Osmium-Promoted Electrophilic Substitution of Anisoles: A Versatile New Method for the Incorporation of Carbon Substituents

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A structurally and electronically diverse set of anisoles are dihapto-coordinated to the π-base pentaammineosmium(II) and treated with a variety of carbon electrophiles (e.g. Michael acceptors, acetals). After deprotonation of a 4*H*-anisolium intermediate with a tertiary amine base, C(4)-substituted anisole complexes are isolated. The functionalized arenes are removed from the metal center either by mild heating or treatment with an oxidant (e.g. AgOTf, DDQ, CAN). The resulting substituted anisoles are isolated with yields ranging from 55−95%.

Introduction

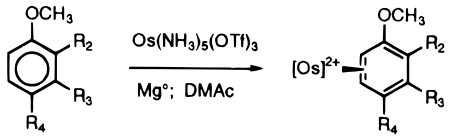
Friedel−Crafts alkylation is considered one of the most powerful synthetic tools available for attaching carbon substituents to an arene ring, yet this reaction is not without its limitations.[1] Regioselectivity is typically poor, and multiple alkylations result in low yields and formidable purification procedures. In addition, isomerization of primary alkyl groups is commonplace, and the harsh reaction conditions required are incompatible with many functional groups.

The π-base pentaammineosmium(II) coordinates arenes in a dihapto fashion rendering the aromatic π-system partially localized. In particular, when the arene bears a single donor group, the metal activates the arene toward electrophilic addition reactions at C(4).[2] In the case of anisole, phenol, or aniline, a strong π-backbonding interaction with the metal center stabilizes the resulting 4*H*-arenium ligand so that this otherwise transient intermediate is stable toward deprotonation. As a consequence, multiple alkylations of the ring are avoided. In the following account, we describe a convenient synthetic procedure for the mild, selective electrophilic substitution of anisoles with several common carbon electrophiles in which the individual steps of electrophilic addition and deprotonation are moderated by the influence of the osmium(II) metal center.

Results

Synthesis of η^2-Anisole Complexes. The one-electron reduction of $Os(NH_3)_5(OTf)_3$ in the presence of various anisole ligands provides the series of compounds **1**−**6** often in quantitative yield (Table 1). In all cases the metal center preferentially binds to the arene across C(5) and C(6), although a dynamic equilibrium exists among various linkage isomers. Most compounds show well resolved ^{1}H NMR resonances for the ring protons in the range of 4.5−7.0 ppm, where the furthest upfield peaks correspond to the coordinated methine groups. The exception is the 2-methylanisole complex (**2**). It shows a severely broadened ^{1}H NMR spectrum at 20 °C, but when the ^{1}H NMR spectrum of **2** is recorded at −45 °C, the proton signals become well resolved. Cyclic voltammetric data for **1**−**6** indicate a chemically irreversible oxidation wave ranging from $E_{p,a} = +0.30$ to 0.70 V (NHE), consistent with data compiled for other η^2-arene complexes.[3] As expected, more electron-deficient arenes form complexes that are more difficult to oxidize, and their oxidation potentials are observed at the higher end of this range. Over time, all these η^2-arene complexes undergo substitution for solvent, but the half-life for solvolysis is sufficiently long (typically, $t_{1/2} > 1$ d at 20 °C in CH_3CN), so that substitution does not interfere with the intended alkylation reaction (*vide infra*). The 2-methylanisole complex **2** is an exception as its substitution half-life in solution is only 15 min at 20 °C. Extended exposure of complexes **1**−**6** to air or harsh oxidants results in loss of the anisole ligand, so these compounds are handled and stored under an inert atmosphere.

Table 1. Complexation of Various Anisoles with Pentaammineosmium(II)



compd	R_2	R_3	R_4	yield (%)
1	H	H	H	96
2	CH_3	H	H	94
3	H	CH_3	H	93
4	H	H	CH_3	96
5	H	OCH_3	H	99
6	H	CF_3	H	78

Electrophilic Additions to Anisole Complexes. As described in our preliminary communication,[2] the anisole complex **1** readily undergoes electrophilic substitution at C(4) with methylacetonitrilium triflate at 20 °C. Other carbon electrophiles such as Michael acceptors, alkyl triflates, and acetals fail to react under these conditions. However, when an acetonitrile solution of **1** is treated with methyl vinyl ketone in the presence of HOTf at −40 °C, a dark purple color appears due to the formation of the 4*H*-anisolium intermediates shown in Figure 1 (*vide*

[⊗] Abstract published in *Advance ACS Abstracts,* December 15, 1996.

(1) Roberts, R. M.; Khalaf, A. A. *Friedel-Crafts Alkylation Chemistry: A Century of Discovery*; M. Dekker: New York, 1984.

(2) (a) Kopach, M. E.; Gonzalez, J.; Harman, W. D. *J. Am. Chem Soc.* **1991**, *113*, 8972. (b) Kopach, M. E.; Harman, W. D. *J. Org. Chem.* **1994**, *59*, 6506.

(3) Harman, W. D.; Sekine, M.; Taube, H. *J. Am. Chem. Soc.* **1988**, *110*, 5725.

S0022-3263(96)01983-4 CCC: $14.00

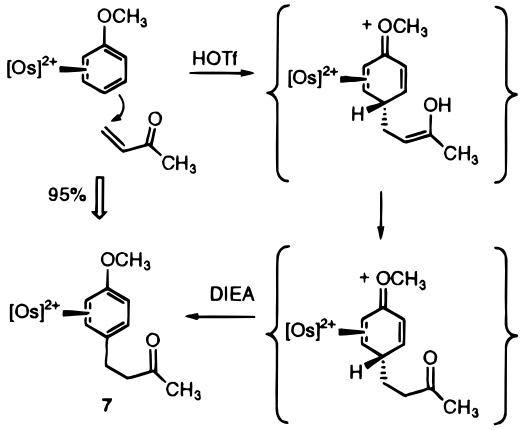


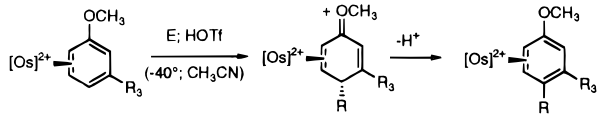
Figure 1. The reaction of methyl vinyl ketone and the η^2-anisole complex of pentaammineosmium(II).

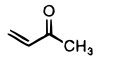
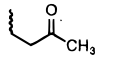
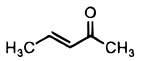
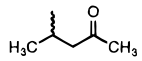
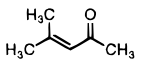
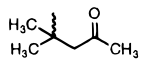
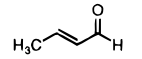
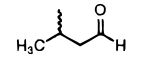
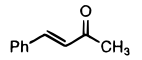
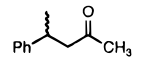
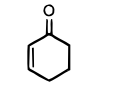
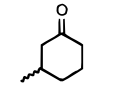
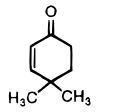
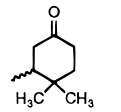
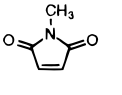
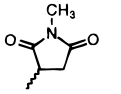
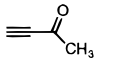
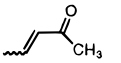
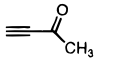
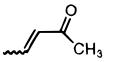
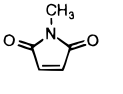
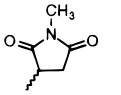
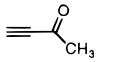
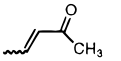
infra).[4] Subsequent treatment of the solution with a tertiary amine base (−40 °C), deprotonates the arenium complex at C(4) to yield the C(4)-substituted anisole complex (**7**). Addition of this reaction mixture to an excess of ether/CH_2Cl_2 induces precipitation of **7** in 95% yield. Supporting data for the assignment of **7** include four doublets in the ^{1}H NMR from 4.87 to 6.11 ppm indicative of a *para*-substituted η^2-arene ligand, and the appearance of a carbonyl (δ 210.0) and two methylene resonances (^{13}C and DEPT) confirming the attachment of the butanone chain. No evidence for other isomers was detected in the product ^{1}H or ^{13}C NMR spectra. Cyclic voltammetric data of **7** are also consistent with an η^2-coordinated arene, showing an irreversible anodic peak at $E_{p,a}$ = 0.43 V (NHE).[5]

In Table 2 the scope of this Michael addition/deprotonation sequence is illustrated. Olefins with a single ketone or aldehyde activating group (**7**−**13**) readily react with the parent anisole complex **1** to give 4-alkylated anisole derivatives with yields generally >90%. *N*-methylmaleimide (**14**) and 3-butyn-2-one (**15**) also give satisfactory results. In cases where a chiral center is formed adjacent to the ring, a mixture of diastereomers is often observed for the substituted arene complexes. The diastereomeric ratio, however, is time dependent as a result of a 5,6-η^2−2,3-η^2 linkage isomerization that effectively epimerizes the asymmetric center formed by metal coordination (Figure 2). As an example, the reaction of **1** with 2-cyclohexen-1-one was monitored over the course of deprotonation and isomerization by ^{1}H NMR. Initially, the sample of the 4*H*-anisolium complex is formed at −40 °C as a 10:1 ratio of diastereomers. After addition of base (d_5-pyridine), the solution of the 4-alkylated anisole **12** was allowed to gradually warm to 20 °C. During this period, the diastereomer ratio was observed to change from 10:1 to its equilibrium ratio of 1:1. In contrast, the closely related 4,4-dimethylcyclohexanone adduct **13** has a significant thermodynamic preference for one diastereomer (de = 90%). In general, if the two substituents on the chiral center differ greatly in size, a single diastereomer is observed for the 4-substituted anisole complex (e.g. **8**−**14**; Table 2).

When the anisole complex is substituted at C(3) by an electron-donating or electron-withdrawing group, conjugate addition still takes place exclusively at C(4) to generate 3,4-disubstituted anisole complexes (Table 2). When C(3) is substituted by the electron-withdrawing substituent CF_3 (i.e. **6**), the reactivity of the complex is

Table 2. Conjugate Addition Reactions with Various η^2-Anisole Complexes



R_3	E	R	Product	Yield(%)[a]
H			**7**	96
H			**8**	87(81% de)
H			**9**	> 90[b]
H			**10**	95 (> 90% de)
H			**11**	> 90(>90% de)[b]
H			**12**	95 (0% de)
H			**13**	91(90%de)
H			**14**	80(>90%de)
H			**15**	98
CH_3			**16**	93
CH_3			**17**	82(>90%de)
CF_3			**18**	89

a Represents isolated yield; b Represents yield in solution (NMR)

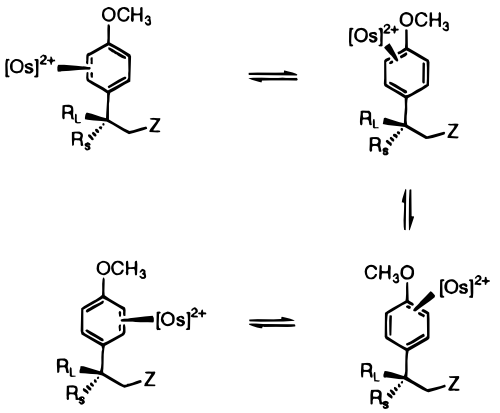
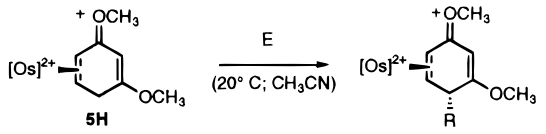


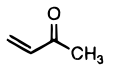
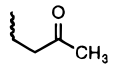
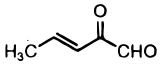
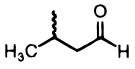
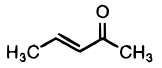
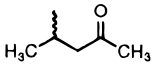
Figure 2. The isomerization of an η^2-arene complex with a substituent bearing a stereogenic center.

(4) For an example of a well characterized 4H-anisolium complex see reference 2b.

(5) Conditions: CH_3CN, 100 mV/s, TBAH. See reference 3.

Table 3. Conjugate Addition Reactions with the 1,3-Dimethoxybenzene Complex 5 via the 4*H*-Arenium Intermediate 5H



E	R	Product	Yield(%)[a]
		**19**	94
		**20**	89 (60%de)
		**21**	89 (60%de)
		**22**	93 (33%de)

a Represents isolated yield

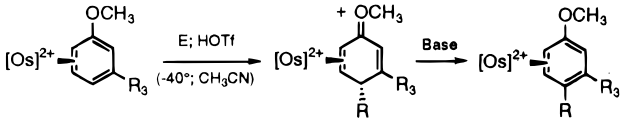
decreased substantially and most Michael acceptors fail to react under the previously demonstrated conditions. However, when **6** is treated with 3-butyn-2-one and $BF_3 \cdot OEt_2$ at −40 °C, a brilliant purple solution develops that forms the enone substitution product **18** when treated with base.

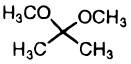
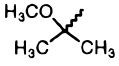
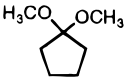
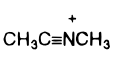
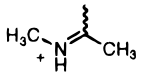
For the special case of the 1,3-dimethoxybenzene complex **5**, reactions are most conveniently accomplished by adding the electrophile directly to a sample of the 4*H*-anisolium species **5H**, the product of a C(4) protonation of compound **5** (Table 3). Unlike the parent anisolium species,[2b] compound **5H** is stable indefinitely as a solid at 20 °C. A ^{1}H NMR spectrum of **5H** (20 °C, CD_3CN) shows three olefinic protons, two methoxy groups, and *cis*- and *trans*-ammine signals shifted downfield from its dimethoxybenzene complex precursor. ^{13}C NMR resonances at 205.7 and 193.5 ppm as well as a methylene carbon resonance at 35.6 ppm indicate the nonaromatic nature of the carbocycle.

When an acetonitrile solution of **5H** is treated with a slight excess of MVK and precipitated from solution, a new product (**19**) is isolated whose NMR features are similar to those of **5H**, but with additional ^{1}H and ^{13}C signals corresponding to an oxobutyl group. Unexpectedly, attempts to deprotonate the corresponding anisolium complexes at C(4) by an amine base (e.g. DIEA) fail to return the 3,4-disubstituted anisole complex. However, the arene itself (4-(2,4-dimethoxyphenyl)butan-2-one) may be obtained via exposure of an acetone solution of **19** to air. The scope of Michael acceptor for **5** is similar to that for the parent anisole complex **1**, and several examples appear in Table 3.

Several other carbon electrophiles were also screened for reactivity with the parent anisole complex **1**, and those that give satisfactory results are summarized in Table 4. The parent anisole complex **1** reacts efficiently with acetals to form 4-methoxybenzyl ethers. For example, when an acetonitrile solution of **1** is cooled to −40 °C and treated with a mixture of HOTf (2−3 equiv) and acetaldehyde diethyl acetal (1.1 equiv) the solution becomes deep blue. Upon addition of pyridine, the color changes back to amber, and subsequent addition to ether/

Table 4. Assorted C(4) Addition Reactions with Carbon Electrophiles and η^2-Anisole Complexes



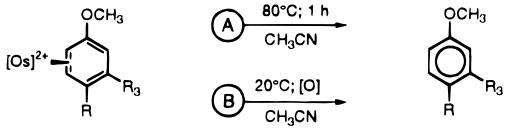
R_3	E	R	Yield(%)	Product
H	$H_3CCH(OEt)_2$		92	**23**
H			88	**24**
H			88	**25**
CH_3	$H_2C(OEt)_2$		92	**26**
H	$CH(OEt)_3$	CHO	86	**27**
H			88	**28**

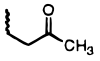
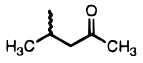
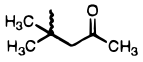
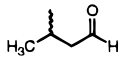
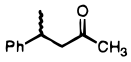
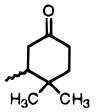
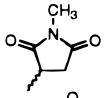
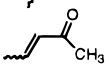
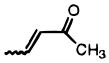
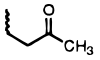
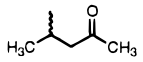
CH_2Cl_2 (1:1) precipitates compound **23**. A ^{1}H NMR spectrum of **23** indicates the formation of one dominant diastereomer whose features include four arene resonances in the range of 6.5−5.0 ppm, a single ethoxy group with diastereotopic methylene protons, and a methyl signal split into a doublet. Satisfactory results are obtained even for the hindered acetals formed from acetone (**24**) or cyclopentanone (**25**).

Acylation or formylation at the 4-position of the anisole complex **1** is best accomplished either by reaction with methylacetonitrilium triflate or an ortho ester followed by hydrolysis. One example of each of these reactions is provided in Table 4. In the case of nitrilium addition, the complex is most conveniently isolated as the iminium salt, whereas the reaction product resulting from triethyl orthoformate addition is hydrolyzed *in situ* prior to isolation. Of note, the iminium-substituted anisole ligand of complex **28** is unusually resistant to hydrolysis requiring decomplexation before it may be converted into 4′-methoxyacetophenone (93%). Electrophiles bearing a labile halide (e.g. acyl and alkyl halides) were avoided out of concern that precipitation of the osmium complex as a halide salt would compromise the intended reaction. In addition, less reactive Michael acceptors (e.g. methyl acrylate or acrylonitrile) fail to react under the stated reaction conditions.

In the absence of electron-withdrawing groups on the anisole ring, substituted arenes can be decomplexed by a simple ligand substitution procedure. Heating a substituted anisole complex in a coordinating solvent such as acetonitrile (70 °C, 1 h) results in decomplexation of the organic ligand and formation of $[Os(NH_3)_5(CH_3CN)]^{3+}$. This inorganic byproduct is easily separable from the desired organic material by precipitation in ether (see Experimental Section). In an alternative method, arenes are readily liberated at lower temperature (20 °C) by use

Table 5. Isolated Yields for the Decomplexation of η^2-Anisole Products

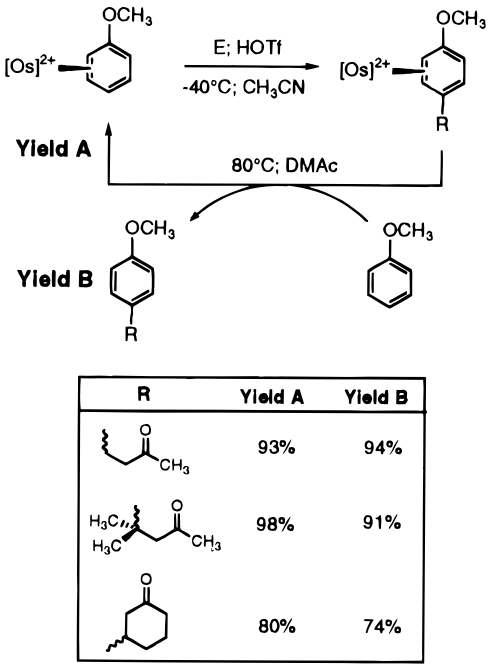


Complex	R_3	R	Method	Yield(%)[a]	Product
7	H		B	84	29
8	H		A	93	30
9	H		B	79	31
10	H		B	59	32
11	H		A	70	33
12	H		A	94	34
13	H		A	85	35
14	H		B	81	36
16	CH_3		B	89	37
18	CF_3		B	73	38
19	OCH_3		B	76	39
20	OCH_3		B	77	40
23	H		A	90	41
25	H		A	95	42
28	H		B	93	43

a Represents isolated yield

of a one-electron oxidant (e.g. AgOTf or CAN). This approach is particularly useful when the anisole ligand contains an electron-withdrawing group (e.g. **18**, **28**), an alternative coordination site (e.g. **15**, **16**), or a sensitive functional group (e.g. **10**). Isolated yields of the substituted anisoles were generally in the range of 80−90% for either method (Table 5).

In many cases, the pentaammineosmium(II) metal center may be directly recycled through what formally is a catalytic cycle (Figure 3). For example, the anisole complex **1** may be alkylated at C(4) by MVK and deprotonated to give the 4-alkylated anisole complex **7**. Heating a DMA solution of **7** to 80 °C in the presence of an excess of anisole regenerates the parent anisole



R	Yield A	Yield B
	93%	94%
	98%	91%
	80%	74%

Figure 3. A formal catalytic cycle for the conversion of anisole to a C(4)-substituted anisole.

complex **1** in 93% isolated yield, while returning 4-(*p*-methoxyphenyl)butan-2-one in 95% yield. While this cycle is highly efficient for most Michael addition products, yields are somewhat lower for the benzyl ethers derived from acetals as a result of a more sluggish ligand substitution rate. Raising the reaction temperature above 80 °C or changing solvent to methanol results in significant decomposition of the pentaammineosmium(II) system, as well as formation of a new compound that we believe to be the binuclear species[{$Os(NH_3)_5$}$_2$(η^2:η^2-anisole)](OTf)$_4$.[6]

Although 4-substituted anisole complexes can also undergo electrophilic addition at C(4), the scope of this reaction appears to be limited to either unhindered (e.g. MVK or 3-butyn-2-one) or doubly activated (e.g. *N*-methylmaleimide) Michael acceptors. For example, when the 4-methylanisole complex **4** is treated with MVK, the η^2-(α-4-methyl)anisolium species **44** is isolated as the sole product (97%; Figure 4). In contrast to the 4*H*-anisolium complexes bearing a methine proton at C(4), the triflate salt of **44** is stable indefinitely in the solid state. Although this material is surprisingly resistant to hydrolysis, (e.g. at 25 °C in D_2O, $t_{1/2}$ > 2 h) it may be converted to the corresponding 4-methyl-η^2-cyclohexadienone complex **45** and then oxidized to give 4-methyl-4-(2-oxobutyl)-2,5-cyclohexadien-1-one in 69% yield. When the 4-methylansiole complex **4** is combined with *N*-methylacetonitrilium triflate, alkylation at C(2) results in the formation of a 2-methoxy-*N*-methylacetophenone imine complex **46**. Hydrolysis of **46** followed by oxidation (AgOTf) gives 5-methyl-2-methoxyacetophenone (**47**; 55%) (Figure 4).

Discussion

The alkylation of anisoles via an electrophilic substitution mechanism (i.e. Friedel−Crafts methodology) has several limitations that sometimes compromise its utility

(6) Harman, W. D.; Taube, H. *J. Am. Chem. Soc.* **1987**, *109*, 1883.

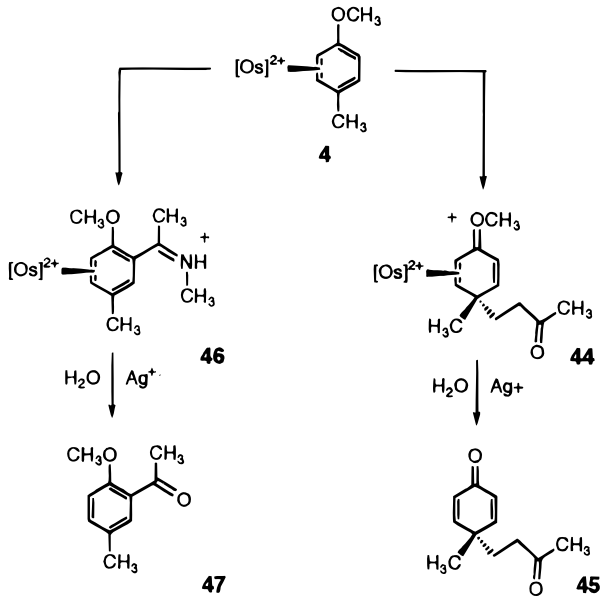


Figure 4. A contrast in the reactions of a C(4)-substituted η^2-anisole complex with acetonitrilium ion and methyl vinyl ketone.

as a tool for organic synthesis. Due to the stability of the aromatic ring system, reaction conditions required for alkylation are severe utilizing high temperatures or harsh Lewis acids to promote the reaction. As a result, many functional groups are either incompatible (e.g. aldehydes, ketones, acid-sensitive protecting groups) or they compromise the effectiveness of the Lewis acid (e.g. alcohols, amines, amides). Further, primary alkylating agents often undergo isomerization under the reaction conditions required for electrophilic substitution.[7]

By complexing anisole to the pentaammineosmium(II) system, the arene is rendered more nucleophilic through the localization of the π-electrons and the donation of electron-density by metal-to-ligand backbonding. Consider that the pK_a for the benzenium cation is estimated to be -24.0 in acetonitrile,[8] whereas that for the pentaammineosmium(II) complex is ~ 1.[9] Thus, coordination increases the basicity of the arene by approximately *25 orders of magnitude*.[10] Consequently, a successful electrophilic addition can be carried out under much milder conditions than for the uncoordinated arene. Michael additions are accomplished at -40 °C in the presence of acidic acetonitrile, conditions amenable to sensitive functionalities such as aliphatic aldehydes (e.g. **10**). Furthermore, addition of an acetal to anisole is easily accomplished (Table 4) even though the byproduct is an alcohol.

Previous investigations of phenol[11] and aniline[12] complexes of pentaammineosmium(II) reveal two important mechanisms for the stabilization of 4*H*-arene and arenium complexes that prevent the possibility of multiple

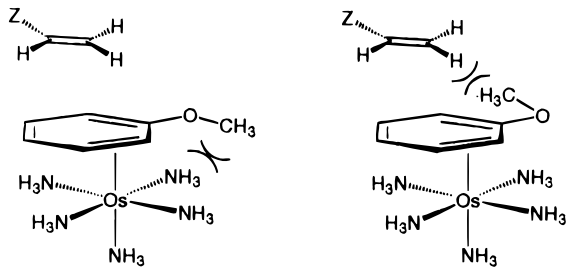
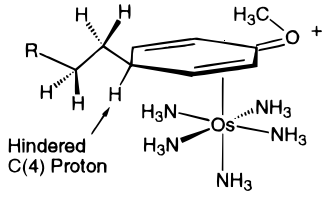


Figure 5. Steric interference in addition of a Michael acceptor to C(2) of an η^2-anisole complex.

alkylation of the arene. As mentioned above, the strong π-basic nature of the osmium(II) group stabilizes the 4*H*-arenium fragment through backbonding and deprotonation is not spontaneous in acidic acetonitrile at -40 °C.[13] In addition to this thermodynamic feature, deprotonation is also inhibited as a result of the congested environment of the acidic sp^3 methine proton resulting from the electrophilic addition (inset A). Given that the carbon



electrophile attacks the arene from the *exo* face,[14] the C(4) proton has an endo orientation and is shielded both by the electrophile skeleton and the pentaammineosmium framework. Whereas alcohols readily deprotonate the exposed exo C(4) proton of the parent 4*H*-anisolium complex (even at -40 °C),[2b] the 4*H*-anisolium intermediates for the reactions shown in Table 4 resist rearomatization even though an alcohol is the byproduct of the acetal addition. As a result, multiple alkylations are completely avoided.

The high C(4) regioselectivity observed for the electrophilic addition to the parent anisole complex is also likely the result of both kinetic and thermodynamic factors. Our investigation of η^2-phenol complexes revealed a thermodynamic preference for the *2,3*-η^2-2,5-cyclohexadienone tautomer over its 2,3-η^2-2,4-cyclohexadienone isomer, possibly due to the conjugation in the uncoordinated portion of the ring π-system. If this relationship holds for the anisolium systems as well, the addition to C(4) could be rationalized on thermodynamic grounds. Also deserving consideration, however, is the steric influence of the methoxy substituent. Either a 2*H*- or 4*H*-anisolium system requires that the methoxy group lie in the plane of the arene. Molecular models show a steric interaction of this methyl group and the pentaammineosmium framework unless the oxygen substituent adapts an *anti* orientation with respect to the metal, and this arrangement would interfere with the approach of an electrophile to C(2) (Figure 5). Consider that while both 3-methyl- and 4-methylanisole complexes have substitution half-lives of several days at 20 °C in CH_3CN, the

(7) For a review of rearrangements of alkylating agents and alkyl substituents, see reference 1, Chapters 2 and 8 and references therein.

(8) Nagaoka, T.; Berinstain, D; Griller, A. B.; Wayner, D. D. M. *J. Org. Chem.* **1990**, *55*, 3707.

(9) This would correspond to a pK_a of about -8 in water for the osmium(II) complex.

(10) Winemiller, M. D.; Kopach, M. E.; Harman, W. D. Submitted for publication.

(11) (a) Kopach, M. E.; Hipple, W. G.; Harman, W. D. *J. Am. Chem. Soc.* **1992**, *114*, 1737. (b) Kopach, M. E.; Harman, W. D. *J. Am. Chem. Soc.* **1994**, *116*, 6581.

(12) Kolis, S. P.; Gonzalez, J.; Bright, L. M.; Harman, W. D. *Organometallics* **1996**, *15*, 245.

(13) The pK_a for the complex $[Os(NH_3)_5(\eta^2\text{-}4H\text{-anisolium})]^{2+}$ has been determined to be -3.6 ± 1 whereas that for acetonitrililium cation is -10. See reference 10.

(14) We have observed electrophilic addition reactions to aromatic rings of pentaammineosmium(II) complexes for phenols, anilines, pyrroles, furans, and napththalenes, and in all cases encountered, the electrophile adds to the exo face of the ring.

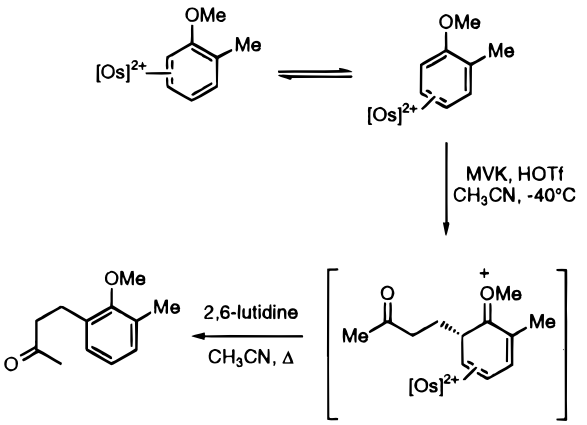


Figure 6. Reactivity of a C(2)-substituted η^2-anisole complex with methyl vinyl ketone.

2-methylanisole derivative has a half-life in solution of ~15 min. Presumably a steric interaction of the methoxy substituent with the C(2) methyl group forces the methoxy group to adopt a conformation in which it interferes with the pentaammineosmium(II) framework. The net result of this is a destabilization of the complex.

Consistent with the observation that the methoxy group does not prefer being coplanar with a substituent at C(2), the 2-methylanisole complex does not react in the same fashion as other 3- or 4-substituted anisole complexes (Figure 6). Rather, upon subjecting the 2-methylanisole complex and MVK to the usual electrophilic addition conditions, a dark green (rather than the usual dark purple) color is observed. Subsequent decomplexation and isolation of the organic compound reveals that the anisole has reacted at the unsubstituted *ortho*-position to yield a 1,2,3-trisubstituted arene.[15] This addition is likely accomplished by the metal center undergoing a rapid linkage isomerization to the C(4)−C(5) double bond, followed by electrophilic addition to C(6). This behavior is consistent with behavior of arene complexes that do not contain an electron-releasing substituent (e.g. benzene, toluene) and is the focus of continued studies in these laboratories.

The unusually stable nature of the 4*H*-anisolium intermediate deserves further comment. As mentioned above, when C(4) is a quaternary carbon (e.g. **44**) or when C(3) is substituted with a methoxy group (Table 3), the 4*H*-arenium complex is stable enough to be isolated as its triflate salt. Remarkably, these 4*H*-anisolium complexes are moderately stable toward hydrolysis, even in aqueous solution at 20 °C, and this property is likely a direct result of the metal π-backbonding. For the C(3)-substituted 4*H*-anisolium complex **19**, the system is so stable that neither hydrolysis (80 °C in water!) nor deprotonation at C(4) (amine bases) has been observed. For more typical 4*H*-anisolium complexes, however, the arene is sufficiently electrophilic that, in addition to hydrolysis and deprotonation, nucleophilies react at either C(1) or C(3) thus constituting a general synthetic approach to nonaromatic ring systems.[16]

(15) This compound has been characterized by NMR: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.99 (m, 3H), 3.73 (s, 3H), 2.88 (m, 2H), 2.77 (m, 2H), 2.29 (s, 3H), 2.15 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 208.3 (C), 156.8 (C), 133.9 (C), 131.2 (C), 129.6 (CH), 127.8 (CH), 124.2 (CH), 60.5 (CH_3), 44.7 (CH_2), 30.2 (CH_3), 24.7 (CH_2), 16.4 (CH_3).

(16) Kopach, M. E.; Kolis, S. P.; Liu, R.; Harman, W. D. Manuscript in preparation.

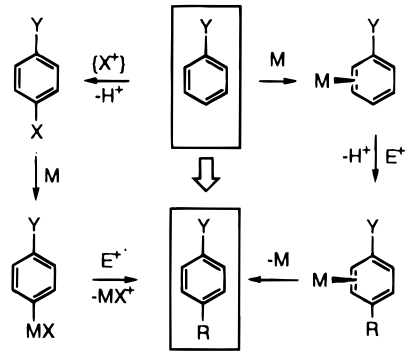


Figure 7. A comparison of methods for the C(4) alkylation of a substituted arene (Y = electron donor group; E = carbon electrophile).

The osmium-promoted electrophilic substitution of arenes (Tables 2−4) is complementary to the chemistry of aryl cuprates[17] or arylboronic acids[18] as these strategies all involve C−C coupling of a nucleophilic arene (Figure 7). Using the described osmium methodology, the active nucleophile may be directly prepared from the desired anisole in a single step from $Os(NH_3)_5(OTf)_3$ under neutral conditions, without the need of obtaining the appropriately halogenated arene precursor. Complexation of the arene may be carried out in the presence of esters, amides, silyl ethers and other common protecting groups as well as unmasked alcohols or tertiary amines, and may even be achieved in water or methanol with as little as 1 equiv of the desired ligand.[19] Electrophilic addition at C(4) is generally accomplished in good yield even for cases in which a quaternary carbon is formed (e.g. **9**, **24**, **25**), or when the anisole bears an adjacent substituent (e.g. CH_3, CF_3, OCH_3 at C(3)). Finally, substituted anisoles may be recovered and their anisole precursor regenerated in a single step (Figure 3).

Conclusions

Coordination of the pentaammineosmium(II) metal center to various anisoles dramatically increases the nucleophilicity of the arene. Reactions occur with a wide variety of carbon electrophiles in the presence of acidic acetonitrile at −40 °C to form characterizable 4*H*-anisolium intermediates. Upon deprotonation and decomplexation, the 4-substituted anisole is returned in overall yields typically greater than 80%.[20]

Experimental Section[21]

General Procedure for the Synthesis of η^2-Anisole Complexes. $(NH_3)_5Os(OTf)_3$ (2.0 g, 2.77 mmol) is slurried in ~2.0 g of DMA, and ~10 equiv of the desired anisole ligand

(17) For a good review of ayrlcuprates used in conjugate addition reactions see Lipshutz, B. H.; Sengupta, S. *Organic Reactions*; Paquette, L. A., Ed.; John Wiley and Sons: New York, 1992; Vol. 41.

(18) See for example Cho, C. S.; Motofusa, S.; Ohe, K.; Uemura, S. *J. Org. Chem.* **1995**, *60*, 883.

(19) Call, J. T.; Hughes, K. A.; Harman, W. D.; Finn, M. G. *Inorg. Chem.* **1993**, *32*, 2123.

(20) As a result of a reviewer's concern over the cost of the pentaammineosmium(II) reagent, we wish to disclose that OsO_4 may be purchased at an economical price (Colonial Metals) and may be converted to $Os(NH_3)_5(OTf)_3$ in 98% overall yield (see reference 1c). Using these procedures, the cost of any of the final organic products presented in Table 5 falls in the range of $30−35/g. This reflects the cost of osmium over the entire six-step process (taking into account yields) and assumes no recovery of the metal.

(21) Please see supporting information for full characterization data for all compounds. For full description of general experimental details, please see ref 11b.

and activated magnesium (1.0 g) are added. The heterogeneous reaction mixture is allowed to stir for ~1 h, and the solution is filtered through a fritted glass funnel into ~400 mL of a 1:1 Et_2O/CH_2Cl_2 solution. The resulting slurry is filtered through a separate fritted glass funnel, and the resulting tan or yellow solids are isolated typically in >95% yield.

[Os(NH$_3$)$_5$(2-Methyl-η^2-5β,6β-anisole)](OTf)$_2$ (2). Yield: 94%. ^{1}H NMR at 25 °C revealed a fluxional metal complex. ^{1}H NMR (CD_3CN/−40 °C): δ 6.85 (t, 1H, J = 6.3 Hz), 6.13 (d, 1H, J = 8.3 Hz), 4.92 (t, 1H, J = 6.0 Hz), 4.72 (d, 1H, J = 6.0 Hz), 3.97 (br s, 3H), 3.61 (s, 3H), 2.77 (br s, 12 H), 2.02 (s, 3H). ^{13}C NMR (CD_3CN/−40 °C): δ 154.4 (C), 135.5 (CH), 125.7 (CH), 103.8 (C), 61.3 (CH), 56.6 (CH), 54.0 (CH_3), 16.2 (CH_3). Cyclic voltammetry: $E_{p,a}$ = 0.45 V. This compound was purified as its tetraphenylborate salt via ion-exchange chromatography. Anal. Calcd for $C_{56}H_{65}ON_5B_2Os\cdot H_2O$: C, 63.82%; H, 6.41%; N, 6.61%. Found: C, 63.70%; H, 6.42%; N, 6.51%.

[Os(NH$_3$)$_5$(3-Methyl-η^2-5β,6β-anisole)](OTf)$_2$ (3). Yield: 93%. ^{1}H NMR (CD_3CN): δ 6.31 (d, 1H, J = 8.1 Hz), 5.60 (s, 1H), 5.00 (t, 1H), 4.74 (d, 1H, J = 8.1 Hz) 4.05 (br s, 3H), 3.65 (s, 3H), 2.90 (br s, 12 H), 2.18 (s, 3H). ^{13}C NMR (CD_3CN): δ 168.5 (C), 132.0 (C), 120.2 (CH), 96.4 (CH), 62.0 (CH), 54.8 (CH_3), 54.1 (CH), 20.5 (CH_3). Cyclic voltammetry: $E_{p,a}$ = 0.35 V. Anal Calcd for $C_{10}H_{25}N_5O_7S_2F_6Os$: C, 17.27%; H, 3.62%; N, 10.00%. Found: C, 17.52%; H, 3.58%; N, 9.64%.

General Procedure for Electrophilic Substitution Reactions. The desired anisole complex (**1**−**4**; 60−70 mg) is dissolved in acetonitrile (0.5−1.0 g), the electrophile (1−2 equiv) is added, and the solution is cooled to −40 °C. Cold triflic acid (2−3 equiv) in acetonitrile (0.5 g) is added, and the reaction solution immediately turns purple. After 20−30 min, an excess of a tertiary amine base (pyridine, 2,6-lutidine) is added, and the solution changes color to amber. The solution is precipitated into a stirring 1:1 Et_2O/CH_2Cl_2 solution, and the resulting slurry filtered and the solid dried *in vacuo* to yield the substituted anisole complexes. The purity and yields of the individual reactions are highly dependent upon the concentration of electrophile and acid used, and the individual amounts are given before the spectroscopic data for each compound.

[Os(NH$_3$)$_5$(4-(3-Oxo-butyl)-η^2-5β,6β-anisole)](OTf)$_2$ (7): 2.0 equiv of MVK, 1.1 equiv of HOTf. Yield: 96%. ^{1}H NMR (CD_3CN): δ 6.11 (d, 1H, J = 6.9 Hz), 5.45 (d, 1H, J = 6.9 Hz), 5.10 (d, 1H, J = 7.8 Hz), 4.87 (d, 1H, J = 7.8 Hz), 4.11 (br s, 3H), 3.66 (s, 3H), 3.00 (br s, 12 H), 2.20−3.20 (m, 4H), 2.08 (s, 3H). ^{13}C NMR (CD_3CN): δ 210.0 (C), 165.6 (C), 137.8 (C), 113.8 (CH), 91.9 (CH), 61.3 (CH), 54.8 (CH), 54.4 (CH_3), 40.2 (CH_2), 29.2 (CH_3), 28.4 (CH_2). Cyclic voltammetry: $E_{p,a}$ = 0.43 V. This compound was purified as its tetraphenylborate salt via ion-exchange chromatography. Anal. Calcd for $C_{59}H_{69}O_2N_5B_2Os\cdot 2H_2O$: C, 62.82%; H, 6.52%; N, 6.21%. Found: C, 62.53%; H, 6.42%; N, 6.26%.

[Os(NH$_3$)$_5$(3-Methoxy-4α-(3-oxobutyl)-4β-H-η^2-5β,6β-anisolium)](OTf)$_3$ (19). η^2-3-Methoxy-4*H*-anisolium (**5H**, 120 mg, 0.138 mmol) was dissolved in CH_3CN (1.4 g), and MVK (12.5 mg, 0.178 mmol) was added. After 15 min, addition to ether (40 mL) gave a midnight blue precipitate (122 mg, 94%) which was collected, washed with ether, and dried *in vacuo*. ^{1}H NMR (CD_3CN): δ 5.98 (s, 1H), 5.08 (d, 1H, J = 7.5 Hz), 5.01 (d, 1H, J = 7.5 Hz), 4.81 (br s, 3H), 4.26 (s, 3H), 4.06 (s, 3H), 3.42 (br s, 12 H), 2.40−2.90 (m, 4H), 2.21 (s, 3H). 2.07 (m, 1H). ^{13}C NMR (CD_3CN): δ 208.9 (CO), 204.9 (CO), 193.9 (C), 93.1 (CH), 62.0 (CH_3), 60.4 (CH_3), 53.7 (CH), 44.8 (CH), 44.7 (CH), 38.7 (CH_2), 29.8 (CH_3), 29.7 (CH_2). Cyclic voltammetry: $E_{p,a}$ = 1.29 V. Anal. Calcd for $C_{15}H_{31}N_5O_{12}S_3F_9Os$: C, 19.36%; H, 3.36%; N, 7.52%. Found: C, 19.08%; H, 3.24%; N, 7.45%.

[Os(NH$_3$)$_5$(4-(1-Ethoxyethane)-η^2-5β,6β-anisole)](OTf)$_2$ (23): 1.0 equiv of acetaldehyde diethylacetal, 2.5 equiv of HOTf. Yield: 92%. ^{1}H NMR revealed predominantly one diastereomer. ^{1}H NMR (d_6-acetone): δ 6.53 (dd, J = 8.4 Hz, 2.1 Hz, 1H), 5.53 (dd, J = 8.4 Hz, 2.1 Hz, 1H), 5.47 (dd, J = 8.4 Hz, 2.1 Hz, 1H), 5.09 (dd, J = 8.4 Hz, 2.1 Hz, 1H), 4.71 (br s, 3H), 4.30 (q, J = 6.6 Hz, 1H), 3.69 (s, 3H), 3.55 (br s, 12H), 3.40−3.70 (m, 2H), 1.43 (d, J = 6.6 Hz, 3H), 1.21 (t, J = 7.2 Hz, 3H). ^{13}C NMR (d_6-acetone): δ 170.8 (C), 139.9 (C), 121.0 (CH), 93.2 (CH), 80.5 (CH), 64.3 (CH_2), 58.5 (CH), 56.7 (CH), 55.4(CH_3), 19.2 (CH_3), 15.6 (CH_3). Cyclic voltammetry: $E_{p,a}$ = 0.40 V.

General Procedure for the Decomplexation of Arene Complexes. Method A. The desired arene complex (200 mg) is dissolved in CH_3CN (3−5 mL) and is heated in a sealed tube at 80 °C for ~1 h. The resulting solution is allowed to cool and is precipitated in ether. The inorganic salts are filtered off, and the solvent removed *in vacuo* to provide the desired products. The crude products were purified (10:1 hexanes/ether, SiO_2) and subjected to a silica plug before elemental analysis. **Method B:** The desired anisole complex (200 mg) is dissolved in acetone or acetonitrile (2−5 g) and treated with ~1 equiv of an oxidant (DDQ, Ag^+, O_2) and the inorganic salts are separated by precipitation in ether and filtration. The resulting ether solution is concentrated, and the organic compounds are purified by column chromatography (SiO_2) using 10:1 petroleum ether/ether as the elution solvent or prep TLC (see supporting information).

4-(4-Methoxyphenyl)pentan-2-one (30). Yield: 93%. ^{1}H-NMR ($CDCl_3$): δ 7.13 (d, J = 8.4 Hz, 2H), 6.83 (d, J = 8.4 Hz, 2H), 3.77 (s, 3H), 3.20−3.32 (m, 1H), 2.58−2.76 (m, 2H), 2.05 (s, 3H), 1.23 (d, J = 6.9 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 207.9 (C), 157.8 (C), 138.1 (C), 127.5 (CH), 113.7 (CH), 55.1 (CH_3), 52.1 (CH_2), 34.6 (CH), 30.5 (CH_3), 22.1 (CH_3).

1-Methoxy-1-(4-methoxyphenyl)cyclopentane (42). Yield: 95%. ^{1}H NMR ($CDCl_3$): δ 7.33 (d, 2 H, J = 9.0 Hz, H-$C_{2,6}$), 6.88 (d, 2 H, J = 9.0 Hz, H-$C_{3,5}$), 3.81 (s, 3 H, OCH_3), 2.94 (s, 3 H, OCH_3), 2.10−2.20 (m, 2 H), 1.75−1.92 (m, 6 H); ^{13}C NMR ($CDCl_3$): δ 158.50 (C), 135.42 (C), 127.86 (CH), 113.31 (CH), 87.91 (C), 55.19 (CH_3), 50.37 (CH_3), 36.49 (CH_2), 23.01 (CH_2). Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69%, H, 8.79%; Found: C, 75.28%, H, 9.11%. Yield: 95%.

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Supporting Information Available: Detailed synthesis and characterization for all compounds presented herein (10 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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