionic oxo-dienyl intermediate **11** (Scheme 8). Proton transfer from the side chain of the oxo-dienyl cation (cf. deprotonation of **5** to give **6**) to the enolate would give the observed product.

Furthermore (Scheme 7), **6a** reacts with *N*-methylmaleimide in 1 day to give a tricyclic complex **12** in 40% yield. The cycloadduct **12** is formally the result of an unusual [3 + 2] cycloaddition with part of the quinone methide system. In this tricyclic complex, the relative stereochemistry between the hydrogens was unambiguously assigned by 2D $^1H-^1H$ COSY and NOESY experiments. Therefore, this cycloaddition reaction occurs with stereo-control of the three asymmetric carbons. A plausible mechanism for the formation of **12** is depicted in Scheme 8.

Scheme 9



The closest precedent for this reaction is a formal [3 + 2] cycloaddition of *p*-quinone methides with alkenes catalyzed by Lewis acids in which aryl-substituted alkenes capable of bearing a developing positive charge were the best.[6b] In contrast, the reaction here involves an *o*-QM derivative and an electron-poor alkene.

All results show that complex **6a** has a nucleophilic exocyclic carbon, unlike free *o*-quinone methides, which feature an electrophilic exocyclic carbon. The apparent role of the Cp*Ir fragment is to stabilize the mesomeric form **6a′** (Scheme 9). In this limiting structure, the exocyclic carbon acquires a greater electron density than in the free ligand, reflected in the upfield ^{13}C chemical shifts in the range 103−128 ppm and in the reactivity toward electrophiles (H^+, I^+, or $HCCCO_2CH_3$) or an electron-poor cycloaddition partner (*N*-methylmaleimide). Both NMR chemical shift data and reactivity patterns are completely unlike those expected for the carbon of an enone, but similar to those for the carbon of an electron-rich alkoxy-substituted alkene $ROCH{=}CH_2$.

Outlook and Concluding Remarks

In this Account we showed that the first complexes of simple *o*-quinone methides can be prepared in one step from oxo-dienyl complexes in high yields. The latter are precursors used in the Ir-mediated nucleophilic ortho-phenol functionalization reaction. A useful organometallic synthetic procedure that allows the preparation of an antitumor reagent such as 2-methoxyestradiol in good yield along with the starting material recycled in $[Cp^*Ir(\mu\text{-}I)I]_2$, this at least would compensate for the inconvenience of using a fairly expensive metal in organic synthesis. A future development would be to render this reaction catalytic.

We have also shown in this Account that, unlike the free *o*-QM (**1**), the metal complex **6a** is thermally stable, yet shows interesting reactivity. The metal complexation reverses the polarity of the *o*-QM ligand leading to nucleophilic character of the exocyclic methylene carbon, unlike free *o*-QMs, which feature an electrophilic exocyclic carbon. Because unique stability and reactivity are imparted on the quinone methide ligand by the Cp*Ir fragment, reactions of Ir-*o*-QM **6a** with electron-poor alkenes and alkynes are possible.

Future efforts will be directed to prepare other *o*-QM complexes with different metal centers. It is well-known that a small change in the nature of the metal produces a major change in the reactivity of the related complexes. Additionally, the preparation of optically pure *o*-QM complexes[29] represents one of our important goals in view of carrying out asymmetric cycloaddition reactions with a variety of alkenes and alkynes. The results will be published in due course.

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