The Activation of Aromatic Molecules with Pentaammineosmium(II)

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Contents

I. Introduction

In many aspects, arenes and aromatic heterocycles are ideal synthons for complex organic compounds. They are widely available, highly stable, and readily derivatized through electrophilic substitution, but most significantly, they constitute cyclic skeletons composed of unsaturated carbons. Given that chemical substances found in nature are often nonaromatic, the successful utilization of aromatic compounds as synthons for these materials often depends on a chemist's ability to dearomatize them selectively. Methods for achieving this, such as the Birch reduction, have become powerful tools in the synthesis of cyclic and polycyclic natural products.[1−3]

The chemical nature of aromatic systems is profoundly affected by transition metal coordination.[4] For example, complexes such as $(\eta^6\text{-arene})Cr(CO)_3$[5−7] and its cationic analogs (e.g., $FeCp^+$,[8] $RuCp^+$,[9] $Mn(CO)_3^+$)[9−11] are susceptible to nucleophilic substitution or addition, ultimately leading to the formation of substituted arenes or cyclohexadienes respectively. During the past two decades, the application to η^6-arene complexes in organic synthesis has been widely exploited.[12,13]

In a complementary approach, an aromatic system may be activated toward organic transformations by η^2 coordination. The arene bound in this unusual manner can function both as a Lewis base[14,15] and a π acid.[15−24] In the latter mode, the metal−arene bond is stabilized primarily by the interaction of metal d_π orbitals with the π^* system of the arene, an interaction having two important consequences for arene activation. Through π back-bonding, the aromatic π system becomes more electron rich, similar to what is observed for organic arenes bearing electron-donating groups.[25] Additionally, structural data for complexes containing η^2-coordinated aromatic rings show significant distortions in the bond lengths of the ring consistent with a *localization* of π-electron density.[16] Together, these effects activate η^2-bound aromatic systems toward *electrophilic* rather than nucleophilic addition (*vide infra*).

Of the handful of transition metal systems that are known to form stable η^2 complexes with aromatic molecules,[15−24] only pentaammineosmium(II) has been shown to enhance the reactivity of the aromatic

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W. Dean Harman was born in 1960 in Stanford, CA. He received his B.Sc. from Stanford University where he graduated Phi Beta Kappa in 1983. He remained at "The Farm" to attend graduate school under the guidance of Professor Henry Taube, where he was first exposed to the coordination chemistry of ruthenium and osmium. In 1987, he received his Ph.D. from Stanford and stayed on as a research associate with Professor Taube until 1989 when he joined the faculty at the University of Virginia. In 1997, he was promoted to Professor of Chemistry and currently holds a Cavalier Distinguished Teaching Chair. Harman has been named as a Camille and Henry Dreyfus Teacher–Scholar (1992–1995), an NSF Young Investigator (1993–1998), and an Alfred P. Sloan Research Fellow (1994–1996) and has been the recipient of several University teaching awards. He is co-author of over 50 refereed journal publications that collectively explore the diverse interactions of electron-rich transition metal complexes with unsaturated organic molecules. Professor Harman currently lives in Earlysville, VA, at the edge of the Blue Ridge Mountains, with his wife Lisa, and two children, Alorah and Dustin.

ligand toward electrophiles. Thus, although this review is, broadly speaking, concerned with the activation of aromatic systems η^2 coordinated to a transition metal, the scope is limited at present to the chemistry of pentaammineosmium(II).

This review initially covers several aspects of complexation of aromatic molecules, including the scope of aromatic substrate and the thermodynamic and kinetic relationships between various pentaammineosmium(II) complexes, followed by a discussion of their physical and spectroscopic characteristics. The focus of this work, however, is the fundamental organic reactions of these complexes with electrophiles and the subsequent reactions of those products. Several applications of this methodology are illustrated. Although the scope of this review is the chemistry of aromatic complexes, the chemistry of more elementary pentaammineosmium(II) systems is also discussed in a limited context. A more comprehensive review of osmium−ammine chemistry may be found elsewhere.[26]

II. Binding Characteristics of $\{Os(NH_3)_5\}^{2+}$

A. Survey of η^2-Coordinated Ligands

Complexes of pentaammineosmium(II) are most commonly prepared by reducing the Os^{III} precursor $[Os(NH_3)_5(OTf)](OTf)_2$ in the presence of the desired ligand. $[Os(NH_3)_5(OTf)](OTf)_2$ is available from Aldrich Chemical or is readily prepared from OsO_4 (>92% yield in three steps).[27] Typically, the reduction is carried out under a nitrogen atmosphere with magnesium in DMAc or a DMAc/DME mixture. Alternatively, Zn°/Hg° amalgam may be used as the

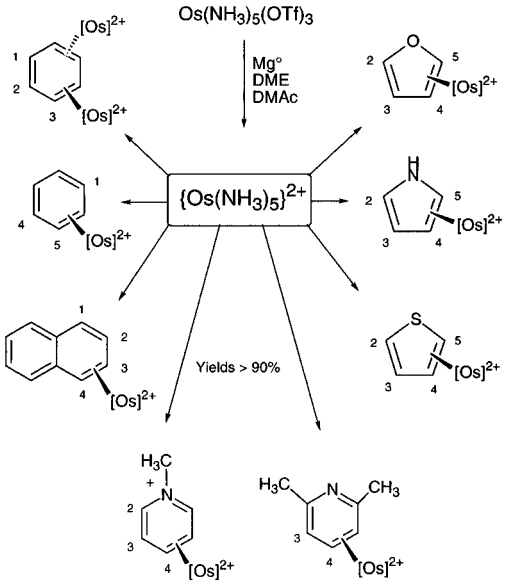


Figure 1. A survey of pentaammineosmium(II) complexes with η^2-bound aromatic ligands.

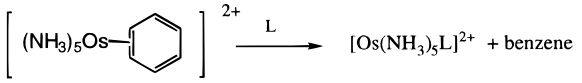
reducing agent if the reaction is carried out in methanol. Using this simple procedure, pentaammineosmium(II) complexes have been prepared with a diverse array of η^2-bound aromatic ligands (Figure 1) including benzenes,[28−30] anisoles,[31,32] anilines,[33−36] phenols,[34,37−39] naphthalenes, and other polyaromatic hydrocarbons,[40] pyridines,[41,42] pyrroles,[43−49] furans,[43,50,51] and thiophenes,[43,52] with yields typically >90%. Where convenient, the ligand is used in approximately a 10-fold excess to minimize the formation of binuclear impurities. However, if the aromatic substrate is precious, as little as 1.1 equiv may be used, provided the reaction is carried out in water[53] or methanol.[54] Carrying out the complexation procedure without a large excess of ligand should be avoided, as these conditions increase the possibility of forming stable binuclear arene complexes (Figure 1).[28,40]

Once formed, pentaammineosmium(II) complexes of aromatic molecules are remarkably substitution-inert, resisting ligand displacement even by strong π acids (e.g., CO, electron-deficient olefins) and good σ donors (e.g., primary amines). Substitution half-lives for aromatic complexes of pentaammineosmium(II) are largely independent of the incoming ligand (Table 1), consistent with a dissociative substitution mechanism.[30] Table 2 provides representative half-lives for several complexes of aromatic ligands in acetonitrile.

B. Binding Selectivities

The ammine ligands of the $\{Os(NH_3)_5\}^{2+}$ system are powerful σ donors that are incapable of a significant π interaction with the filled d_π metal orbitals. Consequently, the metal center is highly reducing (e.g., $E°$ for $[Os(NH_3)_6]^{3+/2+}$ is −0.78 V vs NHE)[26] and shows a strong preference for π-acceptor ligands. Thus, even when the $\{Os(NH_3)_5\}^{2+}$ system (abbreviated herein as $[Os]^{2+}$) is presented with the unhindered amine aniline, the η^2-arene complex successfully competes with nitrogen coordination (*vide infra*).[33] In contrast, when the osmium(II) is able to bind

Table 1. Substitution Rate Data for the Benzene Complex of Pentaammineosmium(II) in Various Solvents



ligand (L)	[L] (M)	k (10^{-6} s^{-1})
acetone	1.0	5.8[a]
	neat	18[b]
acetonitrile	1.0	18[a]
	0.5	17[a]
	neat	35[b]
pyridine	1.0	12[a]
isonicotinamide	0.1	7.1[a]
acetophenone	neat	2.5[b]

[a] Value measured in DME with 10% DMAc added to enhance the solubility of osmium. [b] Value measured in pure solvent.

Table 2. Substitution Half-Life Data for Various η^2-Coordinated Aromatic Complexes of Pentaammineosmium(II) in Acetonitrile

$$[Os(NH_3)_5(L)]^{2+} \xrightarrow{\text{acetonitrile}} [Os(NH_3)_5(\text{acetonitrile})]^{2+} + L$$

ligand	$t_{1/2}$ (h)	T (°C)
TMB	0.5[a]	25
benzene	5.5	25
anisole	34	25
pyrrole	120	25
naphthalene	4	100
thiophene	1	100
furan	4	100

[a] Value measured in acetone-d_6.

nitrogen *and participate in a significant back-bonding interaction* (e.g., pyridine, imidazole, quinoline), η^2 coordination is not observed unless the nitrogen binding site is blocked by either steric crowding (e.g., 2,6-lutidine)[41] or electrophilic addition to the nitrogen lone pair (e.g., *N*-methylpyridinium ion).[42] Other organic π-acceptor ligands that form stable complexes with the pentaammineosmium(II) center and potentially compete with complexation of aromatic molecules include nitriles,[55] aldehydes and some ketones,[56,57] alkenes,[58,59] and alkynes.[60,61] Conversely, esters, amides, ethers, alcohols, water, and most amines (protonated) generally do not interfere with complexation.

As a general rule, the osmium will select a binding site *where it causes the minimum disruption to the* π *system* of the organic molecule. Jones et al.[22] have demonstrated this principle for the system Rh^I-Cp*PMe_3 as have Krüger et al. for $Ni^0(PR_3)_2$ (R = cyclohexyl).[17] Figure 2 further illustrates this point by showing a survey of pentaammineosmium(II) complexes as their dominant linkage isomers (favored by >20:1 in all cases). For arenes bearing a single substituent (C(1)), the metal preferentially binds at C(5) and C(6), allowing linear conjugation of the substituent and unbound portion of the aromatic ring.[30] This is true for *both* electron-rich (e.g., anisole, aniline, phenol) *and* electron-deficient (e.g., diphenylacetylene,[61] benzophenone[62]) arenes, although the effect is most pronounced in the former. Only in cases where steric factors disfavor the 5,6-η^2 isomer does the 4,5-η^2 isomer dominate.[30] For the anisole and aniline complexes, the 5,6-η^2 isomer is approximately 3−5 kcal/mol more stable than its 4,5-η^2 form based on a comparison between isomerization rate data for these substituted benzene complexes and their parent.[62] In contrast, the 4,5-η^2 isomer is electronically favored in pyridinium ions, even for the parent ion.[42]

For the complexes of the heterocycles pyrrole, furan, and thiophene, the 4,5-η^2 isomer is thermodynamically favored, as would be predicted on the basis of simple resonance structure arguments. However, in the case of pyrrole, the 3,4-η^2 isomer is also accessible. Given that the rate of 4,5-η^2 to 2,3-η^2 isomerization for the 2,5-dimethylpyrrole complex is similar to that for the benzene complex and that this rate is *substantially faster* than the corresponding process for the parent pyrrole complex, the 3,4-η^2 isomer is likely only 3−5 kcal/mol higher in energy than its 4,5-η^2 isomer.[49] In contrast to pyrrole, the thiophene and furan complexes of pentaammineosmium(II) appear completely static in ^{1}H NMR (300 MHz) spectra at 20 °C, which suggests that the 3,4-η^2 isomer is much less accessible for the chalcogen heterocycles.[50,52]

When a vinyl group is conjugated to an aromatic ring, coordination is thermodynamically favored outside the aromatic system. In contrast, when a pendant acetyl group is present, the thermodynamic isomer often involves coordination of the aromatic system. For polycyclic aromatic systems, the metal favors the coordination site that minimizes the loss of aromatic stabilization. Thus, naphthalene is preferentially bound at C(3) and C(4),[40] phenanthrene is bound at C(9) and C(10),[63] and 2-methylquinoline,[63]

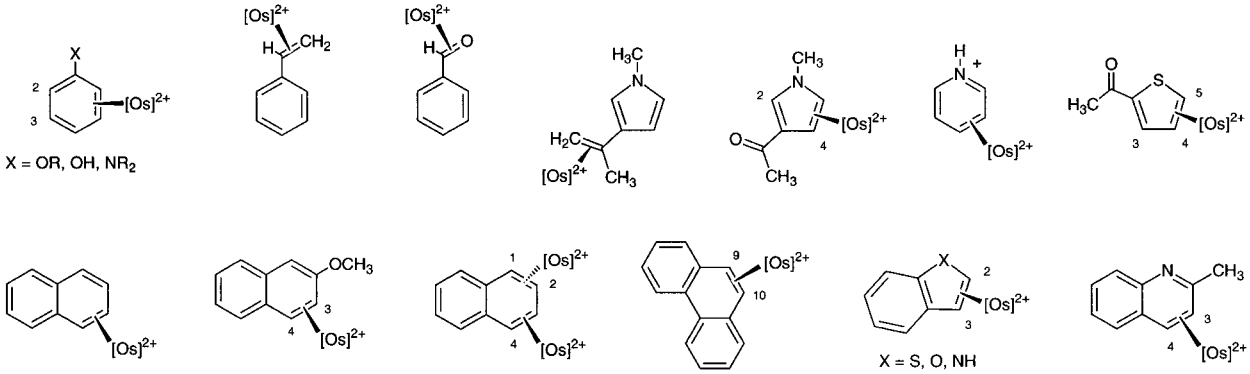


Figure 2. Pentaammineosmium(II) complexes of aromatic ligands showing the most stable linkage isomer. (In all cases, the species shown is favored by >3 kcal/mol over other possible linkage isomers.)

indole, benzofuran, and benzothiophene form complexes where osmium binds the heterocycle rather than the carbocycle (see Figure 2).[52,64] Finally, when two metals bind naphthalene,[40] the thermodynamically favored isomer has the osmium centers bound to a common ring. Although this arrangement requires bringing two cationic systems in close proximity, it minimizes disruption to the π system.

C. Linkage Isomerizations

In general, kinetic binding selectivity in the complexation procedure is relatively poor, but in most cases, osmium(II) has a strong thermodynamic preference for certain coordination sites in complex π systems (see Figure 2). The corresponding barriers for the metal intra- and inter-ring isomerization are relatively low compared to ligand displacement. Figure 3 summarizes a survey of *isoergic*[65] intramolecular linkage isomerization processes for aromatic systems with the corresponding specific rate data. In Figure 4, ^{1}H NMR data for the complex $[Os(NH_3)_5(\eta^2$-benzene$)]^{2+}$ illustrates the relatively low barrier to intra-ring linkage isomerization. Whereas the rate of migration for the metal is approximately 10^4 s^{-1} for the benzene complex at 20 °C, the rate drops to approximately 1 s^{-1} at 20 °C for the closely related anisole species and is now measured most conveniently by spin-saturation exchange (Figure 5). The slower rate for anisole is presumably a reflection of the difference in energy between the 5,6-η^2 and 4,5-

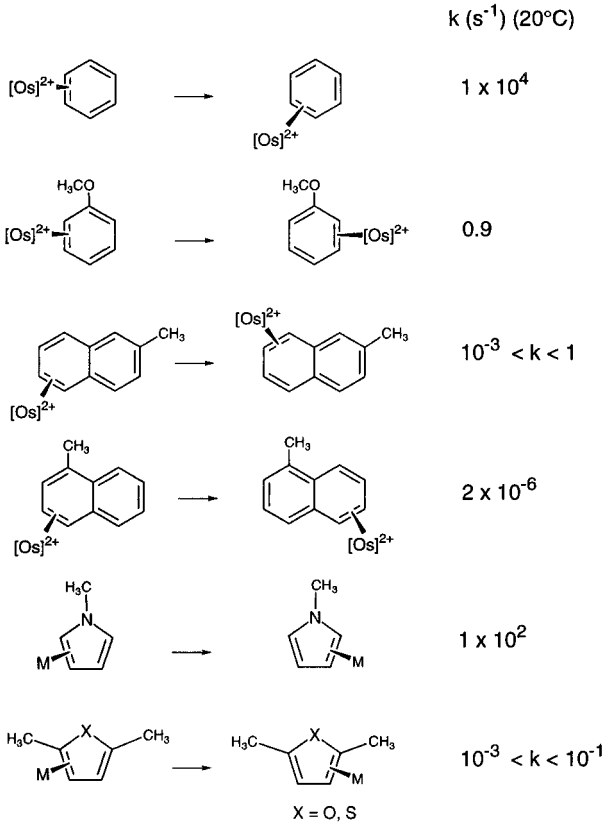


Figure 3. A survey of isoergic linkage isomerizations with corresponding specific rates (20 °C).

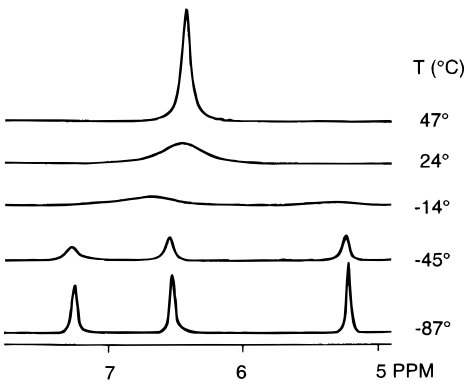


Figure 4. ^{1}H NMR spectra of $[Os(NH_3)_5(\eta^2$-benzene$)]^{2+}$ in acetone-d_6 with varying temperatures.

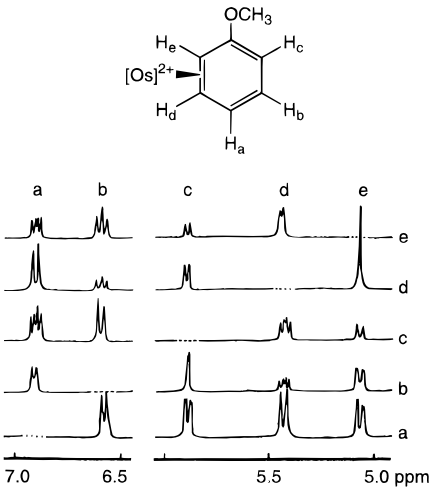


Figure 5. ^{1}H NMR spectra of $[Os(NH_3)_5(\eta^2$-anisole$)]^{2+}$ showing partial spin-saturation exchange at 20 °C.-

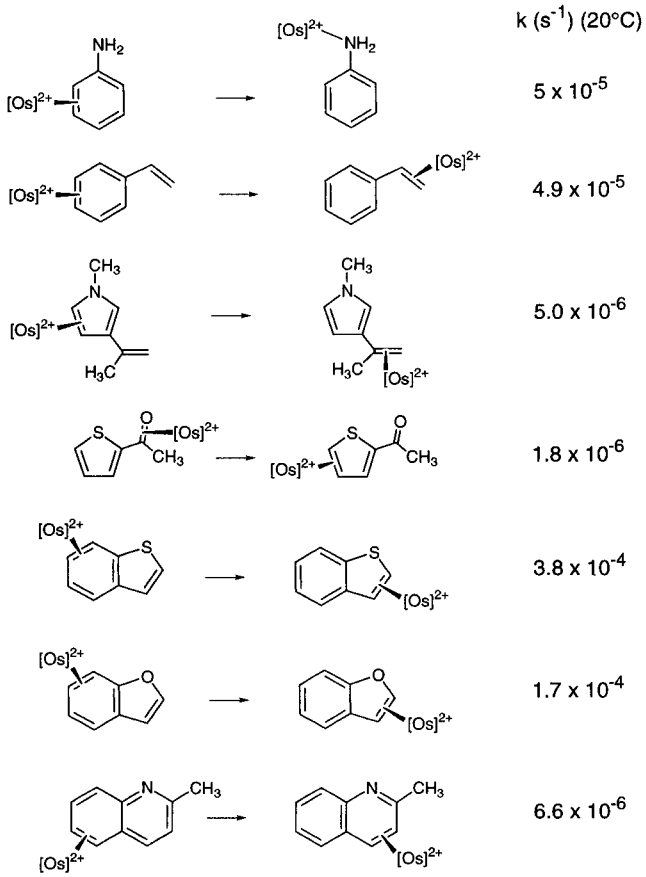


Figure 6. A survey of linkage isomerizations and associated specific rates (20 °C), illustrating the kinetic barrier to metal migration outside aromatic ring.

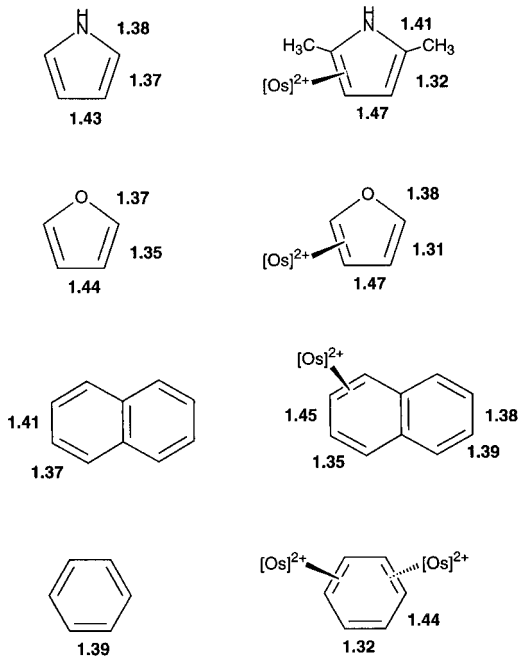


Figure 7. Summary of structural data (values in Å), illustrating a localization of π electron density in η^2-coordinated osmium(II) complexes of aromatic ligands.

η^2 isomers.[30] The corresponding intra-ring isomerization rate for naphthalene is also slower than that for benzene, an observation that again reflects the energy difference between inequivalent isomers (i.e., the 3,4-η^2 and 2,3-η^2 isomers for the naphthalene complex). For the heterocycles pyrrole, furan, and thiophene, the pyrrole complex is at least 10^3 times more fluxional at 20 °C than its congeners.[49,50,52]

When the metal must cross over into an adjacent aromatic ring, as is the case of the intra-ring isomerization of naphthalene, the isomerization rate is approximately $10^{-4}-10^{-6}$ s^{-1} at 20 °C.[63] Similar rates are observed when the metal moves from an aromatic system to a position outside the aromatic ring (Figure 6). These isomerization rates are sufficiently slow that it becomes feasible in some cases to carry out organic transformations on an aromatic system, even if a better binding site (e.g., olefin) is present in the molecule (*vide infra*).[45]

III. Measures of Dearomatization and Back-Bonding

A. X-ray Structure Determinations

Significant distortions in C−C bond lengths indicate a substantial degree of π-electron density localization in the η^2-coordinated aromatic complexes of pentaammineosmium(II), as illustrated in Figure 7. Although no structural data are available for the pentaammineosmium(II) benzene complex, the naphthalene analog has been recently characterized using X-ray diffraction.[63] Note in Figure 7 that complexation introduces distortion to the ring framework consistent with a localized double bond at C(1)−C(2) and single bond at C(2)−C(3). In contrast, the uncoordinated ring actually becomes *more aromatic* with all bond distances approaching 1.39 Å, as they are in free benzene. A crystal structure of the binuclear benzene species has been determined in which pentaammineosmium(II) fragments bind the arene from opposite faces. As expected, the uncoordinated carbons form a bond that has been significantly contracted (1.32 Å) compared to the corresponding value of free benzene. For the heterocycles 2,5-dimethylpyrrole and furan, complexation at C(4) and C(5) results in a lengthening of the C(3)−C(4) bond and a shortening of the C(2)−C(3) bond, perturbations that are again consistent with a substantial localization of electron density.

B. Electrochemistry

Pentaammineosmium(II) complexes readily undergo one-electron oxidation, and the corresponding (III/II) reduction potentials are highly sensitive to the nature of the sixth (organic) ligand (Figure 8); thus, cyclic voltammetry is an excellent diagnostic tool for pentaammineosmium(II) systems. Whereas the hexaammineosmium(II) species is a powerful reducing agent ($E_{1/2} = -0.78$ V, NHE), replacement of one of the ammonia ligands by an unsaturated ligand shifts the potential substantially positive. Moderate σ-bound π acids (e.g., pyridine and acetonitrile) shift the reduction potential positive by about 0.5 V, but

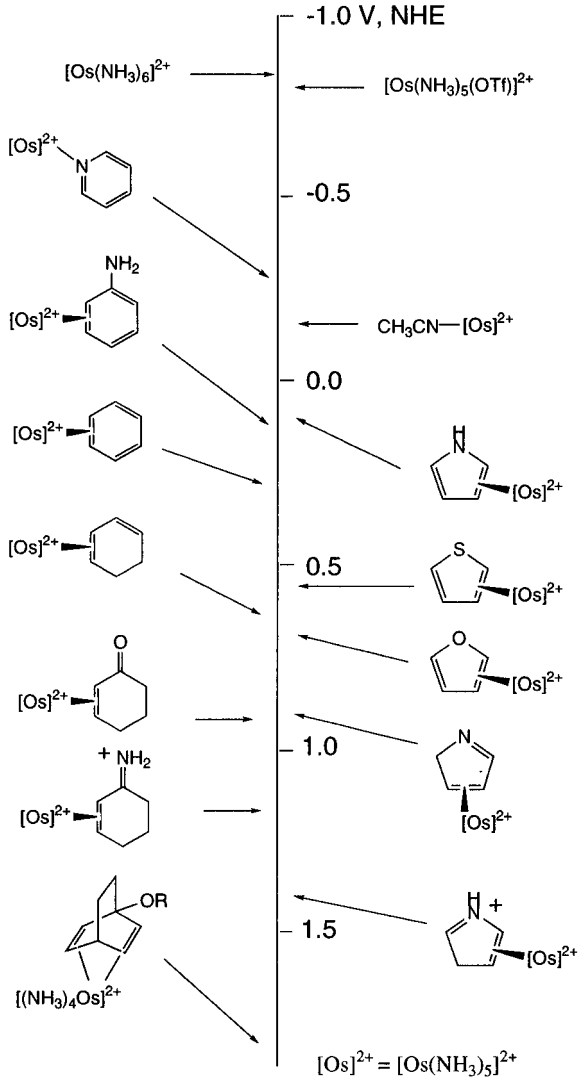


Figure 8. Osmium(III)/osmium(II) reduction potentials for various pentaammineosmium(II) and tetraammineosmium(II) complexes of unsaturated ligands.

for η^2-bound π acids, the potential can shift by as much as 2 V. In general, reduction potentials of arene and aromatic heterocycle complexes of pentaammineosmium(II) fall between 0.0 and 0.7 V, with the electron-rich ring systems (e.g., aniline and pyrrole) having the lowest reduction potentials. Olefin complexes tend to have the higher potentials, especially olefins conjugated to electron-withdrawing groups (e.g., cyclopentenone). Osmium(II) complexes of cationic π acceptors have reduction potentials even higher (1.0−1.5 V), approaching those of tetraammineosmium(II) bis-olefin complexes (see Figure 8).

C. Isomerizations

In several pentaammineosmium(II) systems, equilibrium data have been extracted that provide a quantitative measure of the energetics associated with dearomatization of an arene or aromatic heterocycle upon coordination to osmium(II). These systems are summarized in the sections that follow.

1. Arenes

A series of phenol complexes with varying substitution (phenol, methylphenols, and dimethylphenols) was prepared and spectroscopically characterized.[37] In all cases, the metal binds between C(5) and C(6), away from any alkyl substituents. When any of these complexes is dissolved in CD_3OD containing a catalytic amount of DOTf, an equilibrium is established between the phenol species (A) and their 4*H*- (B) and 2*H*-phenol (C) isomers (Figure 9). For the parent complex, the phenol isomer is thermodynamically favored over its 4*H*-phenol counterpart by a ratio of 5:1. In contrast, for the 2-methyl and 3-methylphenol derivatives, the 4*H*-phenol isomers are favored by a ratio of 3:1. With 3,4-dimethylphenol, a 1:1 ratio of the η^2-2*H*-phenol and phenol isomers is observed. The 2*H*- and 4*H*-phenol isomers are apparently stabilized by alkyl groups on the uncoordinated olefinic carbons. Protonation occurs exclusively from the *exo* face of the arene, and in no case is an isomer detected where a methyl group was forced into an *endo* orientation as a result of an *exo* protonation. Molecular models indicate that such a diastereomer would be highly sterically congested.

For the free organic system, the equilibrium between 2,5-cyclohexadien-1-one and phenol heavily favors the aromatic species. ΔH for the isomerization of phenol to its 4*H*-phenol isomer is estimated to be about 10 kcal/mol.[66] Assuming that $T\Delta S°$ has a relatively small contribution to $\Delta G°$ at 25 °C, $\Delta H°$ for the conversion of phenol to 4*H*-phenol on osmium(II) is about 1 kcal/mol. η^2 coordination reduces $\Delta H°$ of isomerization for phenol by approximately 9 kcal/mol (Figure 10).

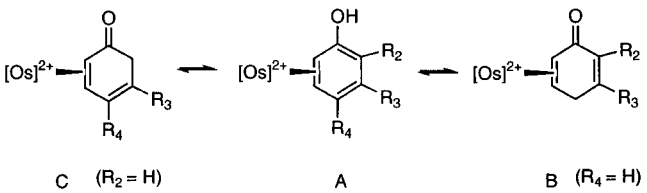


Figure 9. The phenol−dienone equilibrium on pentaammineosmium(II).

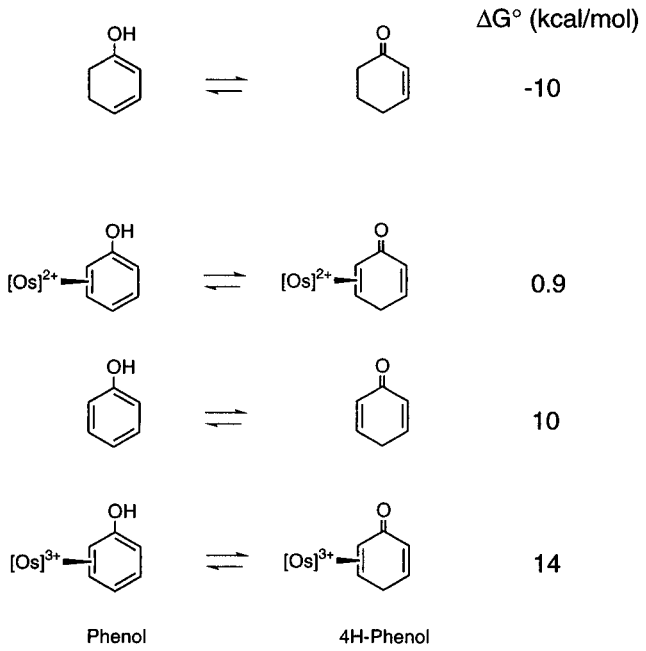


Figure 10. Free energy relationship for the enol−enone equilibrium of the η^2-phenol complexes of osmium(III), uncomplexed phenol, osmium(II), and 1,3-cyclohexadienol.

A useful model for the phenol complex is the compound 1,3-cyclohexadien-1-ol, in which C−H bonds have replaced the C−Os bonds (see Figure 10). From equilibrium constants, $\Delta G°$ for the enolization of 2-cyclohexen-1-one is calculated to be −10 kcal/mol at 25 °C. Thus, although complexation of osmium(II) to phenol dramatically alters the phenol−dienone equilibrium, the assumption that the osmium effectively *removes* the double bond to which it coordinates is too simplistic, and this error becomes even more apparent for osmium(III). Knowing the reduction potentials of the phenol and 4*H*-phenol complexes and the keto−enol equilibrium constant for osmium(II) enables the determination of the corresponding value for osmium(III). The phenol complex is about 14 kcal/mol more stable than its 4*H* isomer (25 °C), a value which indicates that the more electron-deficient osmium(III) is *completely ineffective in stabilizing the dienone isomer compared to the arene*. Thus, η^2 coordination does not necessarily favor the nonaromatic isomer of phenol as a ligand (see Figure 10). Rather, the increased π acidity of the dienone stabilizes the osmium(II) complex and *this strong π interaction* shifts the equilibrium away from the aromatic form upon coordination.[37]

In principle, the ring-bound isomer of the aniline complex could undergo an intramolecular proton transfer and generate a 4*H*-aniline (i.e., a cyclohexadienone imine) species, but no such osmium species has been detected. However, for acetanilide, a neutral 4*H* isomer has been generated from a sequence of alkylation (*vide infra*) and subsequent deprotonation at nitrogen.[36] Over time, however, this species yields to its thermodynamically preferred aromatic isomer. In contrast, anilinium and anisolium complexes of pentaammineosmium(II) (*vide infra*) exist solely as their dearomatized 2*H* or 4*H* isomers. Presumably the more electron-deficient nature of the C(1) substituent increases the π acidity of the 4*H*-arene isomer and stabilizes the electron-rich metal.

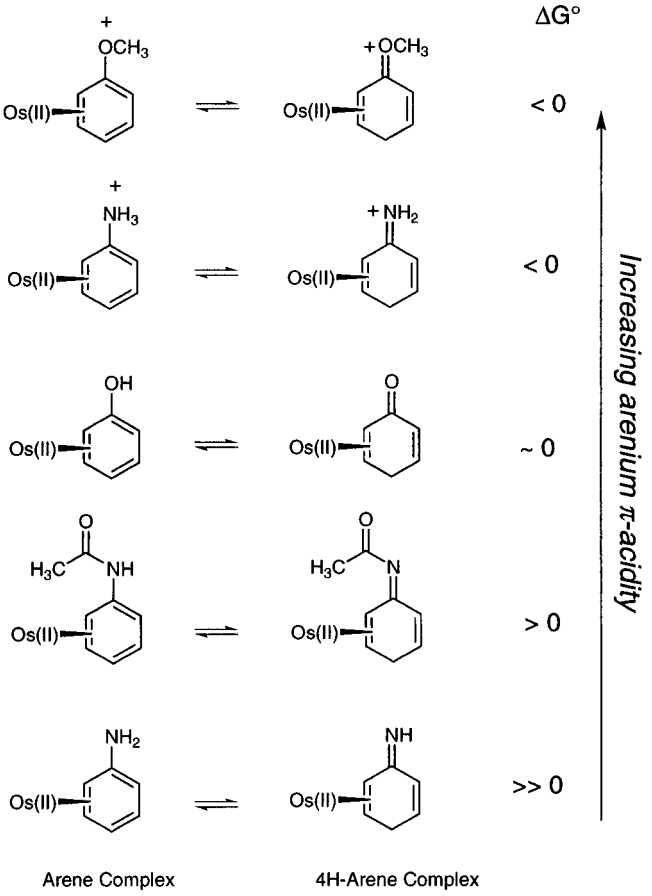


Figure 11. Comparison of thermodynamic relationships for various osmium(II)−arene/arenium complexes and their 4*H*-arene/arenium isomers.

Thus, the 4*H* isomers are increasingly favored over their aromatic forms (Figure 11).

2. Pyrroles

Another useful indicator of metal interaction with an aromatic system comes from isomerization data for η^2-pyrrole complexes[46,49] (Figure 12). By utilizing pK_a data (*vide infra*), the isomerization energy for the conversion of the 2,5-dimethyl-1*H*-pyrrole complex (A) to the corresponding 2*H*-pyrrole species (B) has been estimated as $\Delta G° = 0 \pm 1$ kcal/mol. Although the methyl group adjacent to metal coordination in the 1*H* isomer is certainly a factor in the unexpected stability of the 2*H* isomer, the latter isomer also has a significant steric interaction: The methyl substituent off the tetrahedral carbon for the 2*H*-isomer carbon is in an *endo* orientation, forcing it into the metal center. Consequently, the corresponding 1*H*/2*H* isomerization energy for the parent pyrrole complex is likely to be similar. In a protic solvent such as water, the 1*H*-pyrrole complex of the 2,5-dimethylpyrrole complex is in measurable equilibrium with its 3*H* isomer (C). Therefore, as indicated in Figure 12, the 1*H*-pyrrole, 2*H*-pyrrole, and 3*H*-pyrrole isomers are practically isoergic at 25 °C. By contrast, the corresponding 1*H*-pyrrole → 2*H*-pyrrole isomerization energy has not been experimentally determined, but INDO[67] and MINDO/3 calculations[68] put this value at 14 and 19 kcal/mol respectively. Thus, the highly π-basic osmium(II) metal center causes a dramatic shift in this equilibrium, effectively

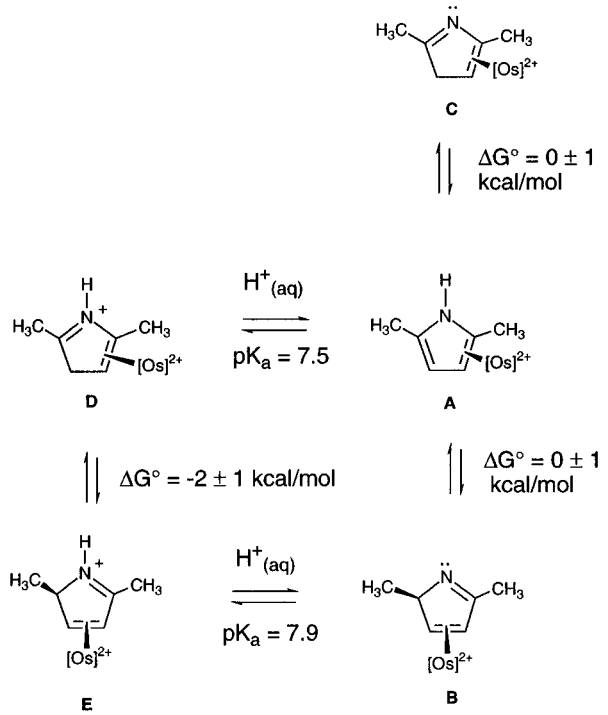


Figure 12. Thermodynamic relationships between a η^2-1*H*-pyrrole complex and its 2*H* and 3*H* isomers and their corresponding conjugate acids.

erasing three-fourths of the estimated 20 kcal of resonance stabilization in the 1*H*-pyrrole.[69]

D. Protonations

1. Arenes

In striking contrast to what is observed with the uncoordinated arenes, osmium complexes of anisole,[32] phenol,[70] and aniline[36] readily undergo protonation at the ring carbons. Provided that C(2) or C(4) is not substituted, all three complexes show a significant thermodynamic preference for *para* protonation (Figure 13). The resulting 4*H*-arenium complexes have the *uncoordinated* portion of the π system in conjugation. (Recall that the 4*H*-phenol complex of osmium(II), a neutral ligand, is thermodynamically more stable than its 2*H*-isomer.[37]) When C(4) is methylated (e.g., *N*,*N*-dimethyl-*p*-toluidine, *p*-methylanisole), the steric interaction between C(4) methyl and osmium that would result from an *exo* C(4) protonation destabilizes this process and C(2) protonation occurs exclusively. In contrast, 4*H*-anilinium complexes containing a 4-methine proton *syn* to the osmium, such as those generated from C(4) alkylation, are readily formed (*vide infra*). In fact, the latter complexes are *more stable kinetically* than the parent 4*H*-anilinium species in that the C(4)-substituent hinders deprotonation at C(4). A similar effect has been observed for C4-substituted 4*H*-phenol complexes of osmium(II).

Alternatively, when the heteroatom bears a substituent that interferes directly with the pentaammineosmium system, the metal may move to C(4) and C(5) and subsequently protonate at C(6). This has been observed in two situations to date. For anilines containing two substituents on nitrogen and none at C(4), (e.g., *N*,*N*-dimethylaniline and *N*,*N*-dimethyl-

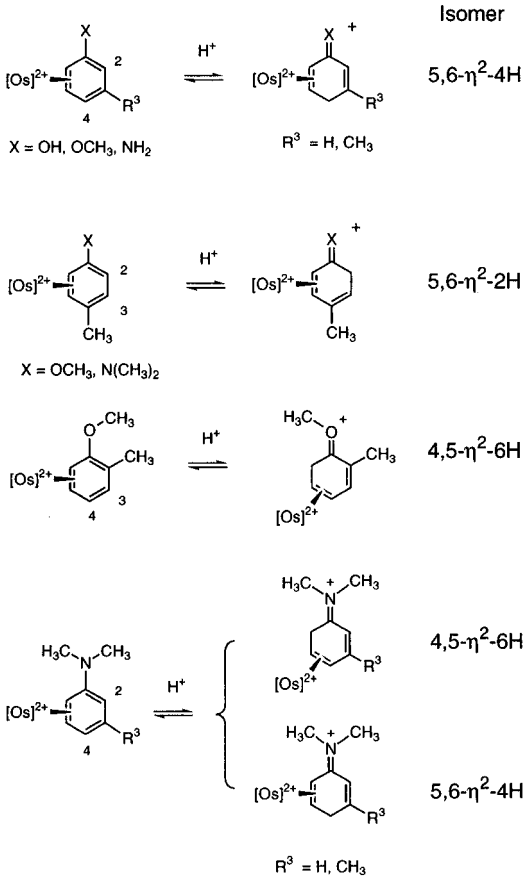


Figure 13. Protonation of assorted η^2-coordinated arene complexes of pentaammineosmium(II).

m-toluidine) the unusual 4,5-η^2-6*H*-aniline isomer competes with direct C(4) protonation. For anisoles bearing a C(2) substituent, the steric interaction between this group and the methoxy substituent forces the latter group to the metalated side of the arene, which induces a 5,6-η^2 to 4,5-η^2 isomerization, and consequently, protonation occurs at C(6). For the *N*,*N*-dimethylaniline complex, the *kinetically* favored protonation site has been determined to be the heteroatom,[36] which is expected to be the case for the anisole complex as well.

The pK_a (aq) of the 2*H*-anilinium complex derived from *N*,*N*-dimethyl-*p*-toluidine has been determined to be 5.5, an astonishingly high value considering that it reflects the direct protonation of an aromatic ring bound by a divalent transition metal. By combining this data with electrochemical data, an estimate of the acidity of the corresponding osmium(III) 5,6-η^2-4*H*-anilinium species has been determined with a p$K_a = -9.4 \pm 0.8$. Thus, for $[Os^{II}(NH_3)_5(4H\text{-anilinium})]^{3+}$ *the acidity increases 14 orders of magnitude as a result of a one-electron oxidation of the metal.* Although the increase in overall charge of the complex is expected to render the ligand more acidic, this dramatic increase in acidity upon oxidation indicates the degree to which the osmium(II) interacts with the π^* system of the conjugated iminium ligand. Thus, as with the phenol system discussed earlier, η^2 coordination is not primarily responsible for altering the reactivity of these aromatic ligands. Rather, the increased π acidity of the localized π system in the 4*H*-arenium system stabilizes the electron-rich osmium(II) complex, and this strong π interaction shifts the equilibrium away from the aromatic isomer.

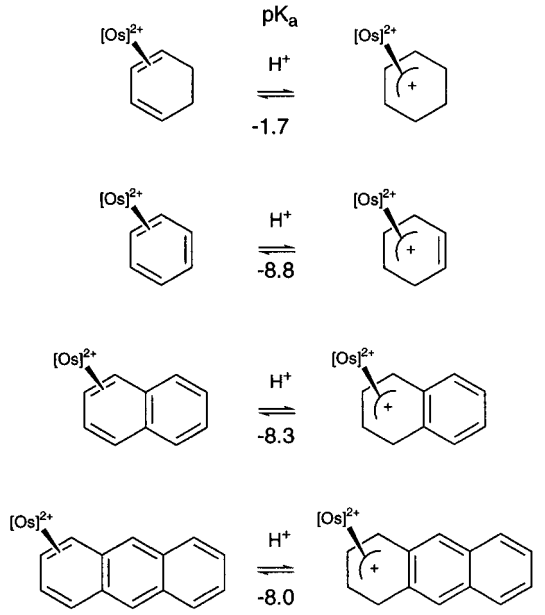


Figure 14. Protonation of several unactivated aromatic hydrocarbons η^2-coordinated to pentaammineosmium(II).

Even unactivated arenes may be protonated to form characterizable arenium complexes, provided that they are formed and maintained at −40 °C or below.[71] The benzene complex is protonated in acetonitrile solution to give an η^3-arenium species, a complex similar to the π-allyl species formed upon protonation of the corresponding cyclohexadiene complex. Similar results are obtained for naphthalene and anthracene, with protonation occurring at C(1) exclusively in either case.[63] Figure 14 presents pK_a values for protonated hydrocarbon complexes. Two important features to note are the greatly reduced acidities of the osmium complexes relative to the free ligands (the pK_a [aq] of the benzenium ion has been estimated as approximately −34),[72] and the relatively small difference between the acidities of the benzene, naphthalene, and anthracene complexes. Were there still large amounts of aromatic stabilization in the osmium complexed aromatic ligands, the acidities of these complexes should reflect this difference. The similarity in observed acidities of these arenium complexes is further evidence for the loss of aromaticity upon coordination by osmium(II).

The protonation of *m*-xylene deserves special comment.[71] In this example, the corresponding arenium remains η^2-coordinated. Apparently, the two methyl groups at terminal positions of the allyl fragment and the metal π back-bonding are sufficient to stabilize this system at temperatures as high as 0 °C (Figure 15). By equilibrating this species with triflic acid in

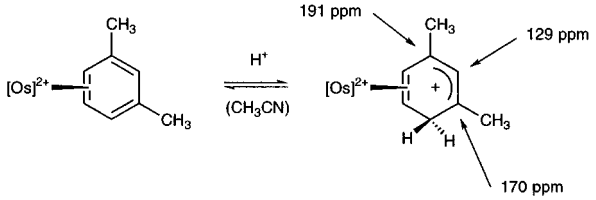


Figure 15. Formation and ^{13}C NMR data for an η^2-xylenium complex of pentaammineosmium(II).

acetonitrile, the pK_a for the *m*-xylenium system has been established to be −6.9 (−40 °C). This value has special significance among the benzenium systems in that it is the only value reported for an arenium system in which the coordination geometry is identical to that of its conjugate base.

2. Pyrroles

Complexes of pyrrole, *N*-methylpyrrole, and 2,5-dimethylpyrrole can be reversibly protonated at C(3) to form stable 3*H*-pyrrolium complexes.[49] In the case of the 2,5-dimethylpyrrole complex (see Figure 12), the 3*H*-pyrrolium species (D) converts to its 2*H*-pyrrolium isomer (E), in which the osmium now coordinates C(3) and (C4). This 2*H*-pyrrolium species, in turn, undergoes deprotonation reversibly at nitrogen to form the neutral 2*H*-pyrrole complex. Comparison of the pK_a values shown in Figure 12 with those reported for various enamines and pyrroles again demonstrates the extent to which the osmium modifies the pyrrolic ligand upon complexation. Thermodynamic protonation of simple enamines occurs at the β carbon,[73] analogous to the protonation of the osmium pyrrole complexes. Typically, the conjugate iminium ions have pK_a values ranging from 9 to 12. For comparison, the iminium ion derived from 2,3-dihydro-1,3,4-trimethylpyrrole has a reported pK_a of 9.6,[73] a value similar to that of the 2,5-dimethylpyrrolium complex, where pK_a = 7.5. As the extent of alkylation is decreased, the pK_a for the pyrrolium complexes decreases and the parent species $[Os(NH_3)_5(3H\text{-pyrrolium})]^{3+}$ exhibits a pK_a of just over 4 (Figure 16). In contrast, the uncoordinated 3*H*-pyrrolium ion is more than 10^{10} more acidic

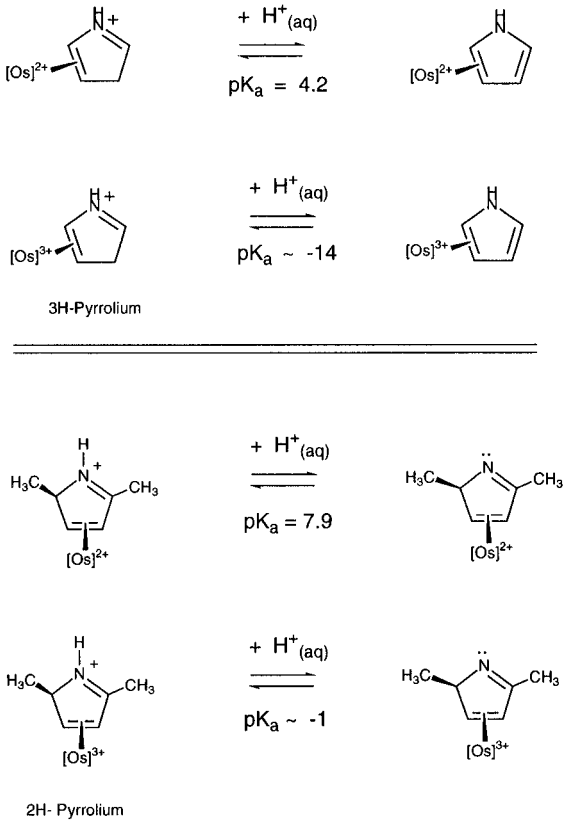


Figure 16. pK_a data for 1*H*- and 2*H*-pyrrole complexes of osmium(II) and osmium(III).

(pK_a approximately −5.9).[74] An approximation for the acidity of the osmium(III)−3*H*-pyrrolium species has been obtained[49] by combining electrochemical data with the acid dissociation equilibrium for the parent pyrrole complex (see Figure 16). A pK_a = −14 represents *an increase in acidity of close to 18 orders of magnitude*. Presumably, the energy associated with rearomatization dominates for the higher oxidation state where the interaction of the metal with the heterocycle π system is poor. A comparison of acidities between the osmium(III) and osmium(II) complexes of the *nonaromatic* 2*H*-pyrrolium species shows an increase of only 9 pK_a units upon oxidation from osmium(II) to osmium(III) (see Figure 16).

E. Other Chemical Measures of Back-Bonding

Although not central to the theme of this review, several other equilibrium measurements have been determined that further illustrate the degree to which pentaammineosmium(II) acts as a π base. Two of the most striking examples are found in the pentaammineosmium(II) complexes of pyrazine and SO_2.[75] Free pyrazine has a pK_b of 13.6, but coordination by osmium(II) lowers the pK_b to 6.6, indicating that pyrazine becomes 7 orders of magnitude *more* basic as a result of π back-bonding. In contrast, the pentaammineruthenium(II) complex of pyrazine has a pK_b of 11.5,[76] not far from the free ligand value. For the complex $[Os(NH_3)_5(SO_2)]^{2+}$, the acidity of the bound SO_2 was found by Sen to be reduced by approximately 5 orders of magnitude relative to the free ligand (evaluated with respect to its conversion to SO_3^- in water).[75] For the ruthenium(II) analog, the effect is similar but not as dramatic,[77] and ruthenium(III) coordination was found to increase the acidity of the SO_2 ligand.[78]

As is common with other metal systems, allyl ethers and 1,3-diene complexes of pentaammineosmium(II) react with acid to form stable π-allyl species (Figure 17). In the case of cyclohexadiene, the corresponding allyl complex has a pK_a of about −2, close to that of $CH_3OH_2^+$. Given that protonation is accompanied by a change in coordination geometry, this data is not as meaningful as some of the pK_a data described earlier, but it does give a sense of the electron-donating ability of the metal. An equilibrium constant has been established for the elimination of methanol from an allyl ether complex to give a diene complex. In striking contrast to what is observed for the organic reaction, the diene and methanol was shown to be favored by a factor of 10^{15} compared to the allyl ether. The strong preference

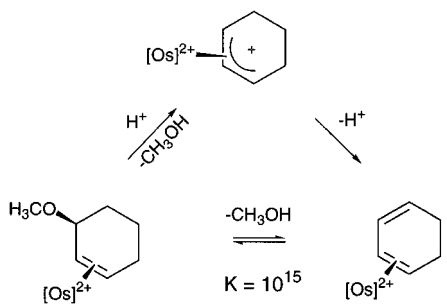


Figure 17. The elimination of methanol from the 3-methoxycyclohexene complex of pentaammineosmium(II).

of the system at equilibrium for the diene is a manifestation of the affinity that the osmium(II) system has for extended π systems.

IV. Organic Reactions of Arene and Arenium Complexes

A. Electrophilic Addition Reactions to Arenes

Most osmium complexes of phenols,[39] anilines,[36] acetanilides,[36] and anisoles[32] undergo electrophilic addition with a high regiochemical preference for C(4) addition. While electrophilic addition to phenol complexes are typically carried out in the presence of a mild base catalyst (e.g., a tertiary amine) or in absence of any catalyst, the other three classes generally require a mild Lewis or Brønsted acid to promote the reaction. The primary advantage of the less activated arenes is that the 4*H*-arenium species resulting from electrophilic addition is more reactive toward nucleophilic additions (*vide infra*).

1. Phenols

When an acetonitrile solution of the phenol complex is treated with 1.0 equiv of both methyl vinyl ketone and pyridine (Figure 18), a 4-alkylated 4*H*-phenol complex (A) is obtained that, based on NOE data, is a product of conjugate addition to the face of the phenol ring opposite that of metal coordination. This complex is stable in solution and shows no signs of decomposition even after standing in acidic CH_3CN solution for 24 h. However, exposure to a moderate base (e.g., Hünig's base) induces rearomatization, yielding the 4-(2-oxobutyl)phenol complex (B). Curiously, even hindered bases of sufficient strength are sucessful in removing H4, and this observation suggests that deprotonation of a *cis* ammonia ligand might be integral to the isomerization mechanism. Heating this complex releases the raspberry ketone product (C) in good yield.[39] An intriguing aspect of this reaction sequence is that in contrast to the 4*H*-phenol complexes generated from isomerization of the phenol ligands (see Figure 9), the dienone complex

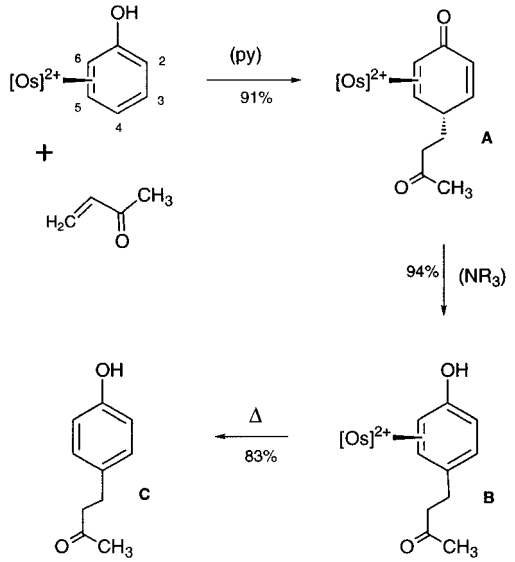


Figure 18. The osmium(II)-promoted *para* alkylation of phenol with MVK.

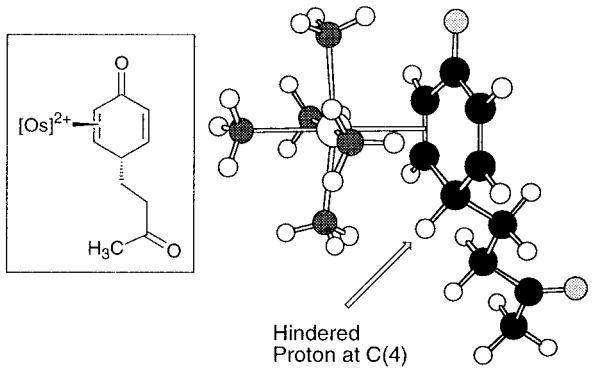


Figure 19. Model of the kinetically stable 4*H*-phenol complex resulting from conjugate addition of MVK and the η^2-phenol complex.

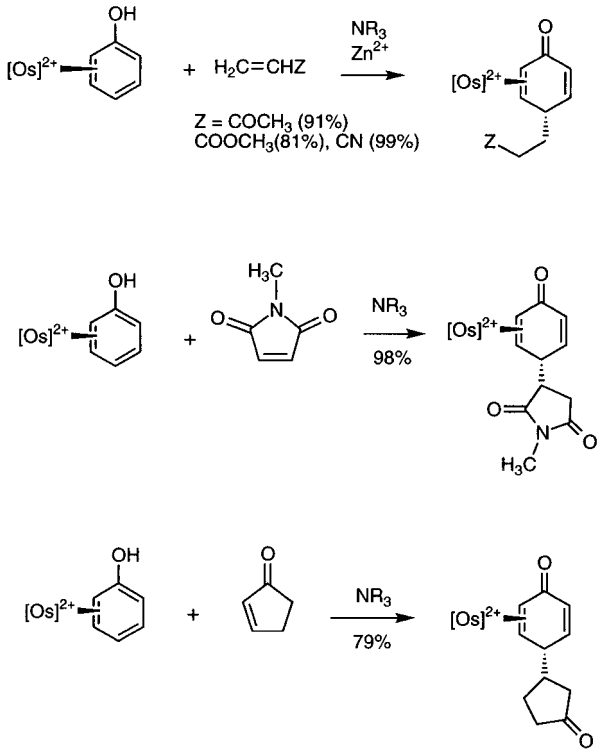


Figure 20. Conjugate addition reactions with the η^2-phenol complex and various Michael acceptors.

(A; see Figure 18) resists isomerization to the arene in acidic solution. This stability is a direct result of the C(4) substituent that limits access of the acidic (C4) proton to potential bases (Figure 19),[39] a feature that is operative in many other pentaammineosmium systems of aromatic ligands as well.

The η^2-phenol complex undergoes conjugate addition at C(4) with a variety of Michael acceptors (Figure 20), including those with β substituents.[39] In most cases, the addition reaction is most conveniently carried out with an amine base as catalyst. Less reactive electrophiles, such as methyl acrylate or acrylonitrile, fail to undergo conjugate addition with the phenol complex in the presence of base alone. However, in the presence of a Lewis acid cocatalyst, conjugate addition may be accomplished in good yield. An excellent example of the versatility of this reaction is shown in Figure 21, showing the aromatic steroid β-estradiol complexed and subsequently alkylated at C(10) (i.e., *para*) exclusively at −40 °C. Since the osmium preferentially binds the α face of

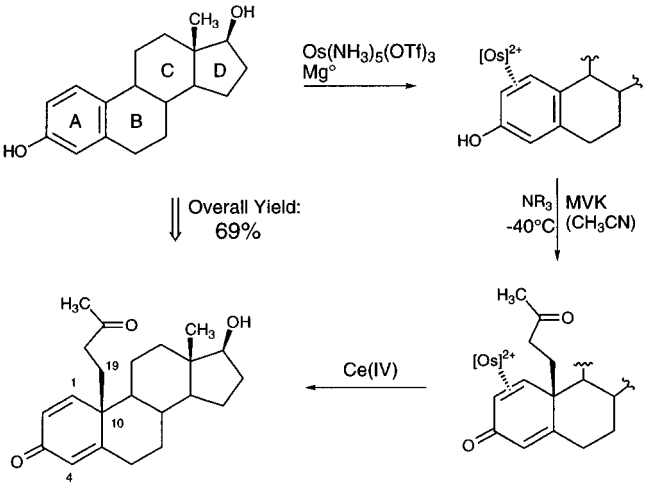


Figure 21. The C(10) alkylation of β-estradiol using osmium(II) to dearomatize the A ring.

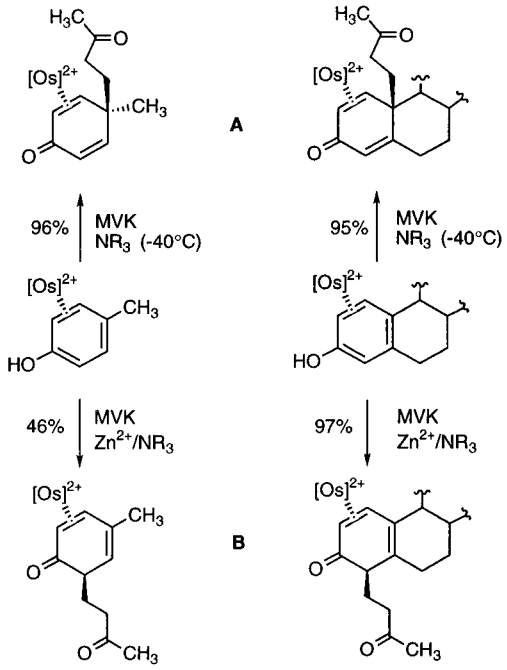


Figure 22. Regiocontrol of the electrophilic addition reaction of MVK and phenol.

the steroid, conjugate addition occurs from the β face, providing the natural stereochemistry of testosterones.[38] The overall yield of this transformation *after* decomplexation of the dienone product is approximately 70%.

Although C(4) addition occurs with phenol complexes even for cases in which C(4) is substituted, in many cases, *ortho* addition is *thermodynamically* favored provided that the electrophile is not too sterically encumbered. In this scenario, the regiochemistry can be effectively controlled by adjusting reaction variables such as temperature, time, and catalyst.[39] Under basic conditions, the active form of the phenol complex is the phenoxide species, which can undergo reversible Michael reactions at C(4) and C(2) *provided that the resulting enolate is not protonated*. Consider, for example, the addition of MVK to the osmium complexes of *p*-cresol and estradiol (Figure 22). At −40 °C in the presence of *either* an amine base or acid alone, the Michael acceptor adds to C(4) of the phenol system, and the resulting

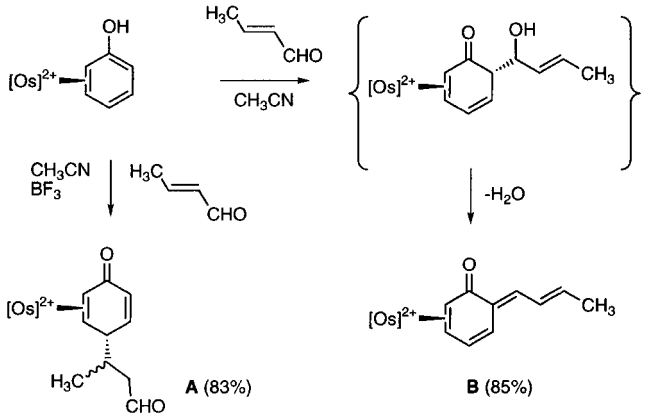


Figure 23. The formation of an η^2-*o*-quinone methide complex from an aldol condensation of crotonaldehyde and the η^2-phenol complex.

enolate is protonated to give the kinetically favored 4*H*-phenol product (A). However, if the reaction is carried out at 20 °C or is run in the presence of a Zn^{2+} cocatalyst *in absence of any Brønsted acid source*, the initial C(4) Michael product may undergo retroaddition, which can eventually lead to the orthoalkylated product (B; see Figure 22). Electrophilic addition at the *ortho* position of η^2-arene complexes has been observed primarily in phenol complexes to date, although one example with 2-methylanisole has been reported.[79] In general, for anisole and N-substituted anilines,[36] the heteroatom substituent is oriented away from metal coordination (5,6-η^2) and, as a consequence, it blocks the uncoordinated *ortho* carbon (C(2)) from undergoing reaction with most electrophiles.

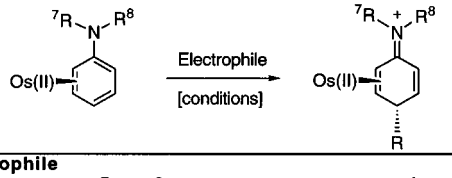
Another interesting example of *ortho* addition to phenol appears in the reaction of crotonaldehyde with the *p*-cresol complex (Figure 23). In the presence of a Lewis acid, a Michael addition occurs cleanly at the *para* position to give the dienone complex (A). However, in the absence of either an acid or base catalyst, an aldol condensation occurs at C(2) to generate an *o*-quinone methide (B). This reaction appears to be general for aldehydes and η^2-phenol complexes, even when the phenol is not substituted at C(4). Interestingly, attempts to form a *p*-quinone methide complex using this approach with a C(2)-substituted phenol were unsuccessful.[70]

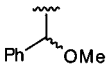
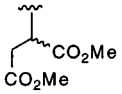
2. Anilines

Because deprotonation of the heteroatom with a moderate base is not facile for anilines and is impossible for anisoles, the electrophilic addition reactions for osmium(II) complexes of these ligands must be activated by Lewis acids. The additives $BF_3{\cdot}OEt_2$, $Sn(OTf)_2$, and TBSOTf among others are tolerated by the metal and may be used to catalyze a variety of electrophilic addition reactions with η^2-anilines. Examples are reported for Michael acceptors and acetals, as well as acylating agents. Several of these reactions are summarized in Table 3. Note that in some cases, the preferred reaction conditions involve *water* as a solvent.

For the parent aniline complex, a complication arises in that the nitrogen-bound isomer is thermodynamically competitive with the ring-bound isomer.

Table 3. Electrophilic Addition Reactions of η^2-Aniline Complexes



Electrophile (Rxn Cond.)[a]	R^7	R^8	R	isomers[b]	Yield(%)[c]
acrolein (**D**)	H	Et	$-CH_2CH_2CHO$	-	81
methyl acrylate (**B**)	H	Et	$-CH_2CH_2CO_2Me$	-	86
acrylonitrile (**A**)	H	Et	$-CH_2CH_2CN$	-	95
2-cyclopenten-1-one (**A, B,C**)	H	Et		4:1 (**C**)	77 (**C**)
benzaldehyde dimethylacetal[a] (**A**)	H	Et		1:1	53
2,2-dimethoxy-propane (**A**)	H	Et	$-C(CH_3)_2OMe$	-	82
2-cyclohexen-1-one (**A**)	Me	Me		6:1	80
dimethyl fumarate (**A**)	Me	Me		2:1	63

[a] Conditions: (**A**) (1) TBSOTf, CH_3CN, 20 °C; (2) H_2O. (**B**) Same as **A**, but at −40 °C. (**C**) (1) HOTf (1 equiv), (2) CH_3OH, 20 °C. (**D**) Same as **C**, but using water as the solvent. [b] Isomer ratio for the steriogenic center located in R. This ratio is based on the relative heights of ^{13}C NMR resonances and is thus approximate. [c] Unoptimized yields.

To overcome this obstacle, the nitrogen is first protected with a TBS group, then complexed. Upon deprotection, this material (A) cleanly gives the 4*H*-anilinium species (B) shown in Figure 24. This compound resists rearomatization and is prepared free of any nitrogen-bound species. Finally, the 4*H*-anilinium species may be treated with a carbon electrophile to afford 4-alkylated 4*H*-anilinium species (C−E) in good yield.

A particularly interesting reaction is found for the acetanilide complex of osmium(II) (A; Figure 25). Even with the poor electron donor properties of an amide, electrophilic addition of MVK may be accomplished at C(4) with excellent regiocontrol.[36] Unlike the 4*H*-anilinium systems, the 4*H*-acetanilidium complex (B) is not stable at 20 °C, but this species may be deprotonated at nitrogen to give a stable 4*H*-acetanilide complex (C). Over time, this species spontaneously reverts to its aromatic isomer (D).

3. Anisoles

In contrast to the aniline systems, the anisole complex undergoes decomposition in the presence of acid at 20 °C, yielding unidentified osmium(III) salts and approximately 0.5 equiv of both anisole and benzene. However, at −40 °C the 4*H*-anisolium species are stable. Thus, reactions of the anisole

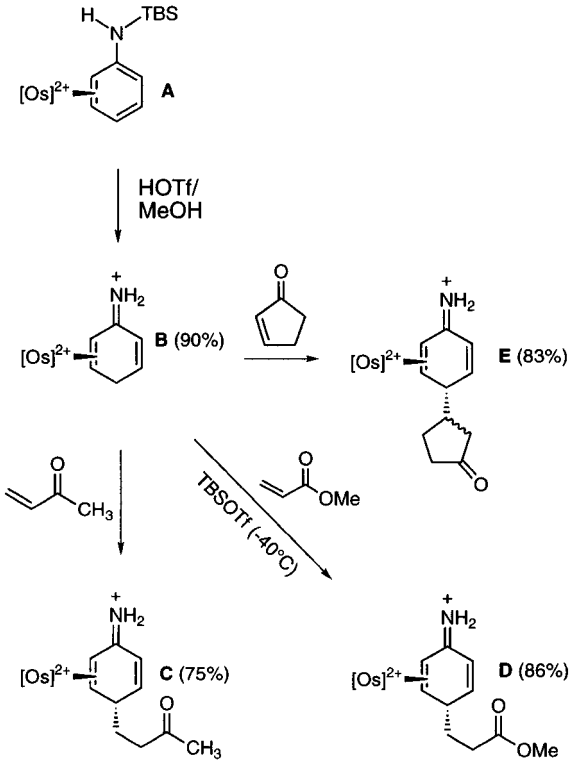


Figure 24. Alkylations of aniline using a silicon protecting group to prevent nitrogen complexation.

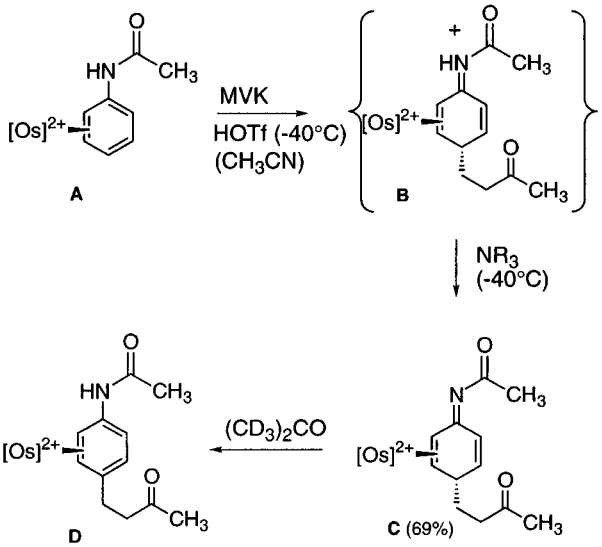
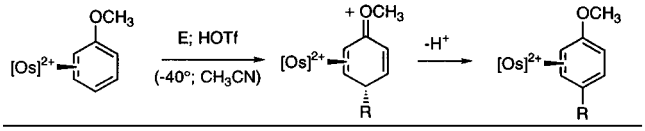


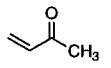
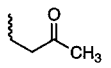
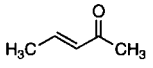
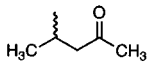
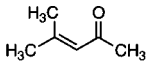
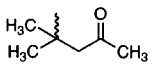
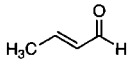
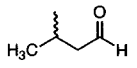
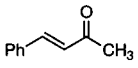
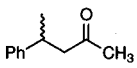
Figure 25. Alkylation of acetanilide complex of osmium(II) and the formation of a 4*H*-acetanilide species.

complex with carbon electrophiles are carried out in the presence of a Lewis or Brønsted acid at low temperature.[79] Table 4 summarizes an assortment of reactions in which the anisole complex has been alkylated and then deprotonated to give the corresponding 4-substituted anisole complex. Suitable electrophiles for this reaction include Michael acceptors, acetals, orthoesters, and nitrilium salts. As with other aromatic systems, the organic ligand is obtained in excellent yield simply by heating a solution of the complex in acetonitrile or by exposing a solution to a one-electron oxidant (e.g., Ag^+, DDQ, Ce(IV)).

Several deviations to the general reactivity pattern of anisoles arise when substituents are present in the

Table 4. Electrophilic Addition Reactions with η^2-Anisole Complex



E	R	Yield(%)[a]
		95
		87(81% de)
		> 90[b]
		95 (> 90% de)
		> 90(>90% de)[b]
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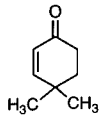
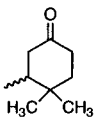
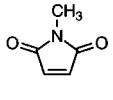
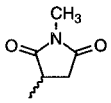
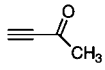
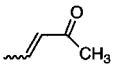
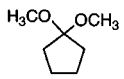
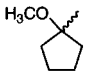
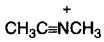
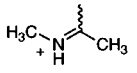
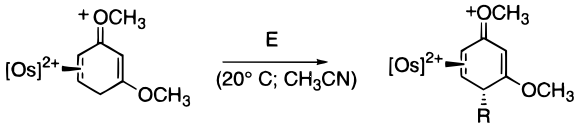
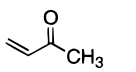
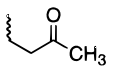
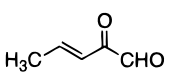
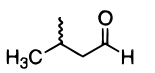
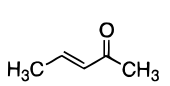
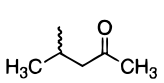
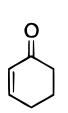
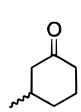
		91(90%de)
		80(>90%de)
		98
		88
$CH(OEt)_3$	CHO	86
		88

[a] Represents isolated yield. [b] Represents yield in solution (NMF).

Table 5. Conjugate Addition Reactions of 3-Methoxyaniline Complex



E	R	Yield(%)[a]
		94
		89 (60%de)
		89 (60%de)
		92 (33%de)

[a] Represents isolated yield.

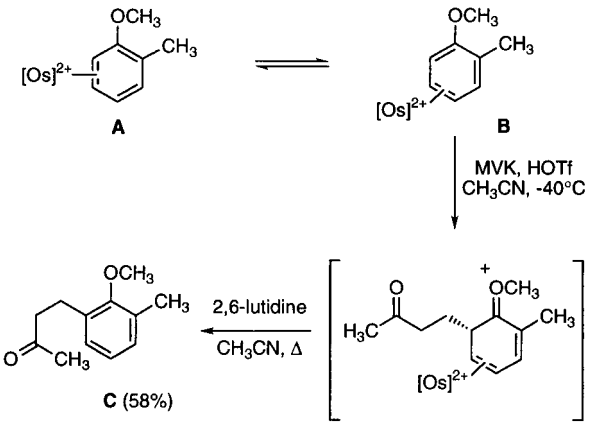


Figure 26. Coordination and the C(6)-selective alkylation of 2-methylanisole.

anisole ring. A substituent at C(3) is in conjugation with the oxonium system resulting from conjugate addition at C(4) and a donor group at this carbon greatly facilitates electrophilic addition (Table 5), and stabilizes the resulting 4*H*-anisolium species to the point that the corresponding osmium salt may be isolated.[79] A methyl substituent at C(2) has the opposite effect (A; Figure 26). In this case, the methyl group interferes with the methoxy group lying in the arene plane. Not only does this retard electrophilic addition at the ring but it also forces the metal to the less congested 4,5-η^2 position (B), where the only reasonable site left for electrophilic addition is C(6). Thus, 2,6-disubstituted anisoles may be prepared (e.g., C). In some but not all cases, a methyl group at C(4) will redirect alkylation to C(2). Two contrasting examples are shown in Figure 27 for the *p*-methylanisole complex. Note that in the case of MVK, electrophilic addition still occurs at C(4) and the resulting anisolium species may be hydrolyzed to the corresponding 2,5-cyclohexadienone.

4. Unactivated Hydrocarbons

Currently unfolding in our laboratories is the chemistry of unactivated aromatic hydrocarbons. Although this study, at present, is not complete, we have established that, as in the case of protonation, carbon electrophiles may be added to the ring to generate characterizable η^3-arenium complexes (Figure 28). Although these compounds are stable only below −30 °C and are highly acidic, they are stable enough to allow reaction with nucleophiles, as is discussed in the next section. In the case of both naphthalene and anthracene, electrophilic addition occurs exclusively at C(1). Note that this is in contrast to the chemistry normally observed for anthracene especially, where addition at C(9) is most common.

B. Intermolecular Nucleophilic Additions of 4*H*-Arenium Complexes

Perhaps the greatest synthetic potential of this *dearomatization* methodology lies in the ability of the

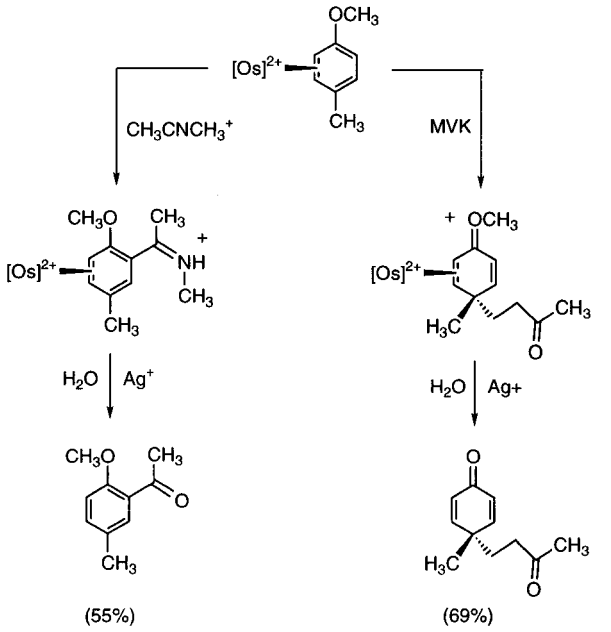


Figure 27. Differing regiochemistry in the reaction of the 4-methylanisole complexes with carbon electrophiles.

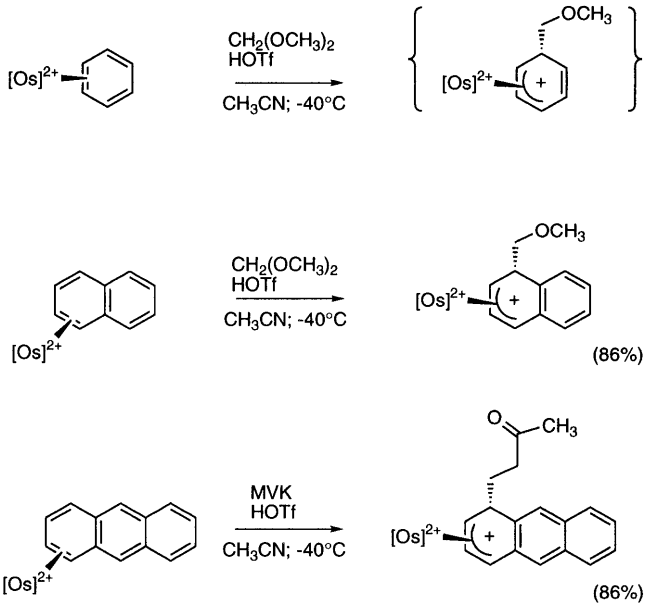


Figure 28. Assorted alkylations of cyclic aromatic hydrocarbon complexes and the formation of η^3-arenium intermediates.

metal to stabilize, through metal-to-ligand back-bonding, the dienone, anilinium, and anisolium intermediates derived from phenol, aniline, and anisole, respectively. This stabilization sets the stage for subsequent nucleophilic addition to the *meta* position, thereby preventing rearomatization of the ring upon decomplexation of the metal.

The strong back-bonding interaction of the pentaammineosmium(II) system with the 2,5-cyclohexadienone ligands formed from phenols significantly reduces the susceptibility of these ligands to nucleophilic attack. Thus, complexes of 4*H*-phenol (i.e., 2,5-cyclohexadienone), shown in Figure 20, fail to undergo reaction with sodium borohydride at 20 °C at any of the ring carbons,[70] nor do they react with nonbasic carbon nucleophiles, such as silyl enol ethers or silyl ketene acetals. Under basic conditions,

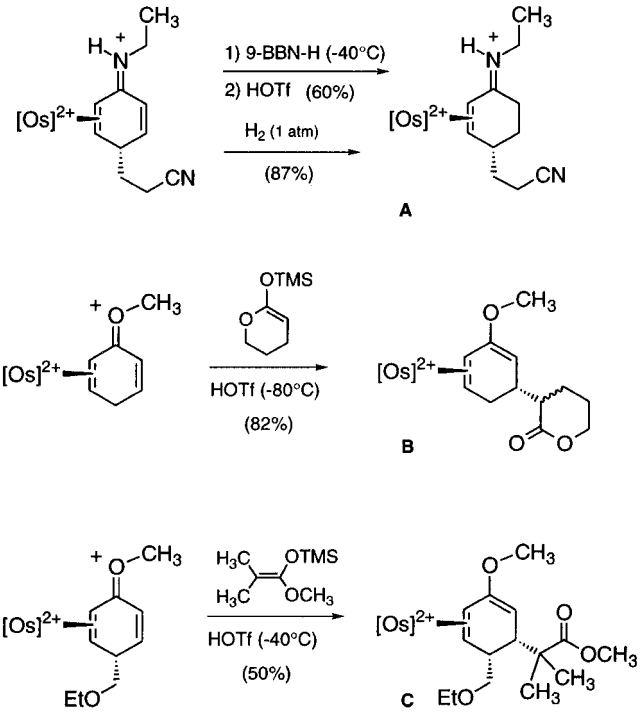


Figure 29. C(3) nucleophilic addition to 4*H*-anisolium and 4*H*-anilinium complexes.

retro-Michael addition or deprotonation at C(4) occurs to return the aromatic precursors or electrophilic substitution products, respectively.[70] By contrast, 4*H*-anilinium complexes, such as those shown in Table 3, are readily reduced by borohydride reagents (e.g., Bu_4NBH_3CN), but difficulties often arise in stopping the reduction at the dienamine stage. By using Li(9-BBNH) at low temperature (−40 °C), the eneiminium species (A) may be isolated in good yield (Figure 29).[36] Unfortunately, like their phenol-based counterparts, the η^2-4*H*-aniliniums also resist reaction with mild carbon nucleophiles such as silyl ketene acetals and enol ethers, and attempts to carry out intra- or intermolecular addition of basic carbon nucleophiles (e.g., enolates) also usually result in retroaddition of the electrophile or deprotonation at C(4).[36]

Although the 4*H*-anisolium complexes derived from anisole are more difficult to form, a wealth of reactivity for these systems has been uncovered leading to complex alicyclics (*vide infra*). In contrast to the 4*H*-phenol and 4*H*-anilinium systems, 4*H*-anisolium complexes readily undergo reaction at C(3) with mild carbon nucleophiles, and numerous examples of both intra- and intermolecular addition have been observed. In all cases observed to date, addition occurs *anti* to the metal (B and C; see Figure 29). Like their nitrogen analogs, 4*H*-anisolium complexes (A; Figure 30) readily react with mild hydride sources, but stopping the reduction at the methoxydiene stage (i.e., B) is often problematic, as any excess of acid produces an oxonium species (C) that is readily reduced. However, a valuable class of materials may be obtained from the stereospecific reduction of 4*H*-anisoliums to allyl ethers (D; see Figure 30). Treatment of these materials with acid causes the elimination of alcohol, and the resulting π-allyl species (E) are useful intermediates in the stereospecific formation of 3,6-disubstituted cyclohexenes (F) containing

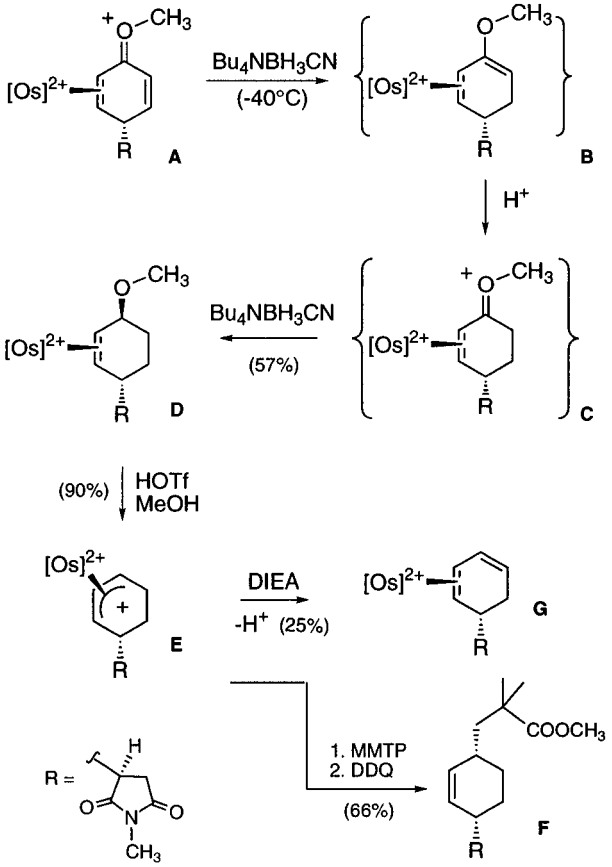


Figure 30. Reduction of 4*H*-anisolium ligand to cyclohexadiene and the subsequent protonation to form a pentaammineosmium π-allyl species.

up to three new stereogenic centers. Alternatively, deprotonation can result in a cyclohexadiene species (G; see Figure 30).

C. Cyclization Reactions

1. [4+2] Cycloadditions

In the presence of $BF_3{\cdot}OEt_2$, anisole complexes undergo Michael addition at C(4) to generate an oxonium−boron−enolate (Figure 31). When the Michael acceptor is *N*-methylmaleimide (A), this intermediate either protonates to give a 4*H*-anisolium species (B) or undergoes ring closure at C(1) to provide what is formally a cycloaddition product of the arene and olefin (C).[32] Given that the organic ligand can be removed from the metal by a one-electron oxidant, such a reaction constitutes a potentially valuable synthetic approach to highly functionalized bicyclo[2.2.2]octadienes (e.g., D). If the pentaammineosmium(II) cycloaddition product is allowed to stand in solution, loss of ammonia occurs to generate the η^4-coordinated tetraammineosmium analog (E; see Figure 31).

When the anisole ligand is substituted at C(4), Michael addition still occurs *para* to the methoxy group provided that the electrophile is sterically unhindered. When 3-butyn-2-one is used as the Michael acceptor and care is taken to eliminate all proton sources, the initially formed boron enolate (F) closes to form an η^2-barrelene complex (G; see Figure 31), which eliminates ammonia to give the tetraammine analog (H). Alternatively, in the presence of a

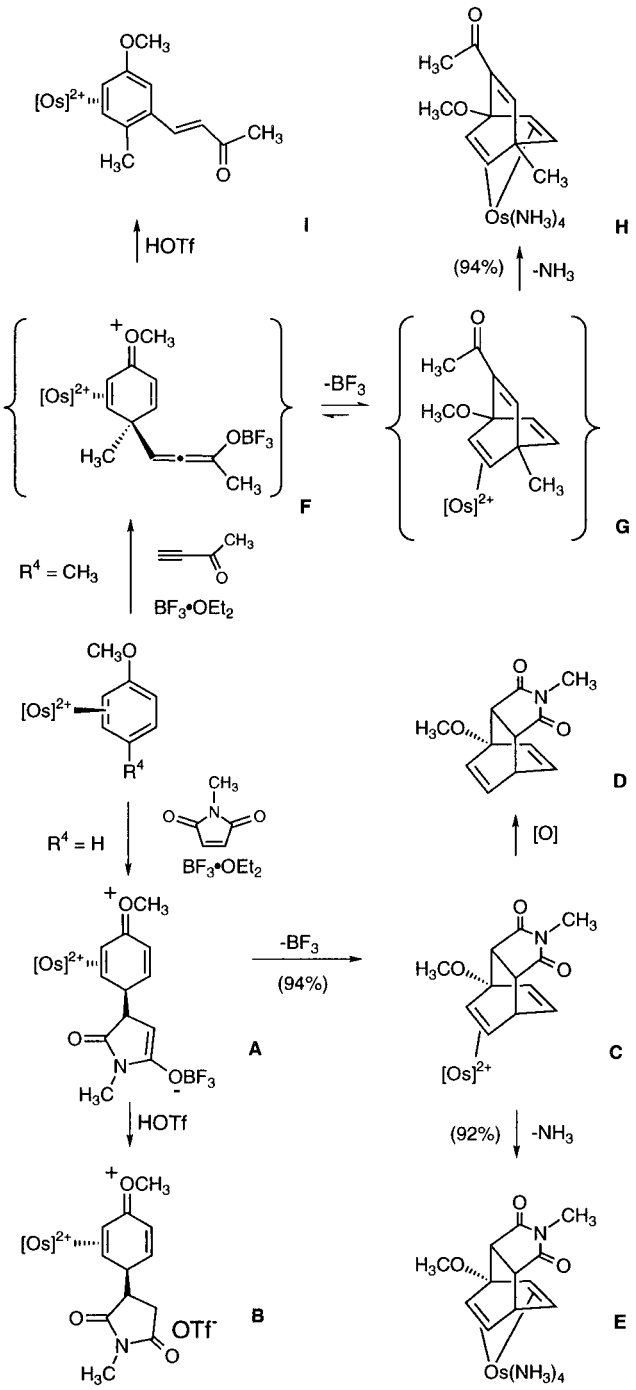


Figure 31. [4+2] cycloaddition reactions of η^2-anisole complexes via a 4*H*-anisolium intermediate and the formation of various bicyclo[2.2.2]octadiene and bicyclo[2.2.2.]-octatriene complexes.

Brønsted acid, the enolate is protonated and the resulting 4*H*-anisolium species, upon warming to 20 °C, undergoes an alkyl migration of the enone from C(4) to C(3) to form the disubstituted anisole species (I) in a reaction analogous to the acid-catalyzed cyclohexadienone−phenol rearrangement.[80]

2. [4+2] Michael–Michael Ring Closures

The 4*H*-anisolium reaction product of MVK and 4-methylanisole (A) offers the possibility of an intramolecular nucleophilic addition at C(3) (Figure 32). When this material is dissolved in a triflic acid/

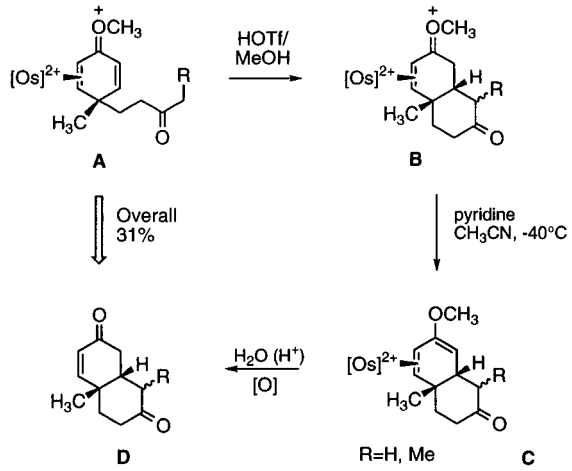


Figure 32. The formation of functionalized *cis*-decalins from an η^2-anisole complex and an enone via a Michael-type cyclization.

acetonitrile solution, no reaction occurs. However, if the reaction is carried out in acidic methanol, nucleophilic addition at C(3) proceeds, resulting in a *cis*-decalin ring system (B; see Figure 32).[70,81] When this reaction sequence is repeated using ethyl vinyl ketone as the Michael acceptor, the methyl analog is obtained as a 6:1 ratio of diastereomers. The resulting oxonium system may be either deprotonated at C(2) to give the methoxy diene complex (C) or hydrolyzed and treated with an oxidant to provide the organic decalin (D).[70] An electrochemical analysis of the intermediates reveals that in the ring-closure sequence, a significant amount of metal oxidation occurs.

3. Michael–Aldol Ring Closures

When C(3) of a 4*H*-anisolium complex bears an alkyl group, the corresponding benzyl protons are highly acidic, enabling addition of a carbon electrophile to this position (Figure 33). For example, if the anisolium complex resulting from MVK addition to 6-methoxy-1,2,3,4-tetrahydronaphthalene (A) is treated with pyridine, deprotonation occurs to generate the methoxytriene (B).[81] Subsequent treatment of this material with TBSOTf induces an intramolecular aldol reaction to generate a tricyclic anisolium intermediate (C) that spontaneously eliminates the silanol to give the corresponding olefin (D). Upon hydrolysis and oxidation, the free dienone (E) is recovered.[81]

4. Diels–Alder Cycloadditions (4-Methoxystyrenes)

Although direct complexation of methoxystyrene would be expected to result in a mixture of linkage isomers (*vide supra*), the 5,6-η^2 ring-bound species can be formed free from its isomers by starting with a *complexed* anisole precursor (Figure 34). Thus, treatment of the anisole complex with an acetal under acidic conditions generates the benzyl ether complex (A). Elimination of alcohol generates a methylated *p*-quinone methide that may be stabilized as the pyridine adduct (B). Subsequent deprotonation gives the 4-methoxystyrene complex (C) in nearly quantitative yield. With the metal partially local-

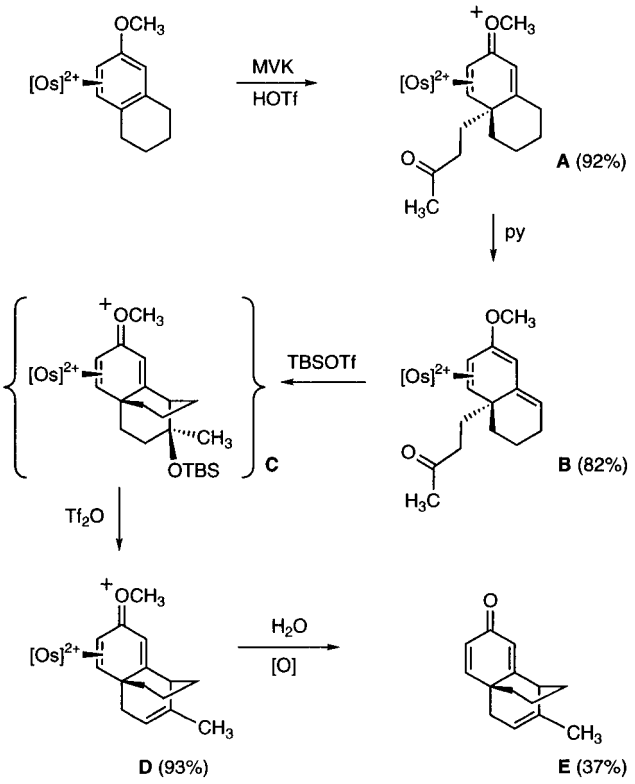


Figure 33. The stereospecific formation of a tricyclic *cis*-decalin species via an intramolecular aldol condensation.

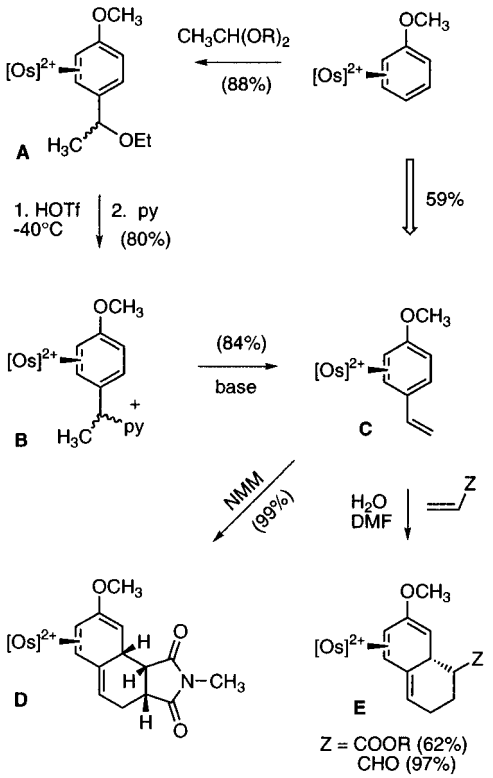


Figure 34. The formation of a *p*-methoxystyrene complex from anisole and its use in Diels−Alder reactions.

izing the arene π system, the styrene complex resembles a vinylogous methoxydiene and readily undergoes Diels−Alder reactions, even in the absence of a Lewis acid. Preliminary data indicate that this cycloaddition reaction is highly stereo- and regioselective (e.g., D), with the addition occurring from the opposite face of the ring from metal coordination and

with the most electron-deficient carbon of the dienophile adding to the β carbon of the vinyl group (e.g., E). Given that the cycloaddition works for a variety of dienophiles and that the procedure for the formation of the styrene is generally applicable to acetals bearing an α proton, the reaction sequence outlined above promises to offer exceptional diversity in the preparation of functionalized decalin systems.[81]

5. [2+2+2] Michael–Michael–Michael Ring Closures

When aniline or anisole complexes are combined with a large excess of a Michael acceptor in the presence of a Lewis acid, the enolate resulting from conjugate addition at C(4) (e.g., A in Figure 35) can, in some cases, be intercepted by another equivalent of the Michael acceptor, and the enolate resulting from this reaction can close at C(3). In contrast to the high stereocontrol generally observed for the arene ring carbons, the newly formed ring is generally formed with poor stereocontrol, and as a result, the product mixture is usually complex. One exception comes from the reaction of the *N*,*N*-dimethylaniline complex with α-methyl-γ-butyrolactone (see Figure 35). Even when this reaction is carried out with only 1 equiv of electrophile, the only recovered products other than starting material are those resulting from the Michael−Michael−Michael sequence. For this system, one stereoisomer dominates and its structure has been elucidated using X-ray diffraction. The highly congested dienamine product (B) resists addition of carbon electrophiles at C(2), but it does undergo protonation at C(2) followed by reduction at C(1) to yield the organic allylamine (C) after oxidative decomplexation. The stereoselectivity for the reduction of the iminium carbon is a rare exception to the general rule that all additions occur at the opposite face of the arene ring from metal coordination. This anomaly is likely a consequence of the highly congested *exo* face of this compound.

6. Benzenium Annelations

η^3-Benzenium systems readily undergo nucleophilic addition with mild carbon electrophiles provided that

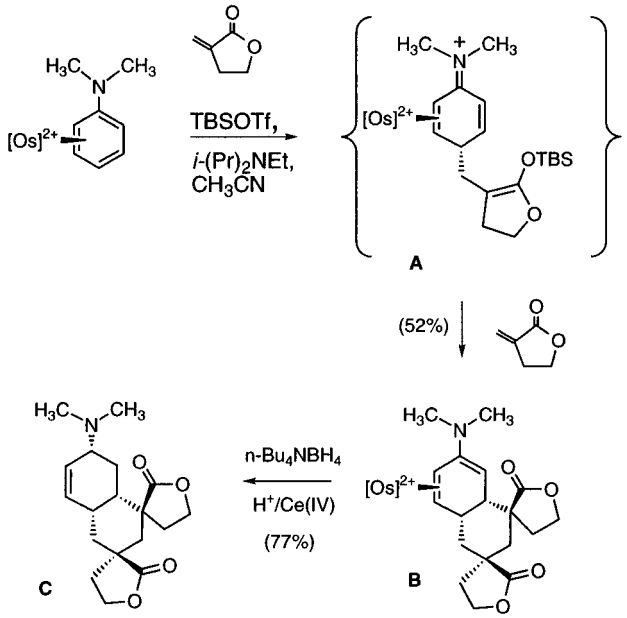


Figure 35. A Michael−Michael−Michael ring-closure reaction sequence with an η^2-aniline complex.

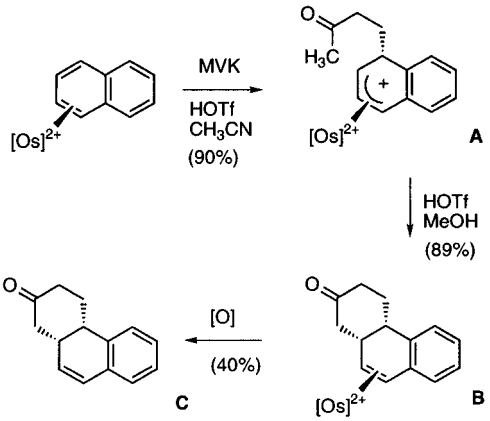


Figure 36. The stereospecific formation of a phenanthrene system from naphthalene and MVK via a 1*H*-naphthalenium intermediate.

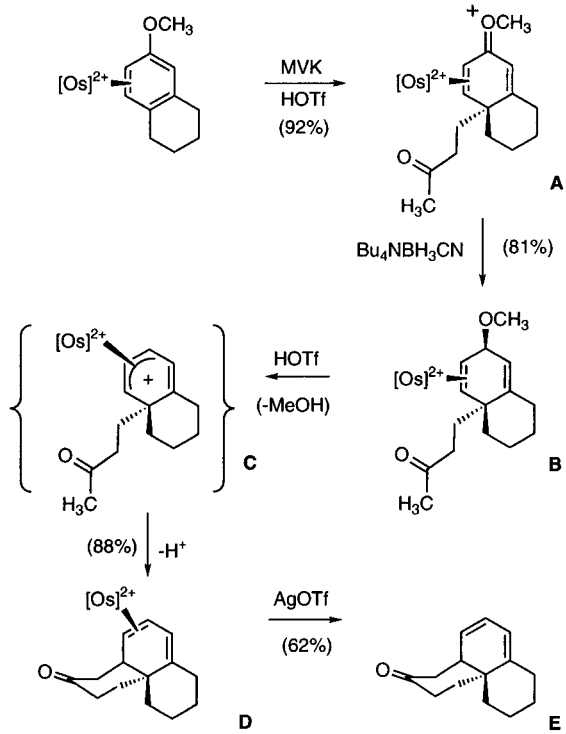


Figure 37. The stereospecific formation of a tricyclic decalin system from a methoxytetralin and MVK via an η^3-benzenium intermediate.

they are not too basic. Because of the highly acidic nature of these systems, the nucleophilic addition is typically performed under acidic conditions. When the naphthalene complex is treated with MVK in acidic acetonitrile, a 1*H*-naphthalenium species is formed (A in Figure 36) that cyclizes in methanol to form the phenanthrene ring system (B). As with the arene systems discussed earlier, both electrophilic addition and nucleophilic addition to the naphthalene ring occur opposite metal coordination, creating a *cis*-ring juncture in the final organic product (C). Alternatively, the benzenium system may be formed indirectly from certain 4*H*-anisolium species. In Figure 37, a methoxytetralin system is first treated with MVK to give an anisolium system (A) that may be reduced at C(1). Note here that the alkyl substitution at C(3) redirects the hydride reduction to C(1). When the methoxydiene product (B) is treated with triflic acid, elimination of methanol results in the

benzenium system (C) which subsequently undergoes cyclization with the pendant oxobutyl group to give a tricyclic system (D).[81]

D. Hydrogenation Reactions

With the osmium partially localizing the π system of an arene, selective hydrogenation to cycloalkenes becomes a simple task. When a methanol solution of the benzene complex is put under 1 atm of hydrogen in the presence of Pd°, the cyclohexene analog is produced in good yield (Figure 38). Repeating this experiment with D_2 generates a single isomer in which all the deuterium is located *anti* to the osmium.[82] Similarly, hydrogenation of the naphthalene complex in the presence of Pd°/C generates the 1,2-dihydronaphthalene complex exclusively. The product of hydrogenation for the anisole complex of pentaammineosmium(II) depends on the reaction medium. In the presence of dry methanol, anisole is converted to 3-methoxycyclohexene on osmium, where the methoxy group is oriented toward the metal. However, if the methanol is not carefully dried, water intercepts the dihydroanisole intermediate producing the cyclohexenone complex (see Figure 38).[31]

In summary, coordination of pentaammineosmium(II) activates the arene toward electrophilic addition and stabilizes the 4*H*-arenium or arene species with respect to rearomatization. Consequently, nucleophilic addition at C(1) or C(3) may be accomplished to give highly functionalized cyclic dienes, enones, and olefins. The steric bulk of the metal requires both electrophilic and nucleophilic additions to occur *anti* to the metal, providing predictable stereocontrol.

V. Organic Reactions of Heterocycles

Although their rates differ significantly, η^2-coordinated pyrrole, furan, and thiophene complexes of

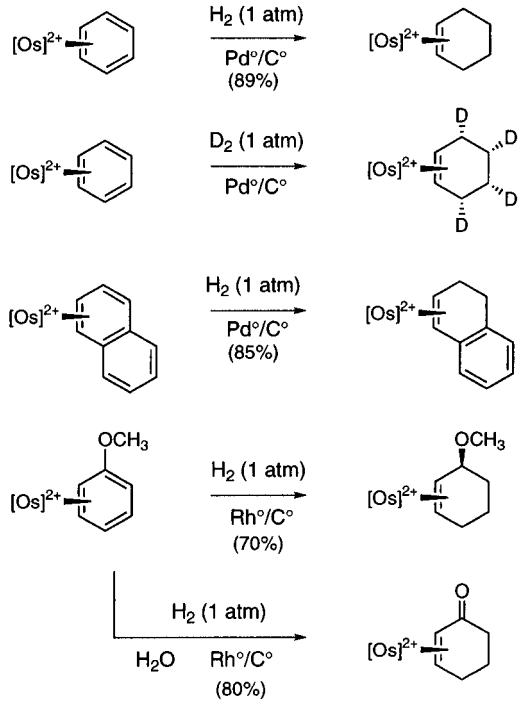


Figure 38. Assorted hydrogenation reactions with η^2-bound arene complexes.

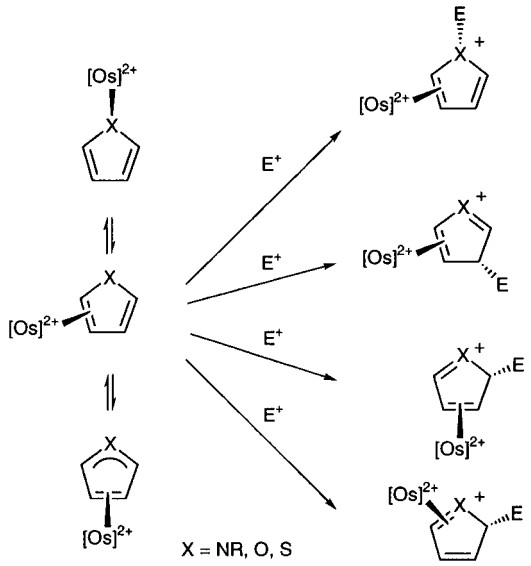


Figure 39. Products of electrophilic addition to osmium(II) heterocycle complexes.

pentaammineosmium(II) readily undergo linkage isomerizations at 20 °C, allowing the metal access to several different positions within the heterocycle. Yet, with one important exception (*vide infra*), reactivity for these systems stems from the dominant 4,5-η^2 isomer (Figure 39). For pyrrole and furan, the most common reaction is electrophilic addition at the uncoordinated β carbon (i.e., C(3)). However, reaction at the heteroatom has also been observed. For thiophene, reaction at the β carbon is almost always preempted by reaction at sulfur or at the uncoordinated α carbon, C(2). The resulting pyrrolium, furanium, and thiophenium complexes are stabilized by the osmium (*vide supra*), often to the point that these complexes may be isolated. Most significantly, they resist rearomatization and readily undergo nucleophilic addition reactions at either C(2) or C(5).

A. Pyrrole and Pyrrolium Complexes

Pyrrole complexes of pentaammineosmium(II) undergo reaction with carbon electrophiles at either C(3) or nitrogen. Although reaction at the β carbon (C(3)) is generally favored thermodynamically, addition to nitrogen does sometimes occur under kinetically controlled conditions. Reaction at nitrogen is most likely to occur for "hard" electrophiles (e.g., CH_3OTf) and when the nitrogen is unsubstituted. This review focuses on carbon electrophiles that add to the β carbon.

1. Electrophilic Addition at C(3)

The 4,5-η^2-*N*-methylpyrrole complex readily adds electrophiles at C(3) to give 3*H*-pyrrolium complexes (Figure 40).[46,49] Electrophiles include nitrilium salts (A), acetic anhydride (B), aldehydes, ketones and acetals (C), Michael acceptors (D), and alkyl triflates (E). For cases in which the corresponding 3*H*-pyrrolium product has a withdrawing group adjacent to the β carbon (e.g., an acyl or iminium group) deprotonation is facile, and the isolated product is usually a β-substituted pyrrole. When alkylating agents are used, the 3*H*-pyrrolium species (e.g., D and E) is surprisingly stable, and a moderate external

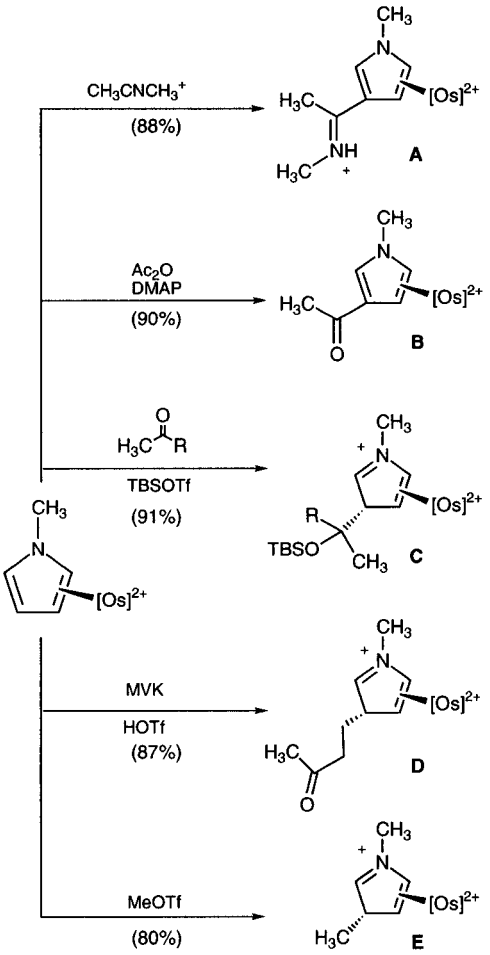


Figure 40. Electrophilic addition at the β carbon of η^2-pyrrole complexes.

base (e.g., DIEA) must be used to achieve rearomatization (*vide supra*). In every case examined, the electrophile adds selectively to the *exo* face. As a result of the stability of these 3*H*-pyrrolium systems, difficulties associated with multiple alkylations and polymerizations are completely avoided, and clean β-substituted pyrroles may be removed from the metal simply by heating.

Although pK_a measurements indicate that the proton on the β tetrahedral carbon should be relatively acidic (pK_a between 4 and 8), a much stronger base is required in practice because of the highly constricted environment of the sp^3 center.[46] An interesting variation of this reaction is shown in Figure 41, in which MVK in the presence of acid adds to *N*-methylpyrrole at C(3), and subsequent loss of the β proton returns the β-substituted pyrrole (A). Subsequent linkage isomerization puts the metal on the *more congested* side of the pyrrole (B), but in this form, the unsubstituted β carbon, C(4), is left exposed and readily undergoes an aldol reaction with the tethered ketone to generate the bicyclic system (C). Dehydration with triflic acid and deprotonation returns the heterocycle to its aromatic form (D).[83] A number of the reactions shown in Figure 40 also occur for the parent pyrrole complex, but for acylation and methylation, the carbon adds primarily at nitrogen.

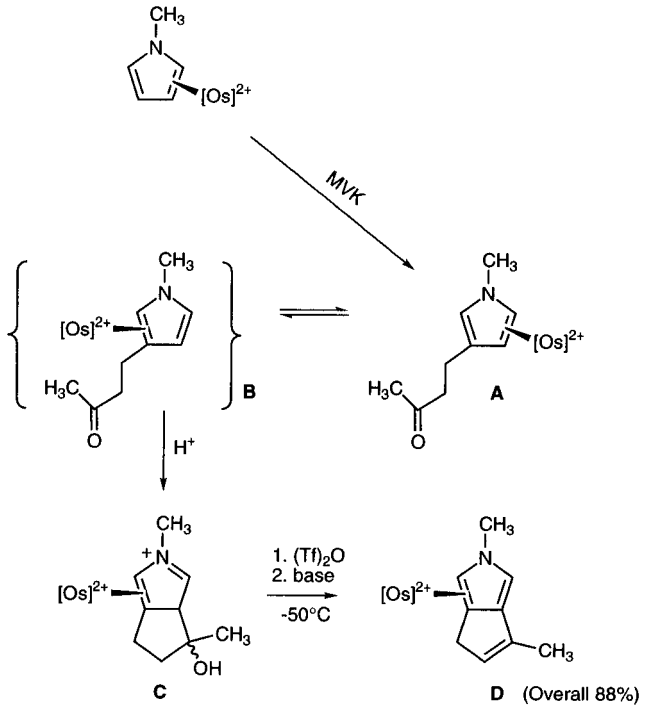


Figure 41. Addition of MVK to *N*-methylpyrrole followed by linkage isomerization and aldol ring closure.

2. Nucleophilic Addition at C(2)

The 3*H*-pyrrolium complexes generated from electrophilic addition (see Figure 40), as well as their 2*H*-pyrrolium counterparts resulting from cycloaddition (see Figure 46) or protonation (see Figure 12), react with mild nucleophiles to form 2- or 3-pyrrolines, respectively (Figure 42). Although the pyrrolium complexes resist rearomatization, strongly basic nucleophiles (e.g., enolates) must be avoided. Conversely, the strong back-bonding interaction deactivates the iminium carbon to the point that hydrolysis is not observed.[46,84] Consequently, vinyl ethers, siloxyalkenes, and even the malonate anion fail to add to C(2). However, cyanide and borohydride anions are effective nucleophiles capable of generating pyrrolines without significant contamination as

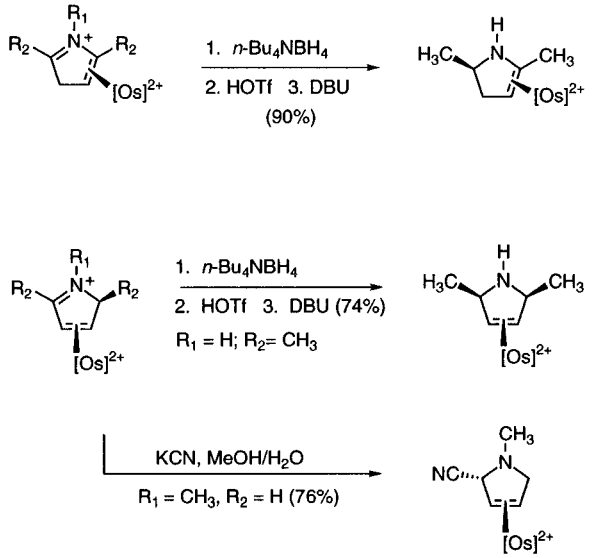


Figure 42. Nucleophilic addition to 2*H*- and 3*H*-pyrrolium complexes.

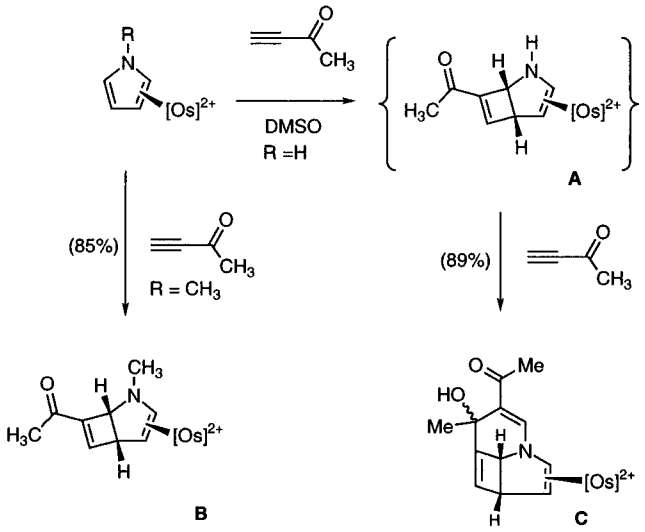


Figure 43. Double conjugate addition of 3-butyn-2-one to pyrrole to give an tricyclic indolizidine.

a result of deprotonation. As was the case for electrophilic addition, nucleophilic addition at C(2) occurs from the *exo* face with high stereocontrol. Only one example of an intramolecular nucleophilic addition has been observed to date (other than the cycloaddition reactions described in Table 7). In this example, the reaction of an electron-deficient alkyne with an η^2-pyrrole complex results in conjugate addition at C(3), followed by closure of the enolate on C(2) to form an azabicyclo[3.2.0]heptadiene (A and B in Figure 43). When the pyrrole is not substituted at nitrogen, a second equivalent of the alkyne (e.g., 3-butyn-2-one) can undergo conjugate addition of the bicyclic pyrroline intermediate at nitrogen, and this step is followed by an intermolecular aldol ring closure to form a tricyclic indolizidine system (C).[46]

3. Vinylpyrrole Complexes and the Synthesis of Indoles

The ease with which electrophiles may be added to the β carbon of pyrroles provides a direct route to β-vinylpyrroles and, subsequently, indoles.[45,85] By several complementary routes, pyrroles are converted into β-vinylpyrrole complexes (Figure 44), often by route of a η^2-bound 2-azafulvenium intermediate (e.g., B and H). A significant feature in these reactions is that the osmium is trapped on the pyrrole ring rather than on the vinyl group that is its thermodynamically favored binding site (as in C, F, and I). Isomerization from ring to vinyl group occurs over a period of days, but the kinetic stability of the β-vinylpyrrole complexes provides the possibility of a cycloaddition reaction with a suitable dienophile. The resulting tetrahydroindole complex (e.g., D and J) is typically formed in good yield with excellent stereocontrol. Subsequent treatment of the tetrahydroindole with DDQ oxidizes the organic system and releases the metal to yield the free indole. Using this procedure, highly functionalized indoles can be prepared with overall yields typically between 40% and 50% (from pyrrole; Table 6). Unfortunately, in the majority of cases, the nitrogen must be alkylated, which imposes a significant limitation to this process as a synthetic approach to indoles.

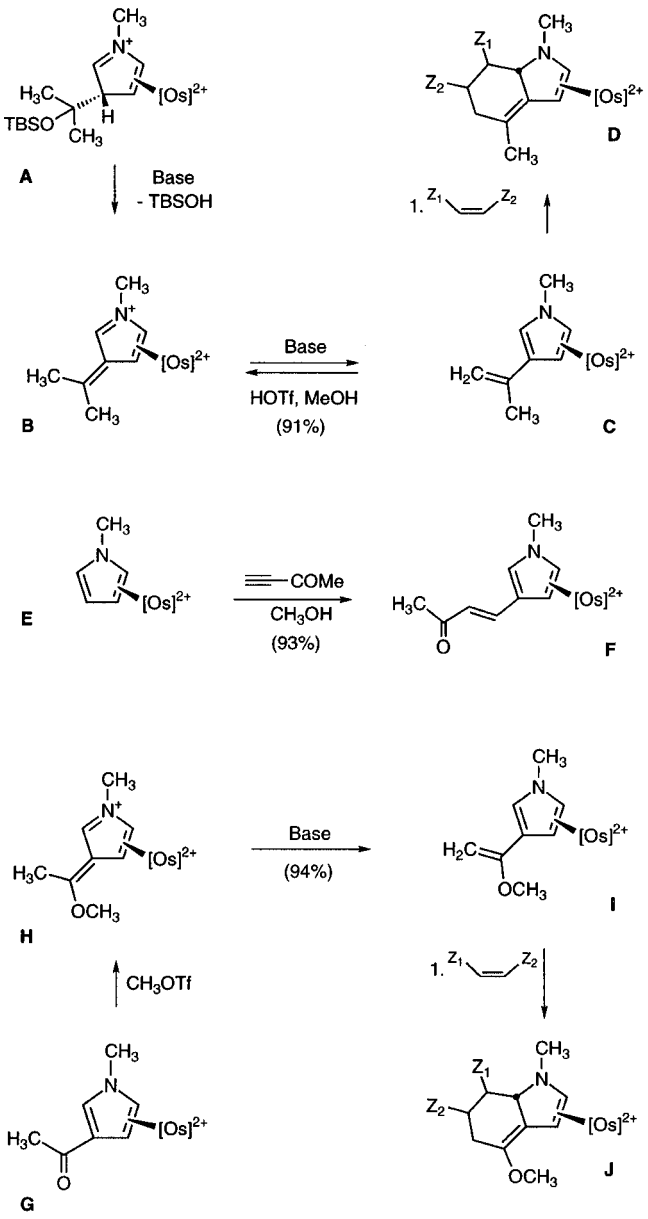


Figure 44. Formation of β-vinylpyrrole complexes and their conversion to trisubstituted indoles.

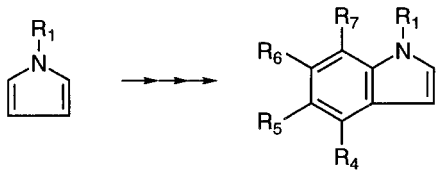
4. Dipolar Cycloaddition Reactions

While osmium heavily favors binding pyrrole across C(4) and C(5) (A in Figure 45), it also has access to the C(3)−C(4) position (B). Although this species is far less stable than its 4,5-η^2 isomer, it can be much more reactive toward certain activated olefins (dipolarophilies).[47] Thus, through osmium coordination, the pyrrole is transformed into an azomethine ylide[43] and reacts with dipolarophiles to generate 7-azabicycloheptene complexes (C) rather than β electrophilic addition products (D).

a. Scope of Reaction.

Table 7 illustrates the scope of the dipolar cycloaddition for pyrroles. Cycloaddition is most likely to occur in preference to a Michael addition at C(3) when the activated olefin cannot form a stabilized enolate (e.g., esters and nitriles) and when the pyrrole has substituents that destabilize the 4,5-η^2 isomer. For example, methyl substituents on either C(1) or C(2) and C(5) of the pyrrole destabilize the 4,5-η^2 isomer, thereby increasing both the rate of

Table 6. Indoles Prepared from *N*-Methylpyrrole



R_1	R_4	R_5	R_6	R_7	Overall Yield[a]
Me	Me	H	-C(O)-N(Ph)-C(O)-		58(74)
Me	Ph	H	-C(O)-N(Ph)-C(O)-		48(60)
Me	Me	H	CO_2Me	CO_2Me	35(42)
Me	Ph	H	CO_2Me	CO_2Me	48(55)
Me	Ph	H	H	CO_2Me	39(49)
Me	H	H	-C(O)-N(Ph)-C(O)-		12(7)
Me	OMe	H	-C(O)-N(Ph)-C(O)-		29(37)
Me	OMe	H	H	CO_2Me	12(17)
Me	H	Ac	-C(O)-N(Ph)-C(O)-		46(52)
Me	H	CO_2Me	-C(O)-N(Ph)-C(O)-		14(17)
Me	CO_2Me	CO_2Me	-C(O)-N(Ph)-C(O)-		49(66)
Me	Ph	Ac	-C(O)-N(Ph)-C(O)-		22(27)
H	H	Ac	-C(O)-N(Ph)-C(O)-		4(5)
Me	Et	Me	-C(O)-CH_2-C(O)-		9(14)
Me	-$(CH_2)_4$-		-C(O)-N(Ph)-C(O)-		38(45)
Me	OMe	Me	CO_2Me	CO_2Me	5(6)
Me	-(CH=CH-)$_2$-		-C(O)-N(Ph)-C(O)-		16(40)
Ar[b]	Me	H	-C(O)-N(Ph)-C(O)-		49(69)
Ar[b]	H	Ac	-C(O)-N(Ph)-C(O)-		50(67)
Me	Ph	H	-C(O)-N(Ph)-C(O)-		40(37)
Me	Me	H	CO_2Me	CO_2Me	42(40)

[a] Values represent the overall isolated yield of purified indole starting from pyrrole. Value in parentheses is yield for decomplexation/oxidation step alone. [b] Ar = 3,5-dimethylbenzyl.

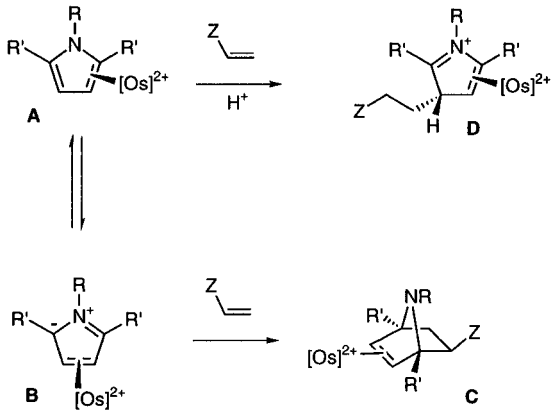
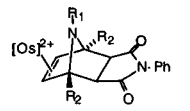
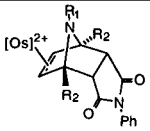
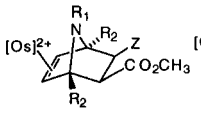
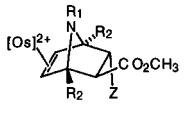
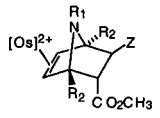
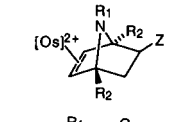
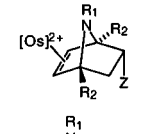
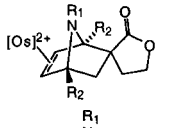
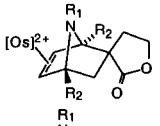
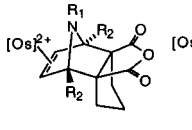
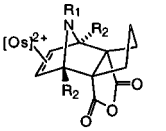


Figure 45. Electrophilic (conjugate) addition and dipolar cycloaddition manifold for η^2-pyrrole complexes.

isomerization and the relative population of the active 3,4-η^2 isomer. Thus, the rate of isomerization, at least for the symmetrical pyrroles investigated, correlates with the rate of cycloaddition provided that the α carbons and the nitrogen are not too hindered. For the 2,5-dimethylpyrrole complex, cycloadducts are obtained in 30 min at 20 °C using dipolarophiles as mild as methyl acrylate and as hindered as cyclopentene-1,2-dicarboxylic anhydride. Note in the latter reaction that four quaternary centers are formed in a single step (see Table 7). By contrast, a substituent on a β carbon *destabilizes* the 3,4-η^2 isomer relative to the 4,5-η^2 form, rendering these complexes unreactive.[47]

Table 7. Cycloadduct Complexes of Pentaamminosmium(II)

a (*exo*)	b (*endo*)	R_1	R_2	Z	a/b[a]	Yld[b]
		H	H		6:1	85
		CH_3	H		1:6	85
		H	CH_3		5:1	89
		CH_3	CH_3		1:1	77
		TMS	H		>1:20	89
		H	CH_3	CO_2R	2:1	82
		H	CH_3	3-Py	9:1	83
		H	H	CO_2R	-	78
		H	CH_3	CO_2R	-	86
		H	CH_3	3-Py	16:1	93
		H	CH_3	CO_2R	12:1	97
		H	CH_3	CN	5:1	83
		CH_3	H	CO_2R	1:1	84
		CH_3	H	CN	1:1	98
		H	CH_3		>20:1[c]	96
		H	CH_3		>10:1	84

[a] The ratios of isomers were determined by ^{1}H NMR integrations. [b] Yields are in % and are reported for the crude mixtures of diastereomers. [c] The *endo* isomer was not detected by ^{1}H NMR.

There is strong evidence that the *exo*/*endo* ratios reported in Table 7 reflect a kinetic rather than thermodynamic preference for the observed stereochemistry.[47] The stereochemistry of the cycloaddition appears to be governed by the steric environment about the pyrrole nitrogen. For cases in which the nitrogen is not substituted, the major product has the electron-withdrawing group in an *exo* configuration. This stereoselectivity, resulting from an *endo* transition state,[86] has been observed for 1,3-dipolar cycloaddition reactions of stabilized azomethine ylides lacking nitrogen substituents.[87] The *endo* selectivity has been explained by consideration of the most favorable orientation of the dipole moments for the azomethine ylide and dipolarophile.

b. Ring Opening to 2H-pyrroles. The cycloadduct complexes are susceptible to an acid-promoted retro-Mannich reaction in which the final product is a 2*H*-pyrrole species. The vulnerability of the cycloadduct toward ring opening depends primarily on the stability of the resulting enolate. Most susceptible are those complexes derived from MVK (for which spontaneous decomposition occurs in solution, even in absence of acid) followed by maleic anhydride, maleimide, esters, or nitriles.[47] The latter two ring-opening reactions in acetonitrile are sufficiently slow that the complexes may be protonated before decomplexation without appreciable ring opening. (In water, however, the isomerization is facile even in the absence of acid.) In Figure 46, treatment of the acrylate-derived cycloadduct complex (A) with 1 equiv

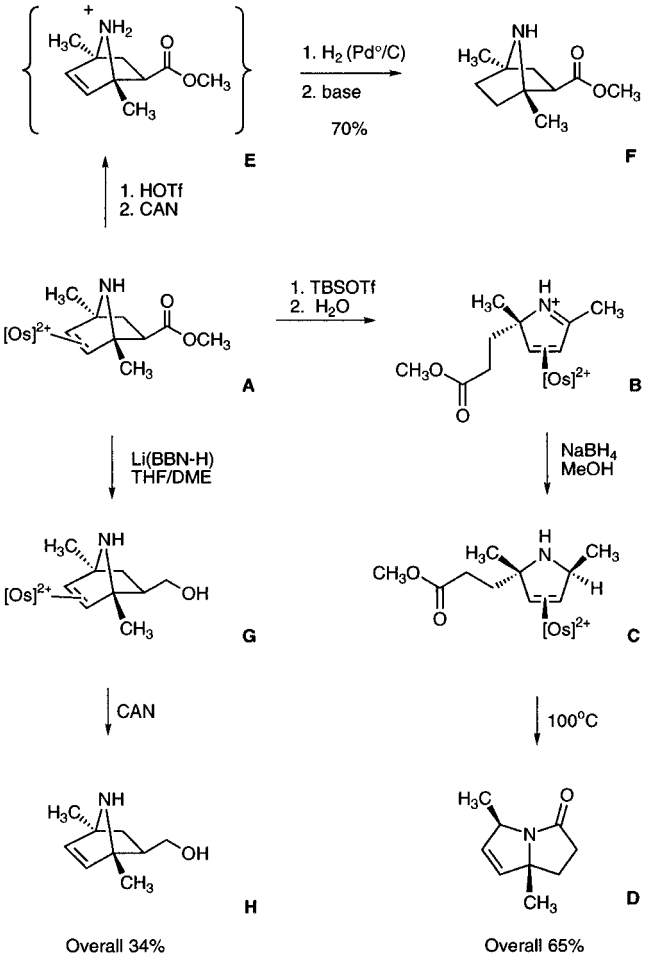


Figure 46. The conversion of a 7-azanorbornene osmium(II) complex to an 7-azanorbornane, 7-azanorbornene, and a pyrrolizidine.

of TBSOTf followed by hydrolysis results in facile ring opening to the 2*H*-pyrrolium complex (B), and this material may be stereoselectively reduced to the corresponding 3-pyrroline (C). Upon decomplexation, the 3-pyrroline with its pendent ester group cyclizes to form the pyrolizidine ring system (D).

c. Synthesis of 7-Azanorbornanes. The pentaammineosmium(II) moiety acts as a protecting group for the 7-azanorbornene nucleus, presumably by reducing the rearomatization driving force in the cycloreversion process. In contrast to the behavior observed for free 7-azanorbornenes bearing electron-withdrawing groups,[88] the osmium(II) complexes in Table 7 are highly resistant to retrocycloadditions, even upon moderate heating.

Thus, before removing the osmium from the azanorbornene, the withdrawing group(s) must be removed or the lone pair on the nitrogen must be protonated (see Figure 46). If the azanorbornene is protonated and removed from the metal (E), the C−C double bond may be hydrogenated (keeping the solution acidic) and the stable azanorbornane (F) can be recovered. Using this procedure, a synthesis has been developed for 2-substituted 7-methyl-7-azabicyclo[2.2.1]heptanes, compounds that have been used as precursors to several cholinergic receptor agonists.[47] Alternatively, the electron-withdrawing substituent(s) on the carbon adjacent to the bridgehead can be reduced (G) and converted into 7-azanorbornenes (H).

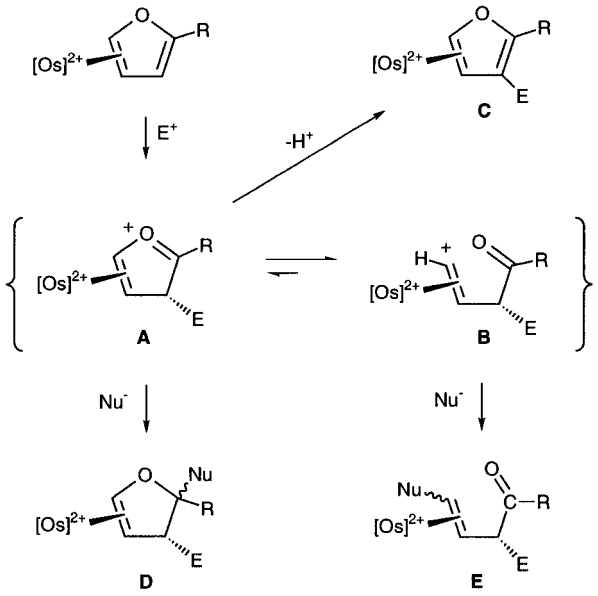


Figure 47. Schematic representation of observed reactions for an η^2-furan complex.

B. Furan and Furanium Complexes

Like its nitrogen analog, the 4,5-η^2-furan complex of pentaammineosmium(II) is susceptible to electrophilic addition at both C(3) and the heteroatom (Figure 47), although many more examples have been observed for the former than for the latter. Addition of a carbon electrophile to C(3) produces a 3*H*-furanium complex (A) that is prone to isomerize to an η^2-vinyl species (B; i.e. a metallocyclopropene). The ability of the osmium(II) moiety to stabilize this "vinyl cation" fragment[89] through η^2 coordination causes the C(5)−O bond for a 3*H*-furanium species to be labile, and an equilibrium is readily established between its "open" and "closed" forms (see Figure 47). Thus, in addition to β-electrophilic substitution at C(3) (C) and nucleophilic addition at C(2) (D), nucleophilic addition at C(5) becomes an important reaction pathway (E).

1. β-Substitution Reactions

An electrophilic addition at C(3) that results in an electron-withdrawing substituent at that position is most prone to undergo substitution partly because of the acidic nature of the methine proton at C(3), but also because of the resonance stabilization of the resulting furan, whose *uncoordinated* fragment resembles a vinyl ether. In Figure 48, two examples are shown in which the net reaction is β-electrophilic substitution. Note in the case of 2-methylfuran that the metal occupies a position away from the methyl substituent. Therefore, electrophilic substitution occurs at the β carbon adjacent to that substituent, yielding a 2,3-disubstituted furan.

2. C(3)–C(2) Tandem Addition Reactions

Figure 49 shows several examples in which the ligated furan sequentially adds an electrophile at C(3) and a nucleophile at C(2). Thus, reaction of 2-

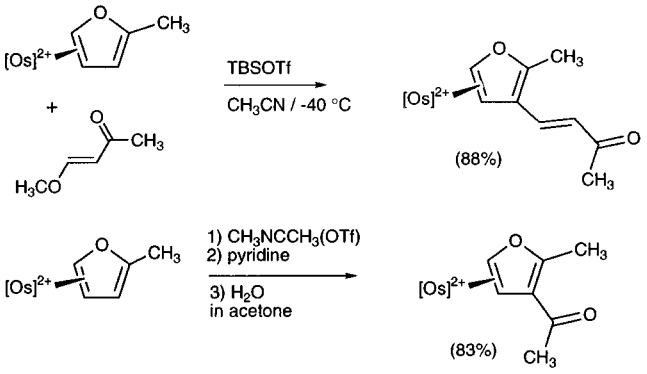


Figure 48. Electrophilic substitution reactions for an η^2-furan complex.

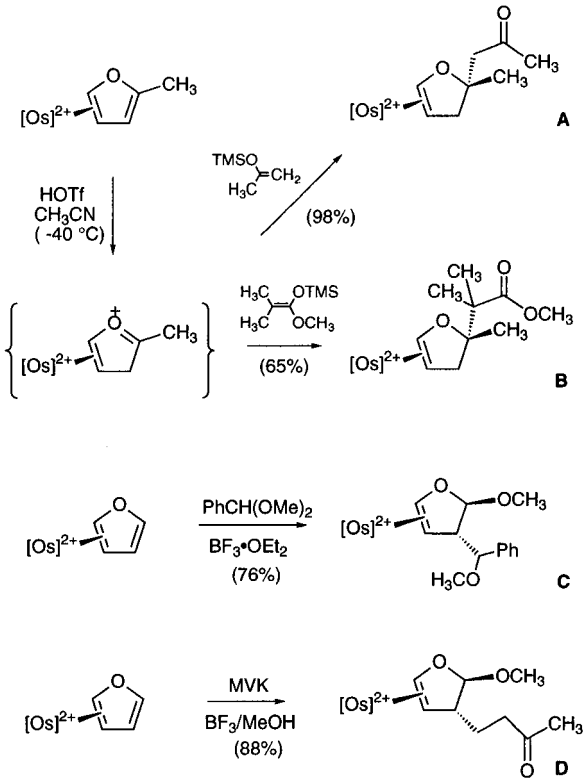


Figure 49. Vicinal addition reactions for η^2-furan complexes.

methylfuran with acid at −40 °C followed by addition of either MMTP or trimethylsiloxypropene results in dihydrofuran complexes (A and B) with a quaternary α carbon. In both cases, nucleophilic addition occurs exclusively to the *exo* face of the furan ring, an observation that suggests that nucleophilic addition occurs to the "closed" 3*H*-furanium species rather than the carbonyl group of the "open" isomer.

Addition of benzaldehyde demethyl acetal in acetonitrile or MVK in methanol in the presence of BF_3•OEt_2 results in the formation of dihydrofuran acetals (C and D). In contrast to practically every other example of nucleophilic addition to a pentaammineosmium(II) system, the methoxy group at C(2) for these acetal products has an orientation *syn* to the osmium. Presumably, this reflects the reversible nature of methoxide addition under acidic conditions, suggesting that this product is thermodynamically favored over its C(5) epimer, whereas the carbon nucleophiles described above for 2-methylfuran represent reactions thought to be under kinetic control.

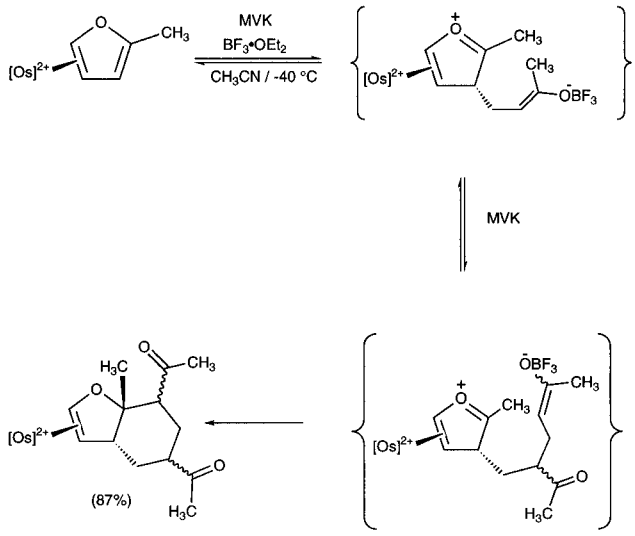


Figure 50. A Michael−Michael−aldol ring-closure reaction sequence for MVK and 2-methylfuran.

In an interesting variation of this reaction, when the 2-methylfuran complex is treated with an excess of MVK and the Lewis acid BF_3•OEt_2, a Michael−Michael−aldol ring-closure sequence follows, generating a benzofuran nucleus. Although the product is formed as a mixture of two diastereomers, the stereochemistry at the furan ring is firmly established as that resulting from the *exo* addition of both electrophile (MVK) and nucleophile (enolate). Treatment of the product mixture with a one-electron oxidant yields the free ligand as a mixture of two isomers (Figure 50).[90]

3. C(3)–C(5) and O–C(5) Tandem Addition Reactions

As described earlier, the 3*H*-furanium system exists in equilibrium with its vinyl cation isomer, and when C(2) is alkylated, this system is especially prone to nucleophilic addition at C(5). Whether this trend is due to the increased steric demand at C(2) or the enhanced stability of a ketone compared to an aldehyde is not clear and exceptions are known, but the examples shown in Figure 51 are typical. When benzaldehyde dimethyl acetal is combined with the 2-methylfuran complex, the sole product is a 5-methoxy-4-penten-2-one complex, the product of electrophilic addition at C(3) followed by methoxy addition to C(5) (A; Figure 51). Noteworthy is the different outcome observed for the parent furan complex. In the latter case, a dihydrofuran acetal is the only product isolated (see Figure 49). Aldehydes react with 2-methylfuran in the presence of a Lewis acid to generate dihydrofuran complexes,[51] but the aldehyde is incorporated in the heterocyclic ring of the product (B). Again, electrophilic addition at C(3) results in cleavage of the C(5)−O bond, and the resulting vinyl cation is intercepted by the alkoxide derived from the aldol process. As a result of the rotation on the C(3)−C(4) bond that is required to form the new heterocycle, the acetal group in the product is in a *syn* orientation to the metal. In contrast, the stereochemistry at the α carbon is derived from the initial aldol reaction, a reversible process. Thus, these complexes adapt a stereochemistry that orients the α substituent away from the metal.[51]

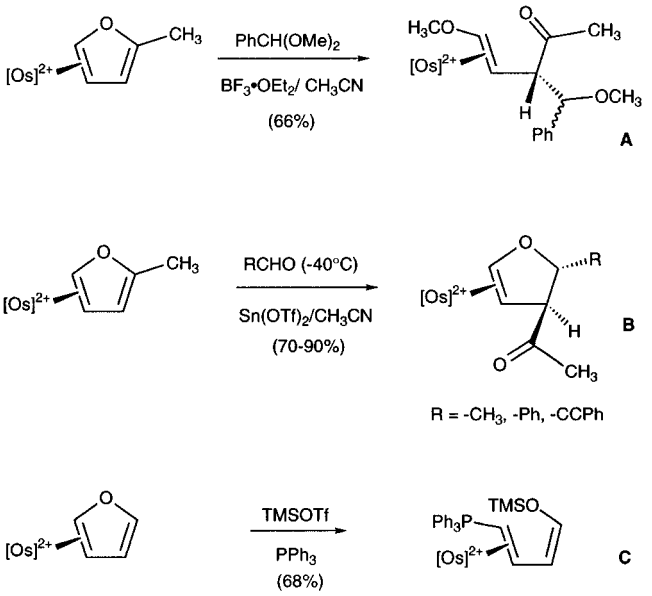


Figure 51. Electrophilic addition at C(3) or O, C−O bond cleavage, and nucleophilic addition at C(5) for an η^2-furan.

Another class of reactions involving vinyl cation intermediates are those involving oxophilic electrophiles in which addition occurs directly at the heteroatom. Figure 51 shows one example in which TMSOTf is used to open the heterocycle and triphenylphosphine is subsequently added to C(5) to generate a siloxyphosphoniumdiene complex (C in Figure 51).

4. Formation of Carbynes

Without a suitable nucleophile, vinyl cation complexes of pentaammineosmium(II) (A; Figure 52) undergo an intramolecular 1,2-hydrogen shift to form Fischer carbynes.[89] Thus, furan complexes of pentaammineosmium(II) are useful precursors to such materials, provided that the furan is not alkylated at both α carbons.[50] Figure 52 shows examples for furan and 2-methylfuran complexes of osmium(II) in which a slow conversion to an γ-oxocarbyne (B) occurs upon treatment with triflic acid (in DMF). As is common for electrophilic carbynes, nucleophiles readily add to form Fischer carbenes. The carbyne complexes (B) in Figure 52 form cyclic acetal carbenes (C) when treated with a basic solution of methanol.[90]

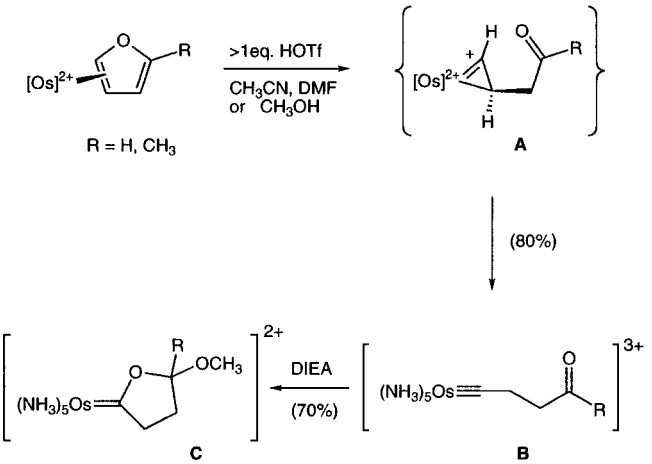


Figure 52. Formation of pentaammineosmium carbyne complexes from η^2-furans.

C. Thiophene and Thiophenium Complexes

1. Electrophilic Addition at C(2)

The complex $[Os(NH_3)_5(\eta^2\text{-thiophene})]^{2+}$ shows considerably different chemistry than its pyrrole or furan analogs. While the latter two heterocycles undergo electrophilic addition primarily at the β carbon, η^2-bound thiophenes react with electrophiles primarily at the unbound α carbon (C(2)). In this regard, the thiophene complex resembles the chemistry of an η^2-diene complex[91] more than an η^2-furan. Thus, reaction with triflic acid[52] or assorted acetals[64] yields 2*H*-thiophenium complexes in which the metal is bound across C(5) and sulfur (Figure 53). These complexes are stable even in aqueous solution. In the case of the acetal addition products, NOE data confirm that electrophilic addition occurs to the *exo face*, as has been consistently observed for the other heterocycle complexes. Similar to what is observed in the furan systems (see Figures 48 and 49), when the thiophene is alkylated, the metal occupies a position away from the substituent. Thus, electrophilic addition occurs adjacent to the original substituent.

2. Electrophilic Addition at S and Ring Opening of Thiophenium

In contrast to the free heterocycle, the thiophene complex readily alkylates at sulfur (e.g., methyl, ethyl, and benzyl) to form *S*-thiophenium species that are stable even in aqueous solution. However, similar to the siloxyfuranium species in Figure 51, the thiophenium complex is in equilibrium with its ring-opened vinyl cation isomer, and this species readily adds nucleophiles at C(5). Nucleophiles for which addition generates the corresponding substituted

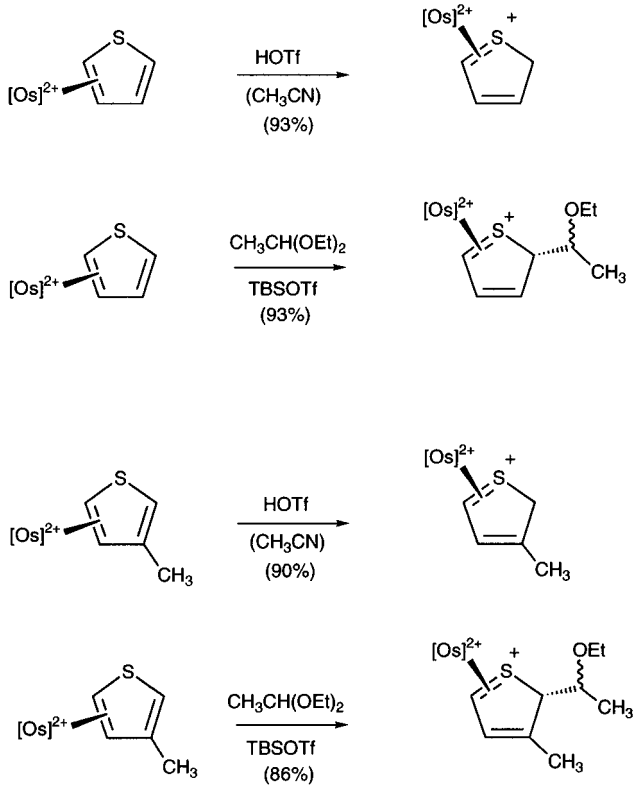


Figure 53. Addition of a proton and carbon electrophile to an η^2-thiophene complex.

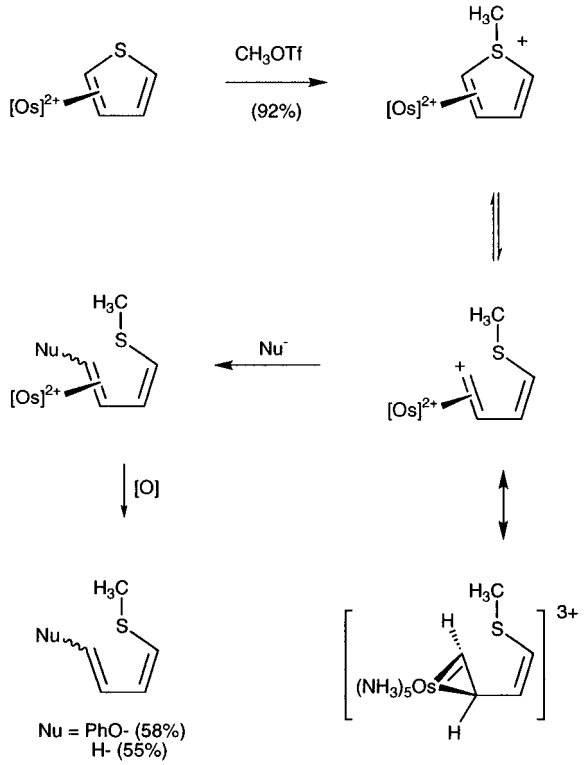


Figure 54. Methylation at sulfur and nucleophilic addition at C(5) for an η^2-thiophene complex via an η^2-vinyl cation intermediate.

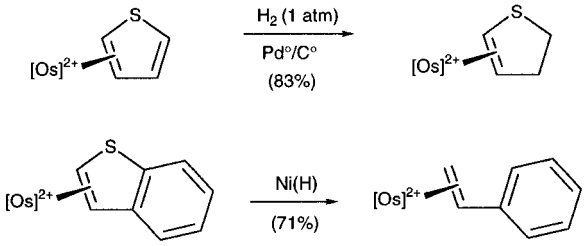


Figure 55. Semihydrogenation of thiophene and desulfurization of benzothiophene with heterogeneous catalysts.

thiodiene complexes include cyanide, hydride, carboxylate, and phenoxide (Figure 54). While these thiodiene ligands are highly susceptible to polymerization, in selected cases they may be removed from the metal intact by treating the complex with a one-electron oxidant.

3. Hydrogenation and Desulfurization

Under appropriate conditions, thiophene complexes may be hydrogenated or desulfurized. Examples of these transformations are shown in Figure 55. The parent thiophene complex may be hydrogenated (1 atm) in the presence of a palladium catalyst to give the 2,3-dihydrothiophene complex as the only product. For comparison, the benzothiophene complex is resistant to hydrogenation but readily undergoes desulfurization with Raney Nickel to form the η^2-styrene complex in good yield.

VI. Concluding Remarks

The true significance of this work lies not so much in the demonstration of a transition metal localizing aromatic π systems, but rather in the ability of an η^2-coordinated metal to activate π systems toward electrophilic addition often at a site away from metal coordination even if this causes disruption of an aromatic system. Thus, arenium, allyl, and even vinyl cations are stabilized by the metal to the point that nucleophilic addition becomes competitive with electrophilic substitution. In this regard, the chemistry exhibited by the osmium system provides a new method for activating unsaturated molecules that is complementary to the more established chemistry of nucleophilic addition to metal-coordinated π systems. The true potential of this approach, however, will not be realized until alternative transition metal systems become available. The successful system, in addition to having the appropriate steric requirements, must contain ancillary ligands that tolerate moderate electrophiles and a metal center that resists oxidative addition, either by direct attack of electrophile or by insertion of a C−H bond. The author hopes that a convincing case has been made to search for new transition metal systems that can function as this type of π base.[92]

Acknowledgment is made to the many fine graduate and postdoctoral researchers that are directly responsible for the work covered in this review. In particular, the author thanks Dr. L. Mark Hodges, Dr. Michael E. Kopach, Dr. Javier Gonzalez, Dr. W. H. Myers, Dr. Ronggang Liu, Dr. Huiyuan Chen, Dr. Stanley P. Kolis, Michael L. Spera, and Mark D. Winemiller for their dedication to producing the highest quality research, and Robert E. Ireland and Henry Taube, whose many insights have helped to inspire this work.

VII. List of Abbreviations

9-BBN	9-borabicyclo[3.3.1]nonane
CAN	ceric ammonium nitrate
DDQ	2,3-dichloro-5,6-dicyanobenzoquinone
DIEA	diisopropylethylamine (Hünig's base)
DMAc	*N*,*N*-dimethylacetamide
DME	1,2-dimethoxyethane
MMTP	1-methoxy-2-methyl-1-(trimethylsiloxy)-2-propene
MVK	methyl vinyl ketone
NMM	*N*-methylmaleimide
OTf	triflate
TBS	*tert*-butyldimethylsilyl
TMB	1,2,3,4 tetramethylbenzene

VIII. References

(1) Mander, L. N. *Synlett* **1991**, 134.
(2) Mander, L. N.; Hook, J. M. *Nat. Prod. Rep.* **1986**, 37.
(3) Mander, L. N. *Comrehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 8, pp 489.
(4) Collman, J. P.; Hegedus, L. S.; Norton, J. R.; Finke, R. G. *Principles and Applications of Organotransition Metal Chemistry*, 2nd ed.; University Science Books: Mill Valley, 1987.
(5) Semmelhack, M. F. *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1990; Vol. 4, p 517.
(6) Semmelhack, M. F.; Schmalz, H. G. *Tetrahedron Lett.* **1996**, *37*, 3089.
(7) Pearson, A. J.; Gontcharov, A. V.; Woodgate, P. D. *Tetrahedron Lett.* **1996**, *37*, 3087.
(8) Astruc, D. *Tetrahedron* **1983**, *39*, 4027.
(9) Pearson, A. J.; Park, J. G. *J. Org. Chem.* **1992**, *57*, 1744.
(10) Pearson, A. J.; Zhu, P. Y. *J. Am. Chem. Soc.* **1993**, *115*, 10376.
(11) Miles, W. H.; Smiley, P. M.; Brinkman, H. R. *J. Chem. Soc., Chem. Commun.* **1989**, 659.

(12) Semmelhack, M. F. *Comprehensive Organometallic Chemistry II*; Abel, E. W., Ed.; Pergamon Press: Oxford, 1995; Vol. 12, Chapters 9.1 and 9.2.
(13) Davies, S. G.; McCarthy, T. D. *Comprehensive Organometallic Chemistry II*; Abel, E. W., Ed.; Pergamon Press: Oxford, 1995; Vol. 12, Chapter 9.3.
(14) Silverthorn, W. E. *Adv. Organomet. Chem.* **1975**, *13*, 48.
(15) Evans, W. J.; Ulibarri, T. A.; Ziller, J. W. *J. Am. Chem. Soc.* **1990**, *112*, 219.
(16) Muetterties, E. L.; Bleeke, J. R.; Wucherer, E. J. *Chem. Rev.* **1982**, *82*, 499.
(17) Brauer, D. J.; Krüger, C. *Inorg. Chem.* **1977**, *16*, 884.
(18) Sweet, J. R.; Graham, W. A. G. *J . Am. Chem. Soc.* **1983**, *105*, 305.
(19) van der Heijden, H.; Orpen, A. G.; Pasman, P. *J. Chem. Soc., Chem. Commun.* **1985**, 1576.
(20) Neithamer, D. R.; Párkányi, L.; Mitchell, J. F.; Wolczanski, P. T. *J. Am. Chem. Soc.* **1988**, *110*, 4421.
(21) Choi, M. G.; Angelici, R. J. *J. Am. Chem. Soc.* **1990**, *112*, 7811.
(22) Chin, R. M.; Dong, L.; Duckett, S. B.; Partridge, M. G.; Jones, W. D.; Perutz, R. N. *J. Am. Chem. Soc.* **1993**, *115*, 7685.
(23) van der Heijden, H.; Orpen, A. G.; Pasman, P.; Boese, R.; Stanger, A.; Stellberg, P.; Shazar, A. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1475.
(24) Tagge, C. D.; Bergman, R. G. *J. Am. Chem. Soc.* **1996**, *118*, 6908.
(25) Pross, A.; Random, L. *Prog. Phys. Org. Chem.* **1981**, *13*, 1.
(26) Harman, W. D.; Lay, P. A. *Recent Advances in Osmium Chemistry*; Sykes, A. G., Ed.; Academic Press, Inc.: San Diego, 1991; Vol. 37, p 219.
(27) Lay, P. A.; Magnuson, R. H.; Taube, H. *Inorg. Synth.* **1986**, *24*, 269.
(28) Harman, W. D.; Taube, H. *J. Am. Chem. Soc.* **1987**, *109*, 1883.
(29) Harman, W. D.; Taube, H. *Inorg. Chem.* **1987**, *26*, 2917.
(30) Harman, W. D.; Sekine, M.; Taube, H. *J. Am. Chem. Soc.* **1988**, *110*, 5725.
(31) Harman, W. D.; Taube, H. *J. Am. Chem. Soc.* **1989**, *112*, 2261.
(32) Kopach, M. E.; Harman, W. D. *J. Org. Chem.* **1994**, *59*, 6506.
(33) Harman, W. D.; Taube, H. *J. Am. Chem. Soc.* **1988**, *110*, 5403.
(34) Kopach, M. E.; Gonzalez, J.; Harman, W. D. *J. Am. Chem. Soc.* **1991**, *113*, 8972.
(35) Gonzalez, J.; Sabat, M.; Harman, W. D. *J. Am. Chem. Soc.* **1993**, *115*, 8857.
(36) Kolis, S. P.; Gonzalez, J.; Bright, L. M.; Harman, W. D. *Organometallics* **1996**, *15*, 245.
(37) Kopach, M. E.; Harman, W. D.; Hipple, W. G. *J. Am. Chem. Soc.* **1992**, *114*, 1736.
(38) Kopach, M. E.; Kelsh, L. P.; Stork, K.; Harman, W. D. *J. Am. Chem. Soc.* **1993**, *115*, 5322.
(39) Kopach, M. E.; Harman, W. D. *J. Am. Chem. Soc.* **1994**, *116*, 6581.
(40) Harman, W. D.; Taube, H. *J. Am. Chem. Soc.* **1988**, *110*, 7555.
(41) Cordone, R.; Taube, H. *J. Am. Chem. Soc.* **1987**, *109*, 8101.
(42) Cordone, R.; Harman, W. D.; Taube, H. *J. Am. Chem. Soc.* **1989**, *111*, 2896.
(43) Cordone, R.; Harman, W. D.; Taube, H. *J. Am. Chem. Soc.* **1989**, *111*, 5969.
(44) Hodges, L. M.; Koontz, J. I.; Gonzalez, J.; Myers, W. H.; Harman, W. D. *J. Org. Chem.* **1993**, *58*, 4788.
(45) Hodges, L. M.; Moody, M.; Harman, W. D. *J. Am. Chem. Soc.* **1994**, *116*, 7931.
(46) Hodges, L. M.; Gonzalez, J.; Koontz, J. I.; Myers, W. H.; Harman, W. D. *J. Org. Chem.* **1995**, *60*, 2125.
(47) Gonzalez, J.; Koontz, J. I.; Myers, W. H.; Hodges, L. M.; Sabat, M.; Nilsson, K. R.; Neely, L. K.; Harman, W. D. *J. Am. Chem. Soc.* **1995**, *117*, 3405.
(48) Myers, W. H.; Sabat, M.; Harman, W. D. *J. Am. Chem. Soc.* **1991**, *113*, 6682.
(49) Myers, W. H.; Koontz, J. I.; Harman, W. D. *J. Am. Chem. Soc.* **1992**, *114*, 5684.
(50) Chen, H.; Hodges, L. M.; Liu, R.; Stevens, W. C.; Sabat, M.; Harman, W. D. *J. Am. Chem. Soc.* **1994**, *116*, 5499.
(51) Liu, R.; Chen, H.; Harman, W. D. *Organometallics* **1995**, *14*, 2861.
(52) Spera, M. L.; Harman, W. D. *Organometallics* **1995**, *14*, 1559.
(53) Call, J. T.; Hughes, K. A.; Harman, W. D.; Finn, M. G. *Inorg. Chem.* **1993**, *32*, 2123.
(54) With 1.2 equiv of anisole in methanol using Zn/Hg as the reducing agent, the mass yield = 95%, but the recovered solid contains approximately 10% of a binuclear complex.
(55) Sekine, M.; Harman, W. D.; Taube, H. *Inorg. Chem.* **1988**, *27*, 3604.
(56) Harman, W. D.; Fairlie, D. P.; Taube, H. *J. Am. Chem. Soc.* **1986**, *108*, 8223.
(57) Harman, W. D.; Sekine, M.; Taube, H. *J. Am. Chem. Soc.* **1988**, *110*, 2439.
(58) Elliott, M. G.; Shepherd, R. E. *Inorg. Chem.* **1988**, *27*, 3332.
(59) Elliott, M. G.; Zhang, S.; Shepherd, R. E. *Inorg. Chem.* **1989**, *28*, 3036.
(60) Harman, W. D.; Dobson, J. C.; Taube, H. *J. Am. Chem. Soc.* **1989**, *111*, 3061.
(61) Harman, W. D.; Wishart, J. F.; Taube, H. *Inorg. Chem.* **1989**, *28*, 2411.
(62) Harman, W. D. Ph.D. Dissertation, Stanford University, 1987.
(63) Winemiller, M. D.; Kelsch, B. A.; Sabat, M.; Harman, W. D. *Organometallics* **1997**, in press.
(64) Spera, M. L.; Harman, W. D. *J. Am. Chem. Soc.* **1997**, in press.
(65) In Figure 3, for cases where the linkage isomerization is not symmetrical, NMR data indicate an equilibrium constant near unity.
(66) Shiner, C. S.; Vorndam, P. E.; Kass, S. R. *J. Am. Chem. Soc.* **1986**, *108*, 5699.
(67) Catalán, J.; de Paz, J. L. G.; Sánchez-Cabezudo, M.; Elguero, J. *Bull. Soc. Chim. Fr.* **1966**, 429.
(68) Karpfen, A.; Schuster, P.; Berner, H. *J. Org. Chem.* **1979**, *44*, 374.
(69) Lloyd, D.; Marshall, D. R. *Chem. Ind. (London)* **1972**, 335.
(70) Kopach, M. E. Ph.D. Dissertation, University of Virginia, 1995.
(71) Winemiller, M. D.; Kopach, M. E.; Harman, W. D. *J. Am. Chem. Soc.* **1997**, *119*, 2096.
(72) Nagaoka, T.; Berinstein, D.; Griller, D.; Wayner, D. M. *J. Org. Chem.* **1990**, *55*, 3707.
(73) Cook, A. G. *Enamines, Synthesis, Structure and Reactions*; Marcel Dekker, Inc.: New York, 1988.
(74) Chadwick, D. J. *Pyrroles: Part One.*; Jones, R. A., Ed.; Wiley: New York, 1990.
(75) Sen, J.; Taube, H. *Acta Chem. Scand. A* **1979**, *33*, 125.
(76) Ford, P.; Rudd, D. P.; Gaunder, R.; Taube, H. *J. Am. Chem. Soc.* **1968**, *90*, 3694.
(77) Isied, S. S.; Taube, H. *Inorg. Chem.* **1974**, *13*, 2545.
(78) Brown, G.; Sutton, J.; Taube, H. *J. Am. Chem. Soc.* **1978**, *100*, 2767.
(79) Kolis, S. P.; Kopach, M. E.; Liu, R.; Harman, W. D. *J. Org. Chem.* **1997**, *62*, 130.
(80) Marx, J. C.; Young-Sook, P. H. *J. Org. Chem.* **1988**, *53*, 2866.
(81) Kolis, S. P.; Liu, R.; Kopach, M. E.; Chordia, M. D.; Harman, W. D. Manuscript in preparation. See reference 70.
(82) Harman, W. D.; Taube, H. *J. Am. Chem. Soc.* **1988**, *110*, 7906.
(83) Hodges, L. M. Ph. D Dissertation, University of Virginia, 1995.
(84) Contrary to our original belief, 2,5-dimethylpyrrole and 2-ethylpyrrole complexes do not add water across C(2) and C(3). Rather, a 2*H*-pyrrole isomer is formed in water.
(85) Hodges, L. M.; Spera, M. L.; Moody, M.; Harman, W. D. *J. Am. Chem. Soc.* **1996**, *118*, 7117.
(86) In the Diels−Alder reactions of cyclopentadiene, an *endo* transition state leads to an *endo*-substituted product. In the osmium-promoted dipolar cycloadditions, an *endo* transition state leads to an *exo*-substituted product.
(87) Lakhlifi, T.; Sedqui, A.; Fathi, T.; Laude, B.; Robert, J. F. *Can. J. Chem.* **1994**, *72*, 1417.
(88) Chen, Z.; Trudell, M. L. *Chem. Rev.* **1996**, *96*, 1179.
(89) Chen, H. C.; Harman, W. D. *J. Am. Chem. Soc.* **1996**, *118*, 5672.
(90) Chen, H. C. Ph.D. Dissertation, University of Virginia, 1996.
(91) Spera, M. L.; Chin, R. M.; Winemiller, M. D.; Lopez, K.; Sabat, M.; Harman, W. D. *Organometallics* **1996**, *15*, 5447.
(92) By "π base", the author refers to a metal system with a single available coordination site that has a high propensity to back-bond.

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