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Synthetic applications of the dearomatization agent pentaammineosmium(II)

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1. Introduction

With the advent of combinatorial methods and high throughput screening procedures to identify potential new pharmaceuticals, new synthetic methods that allow the rapid, atom efficient and stereospecific synthesis of new molecules are in high demand. Arenes and aromatic heterocycles are, in principle, attractive as precursors to functionalized alicyclic compounds. These materials are widely available, readily derivatized, and most significantly, constitute cyclic skeletons composed almost entirely of unsaturated carbons. Unfortunately, the high degree of aromatic

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Abbreviations: [Os]=Os(II)$(NH_3)_5$; HOTf=Trifluoromethanesulfonic acid (triflic acid); OTf=Trifluoromethanesulfonate; DMA=*N*,*N*-dimethylacetamide; DME=1,2-dimethoxyethane; MVK=Methyl vinyl ketone; EVK=Ethyl vinyl ketone; DIEA=Diisopropylethyl amine (Hünig's base); TBAC= tetra-*n*-Butylammonium cyanoborohydride; TBAB=tetra-*n*-Butylammonium borohydride; CAN=$Ce(NO_3)_6(NH_4)_2$; DDQ=2,3-Dichloro-5,6-dicyanoquinone; NMM=*N*-Methylmaleimide; DEAD=Diethyl azodicarboxylate; SKA=1-Methoxy-2-methyl-1-(trimethylsiloxy)propene; DMM= Dimethoxymethane; MMRC=Michael–Michael-Ring-Closure.

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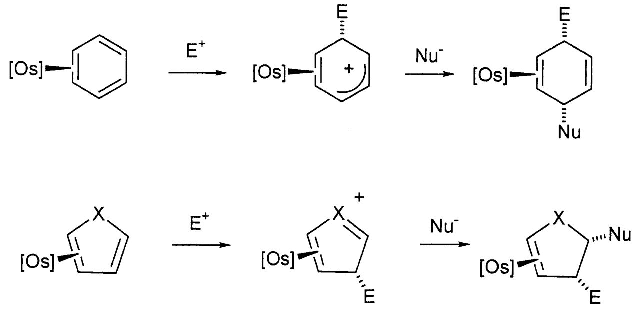
stabilization in these molecules renders them much more prone to substitution rather than controlled addition reactions.

The η^2-coordination of aromatic molecules by the electron-rich, π-basic metal fragment $\{Os(NH_3)_5\}^{2+}$ dramatically alters the normal mode of reactivity for these molecules.[1] Such coordination, stabilized by π-donation from the metal fragment into π^* orbitals of the bound aromatic, effectively removes one olefinic bond from conjugation rendering it dearomatized. This strong back-bonding interaction not only disrupts the ligand π-system, but further activates the uncoordinated portion of the organic ligand so as to make it reactive toward electrophiles. Accordingly, a variety of transformations may be performed on bound aromatics that are otherwise difficult to accomplish employing more traditional approaches. Over the past 12 years, we have been actively engaged in exploring the scope of this latent reactivity and demonstrating its synthetic potential.



The employment of π-basic metal fragments to effect dearomatization compliments current techniques that have been developed. Certainly, the most prominent of these methods is the dissolving metal reaction known as the Birch reduction. This powerful technique has been employed in numerous synthetic strategies and has been extensively studied and reviewed.[2–7] Photochemical activation has also been shown to be a powerful approach and has been used to construct complex polycyclic products rapidly and efficiently from aromatic precursors.[8,9] Also, the incorporation of the electron-withdrawing oxazolidinone ring onto naphthalene has been shown to activate the aromatic ring toward addition of alkyllithium reagents with concurrent dearomatization.[10] Finally, the hexahapto coordination by an electron-deficient transition-metal fragment,[11,12] such as $Cr(CO)_3$,[13–19] $CpRu^+$,[20] $CpFe^+$,[21] or $Mn(CO)_3{}^+$,[22] has been used extensively to activate arenes toward reactions with nucleophiles by withdrawing electron-density from the arene π-system, to ultimately yield dearomatized products.

The following review focuses specifically on the synthetic applications of the $\{Os(NH_3)_5\}^{2+}$ system with an emphasis on the variety of transformations that may be performed on the unbound portion of the arene or aromatic heterocycle. Preparation of aromatic complexes of the type $[Os(NH_3)_5(\eta^2\text{-arene})]^{2+}$, binding selectivities, and basic reactivity of these have been reviewed so only a brief introduction to these topics is included.[23,24]

2. Preparation of $[Os(NH_3)_5(\eta^2\text{-aromatic})]^{2+}$ complexes

Pentaammineosmium(II) forms thermally stable complexes with a variety of aromatic compounds including benzenes, anisoles, anilines, phenols, furans, pyrroles, and thiophenes.[23] The complexes are readily prepared through the reduction of the commercially available Os(III) precursor $[Os(NH_3)_5(OTf)](OTf)_2$ in an excess (1.5–20 equiv.) of the aromatic compound. Magnesium or Zn/Hg may be used as the reducing agent in DMA/DME or methanol, respectively. The complexes are typically isolated by removing the reductant by filtration then adding the filtrate to a stirring solution of Et_2O/CH_2Cl_2 and collecting the resulting precipitate. Excess ligand may be recovered and recycled if necessary. These η^2 complexes of aromatic compounds are stable in solution under inert atmosphere (argon or nitrogen), and the olefin complexes produced from them are usually stable enough to be manipulated in air.

3. Binding selectivity

The regioselectivity of coordination to an aromatic system generally arises from minimizing the disruption to the conjugated system. For example, pentaammineosmium(II) binds anisole preferentially across C(5)–C(6) leaving the uncoordinated portion of the arene in linear conjugation with the methoxy substituent. Similarly, furan and pyrrole are bound primarily across C(4)–C(5) so that the uncoordinated portion of the heterocycle resembles a vinyl ether and an enamine, respectively.

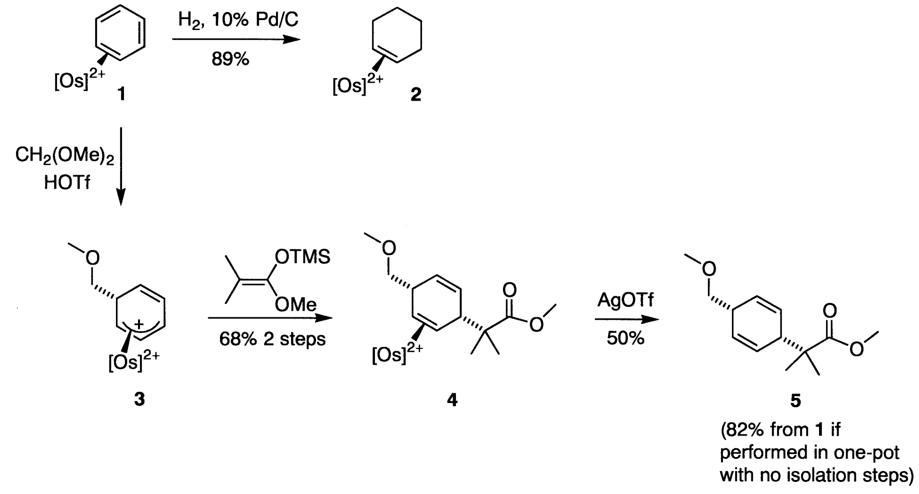
4. Arenes

4.1. Benzene

Benzene may be regarded as the quintessential example of an aromatic compound. Its perfect symmetry, in which the π-electron density is equally distributed among all six carbons in the cyclic skeleton, endows the molecule with exceptionally high stability and inertness.[25] Therefore, effecting the dearomatization of benzene requires overcoming the resonance energy associated with the delocalized π-system, a stabilizing interaction estimated at 36 kcal/mol.[26] This has been accomplished through the employment of harsh conditions including high temperatures, extreme pressures, extended reaction times, and strong Lewis acids.[27]

The simplest transformation that may be facilitated through the complexation of benzene to pentaammineosmium(II) is hydrogenation (Scheme 1).[28] The reaction proceeds under mild conditions (H_2/Pd–C) to produce cyclohexene following oxidative decomplexation of the osmium moiety. Significantly, the metal fragment may be regarded as serving a dual purpose, initially as dearomatization agent and subsequently as a protecting group for the olefin.

Tandem electrophilic/nucleophilic addition reactions to the η^2-benzene complex **1** results in the formation of *p*-disubstituted-1,4-cyclohexadiene derivatives such as **5**. For example, the addition of dimethylacetal to **1**, promoted by



Scheme 1.

HOTf, results in the formation of the benzenium[29] intermediate **3** which may be trapped by the addition of silylketene acetal to form **4**. The stereoselectivity of the addition arises from the approach of both the electrophile and nucleophile to the benzene face opposite metal coordination. Although the high acidity of **3** limits the scope of this reaction owing to competing deprotonation and rearomatization, a number of cyclohexadiene derivatives may be prepared from benzene in moderate yield with a high degree of regio- and stereocontrol.[30]

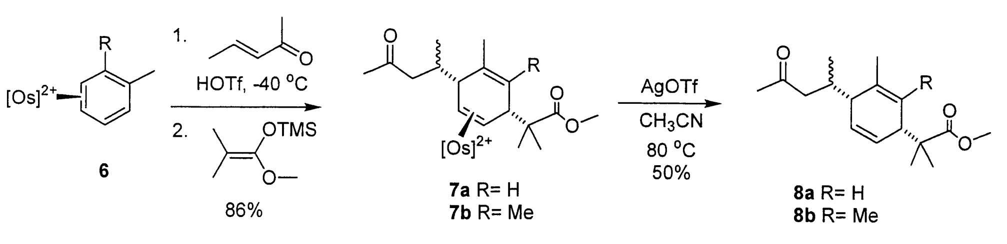
4.2. Toluene and xylene

Complexes of toluene, xylene, and other alkyl substituted derivatives show slightly increased reactivity over the benzene complex owing to the increased stability of the resulting arenium intermediates via hyperconjugation. In addition to dimethoxymethane, electrophiles such as methylvinyl ketone (MVK) or 3-pentene-2-one may be used, resulting in the formation of highly functionalized 1,4-cyclohexadiene derivatives such as **8** with high regio- and stereocontrol (Scheme 2).[30]

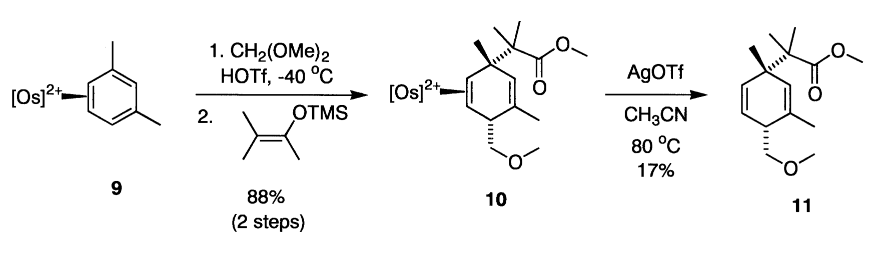
When a 3-substituted toluene derivative such as *m*-xylene (complex **9**) is used as the substrate (Scheme 3), the tandem addition sequence results in the formation of **11** containing a new quaternary carbon center as a consequence of the pentaammineosmium fragment remaining coordinated to the less sterically hindered side of the arenium, away from the *m*-alkyl substituent. Addition of SKA followed by oxidation with AgOTf facilitates demetallation and provides the substituted cyclohexadiene product **11** in 15% overall yield.[31] Although currently unexplored, chemoselective elaboration of the more substituted double bond should be possible as the pentaammineosmium fragment may serve as a protecting group for the less hindered olefin.

4.3. Naphthalene

Upon complexation, the delocalized π-electron density of naphthalene is perturbed so that only the unbound ring remains aromatic and electrophilic additions, therefore, occur exclusively to the bound ring (see **12** Scheme 4). The regioselectivity of the addition is governed by the thermodynamic preference for the metal to coordinate naphthalene across C(1)–C(2), rendering C(4) the most



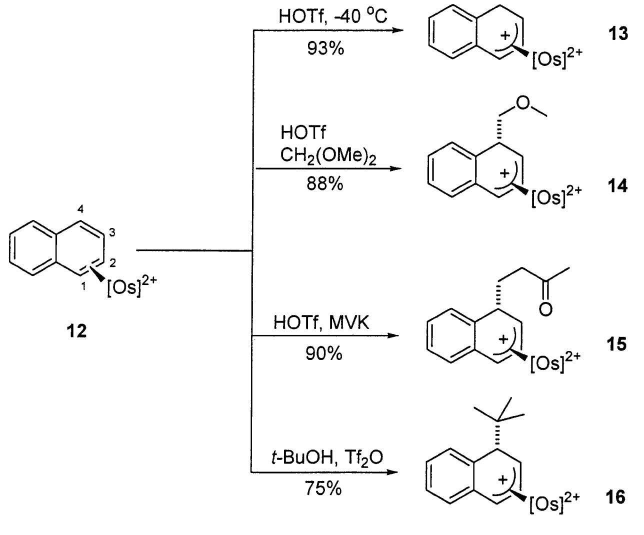
Scheme 2.



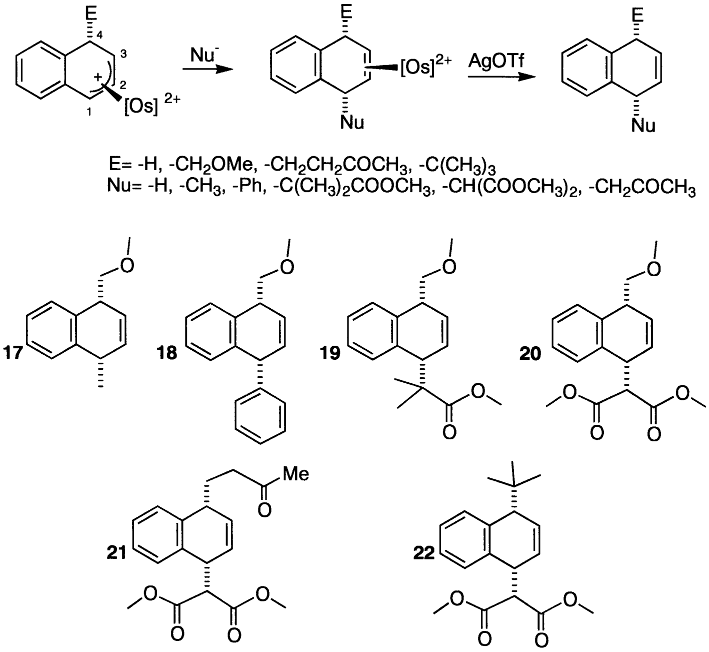
Scheme 3.

nucleophilic position.[32] A wide variety of electrophiles have been added including H^+ (HOTf), acetals (such as dimethoxy methane), Michael acceptors (such as MVK), and tertiary carbocations (such as *t*-BuOH added in the presence of triflic anhydride) generating the 1*H*-naphthalenium intermediates **13**–**16**.[33] These complexes are remarkably stable, persisting for days in solution at −40°C, and have been characterized by ^1H- and ^{13}C NMR. However, at ambient temperature, decomposition ensues, resulting in an intractable mixture of products.

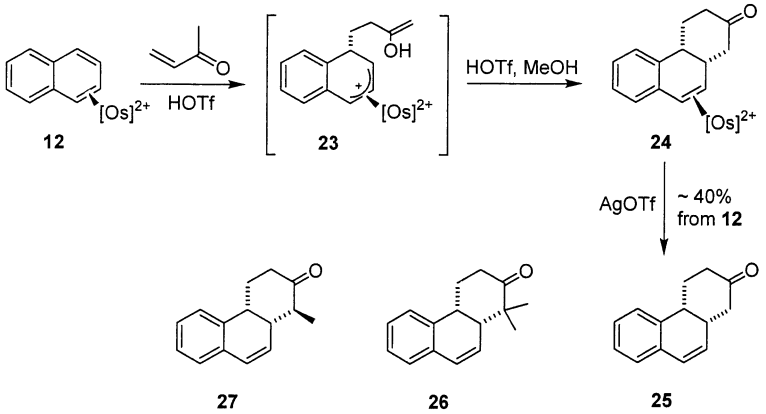
The naphthalenium complexes **13**–**16** will react with a variety of nucleophiles, (Scheme 5) such as hydride, silylketene acetals, enolates (generated from ketones and esters), alkylzincs (dimethylzinc), and arylcuprates (Ph_2CuLi), leading to the formation of *cis*-disubstituted dihydronaphthalene complexes. Interestingly, only 1,4-disubstituted dihydronaphthalene products are recovered following this sequence. This preference for 1,4-addition over 1,2-addition was rationalized by postulating a greater buildup of positive



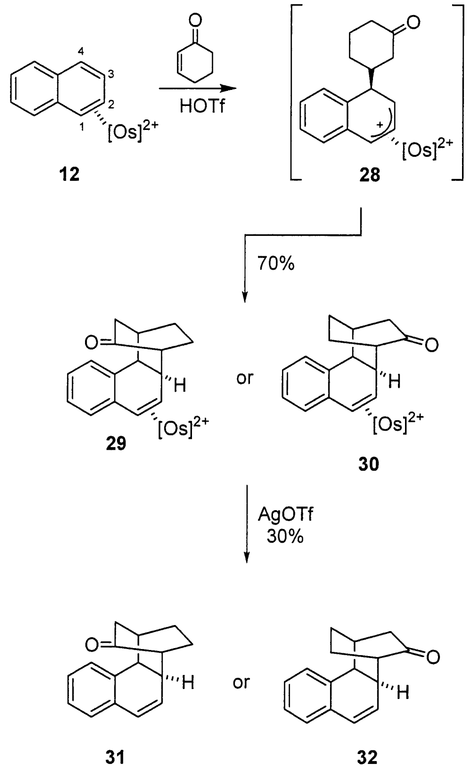
Scheme 4.



Scheme 5.



Scheme 6.



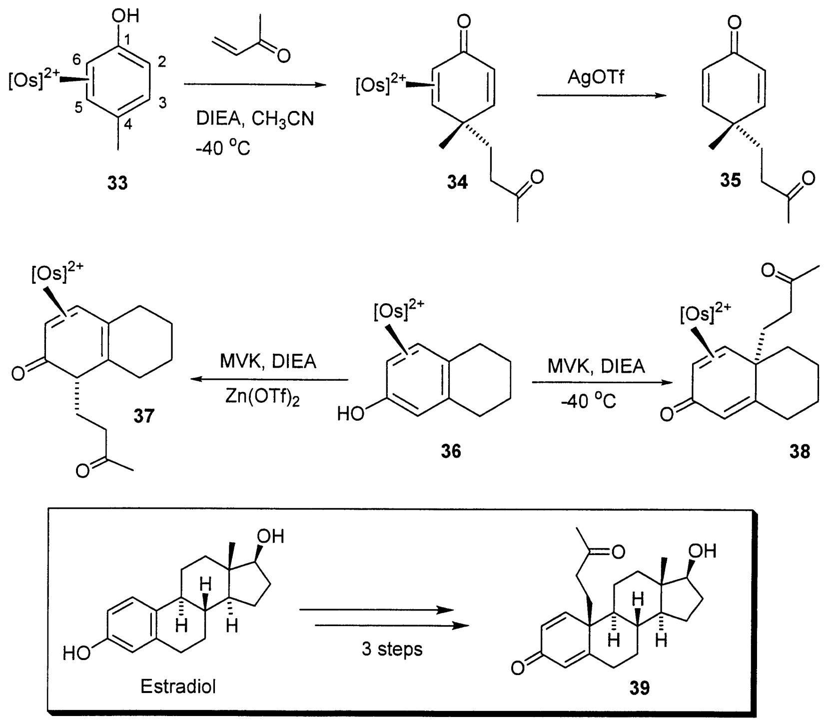
Scheme 7.

charge at the benzylic position, C(1), than at the C(3) position. Nucleophiles, therefore, add predominantly at this position.[33]

Decomplexation (AgOTf) under mildly basic conditions results in isolation of the demetallated *cis*-1,4-disubstituted dihydronaphthalenes **17–22** in moderate to high overall yields (40–77% from naphthalene). Significantly, the synthetic sequence requires only one purification step involving chromatography (after decomplexation), as the intermediate complexes may simply be precipitated into Et_2O/CH_2Cl_2 to remove organic reagents. In addition, the entire sequence of complexation, tandem addition, and decomplexation may be performed outside the glove-box using bench-top conditions.[33]

The synthesis of the tricyclic hydrophenanthrones **25–27** demonstrates the versatility of the methodology (Scheme 6). The polycyclic compounds were prepared through the addition of the appropriate enone in Michael fashion to **12** in the presence of methanolic HOTf. Under equilibrating conditions, the enol is generated which adds to the naphthalenium through intramolecular nucleophilic ring closure. In contrast to the 1,4-regioselectivity observed for intermolecular tandem additions, the intramolecular variation provides the 1,2-dihydronaphthalene derivatives as the sole products. This cyclization results in a *cis*-fused ring juncture arising from both the electrophilic and nucleophilic additions occurring to the naphthalene face opposite metal coordination. The metal-bound tricyclic complexes (such as **24**) may be demetallated (AgOTf) to provide the hexahydrophenanthrones in moderate overall yield (typically ~40%).[34]

When a cyclic enone, such as cyclohexenone, is used as the electrophile/nucleophile (Scheme 7), an unprecedented cyclization occurs to form a bridged polycyclic complex identified as either **29** or **30** in 70% yield. This product was isolated as a single diastereomer. However, the exact stereochemistry could not be determined based on the



Scheme 8.

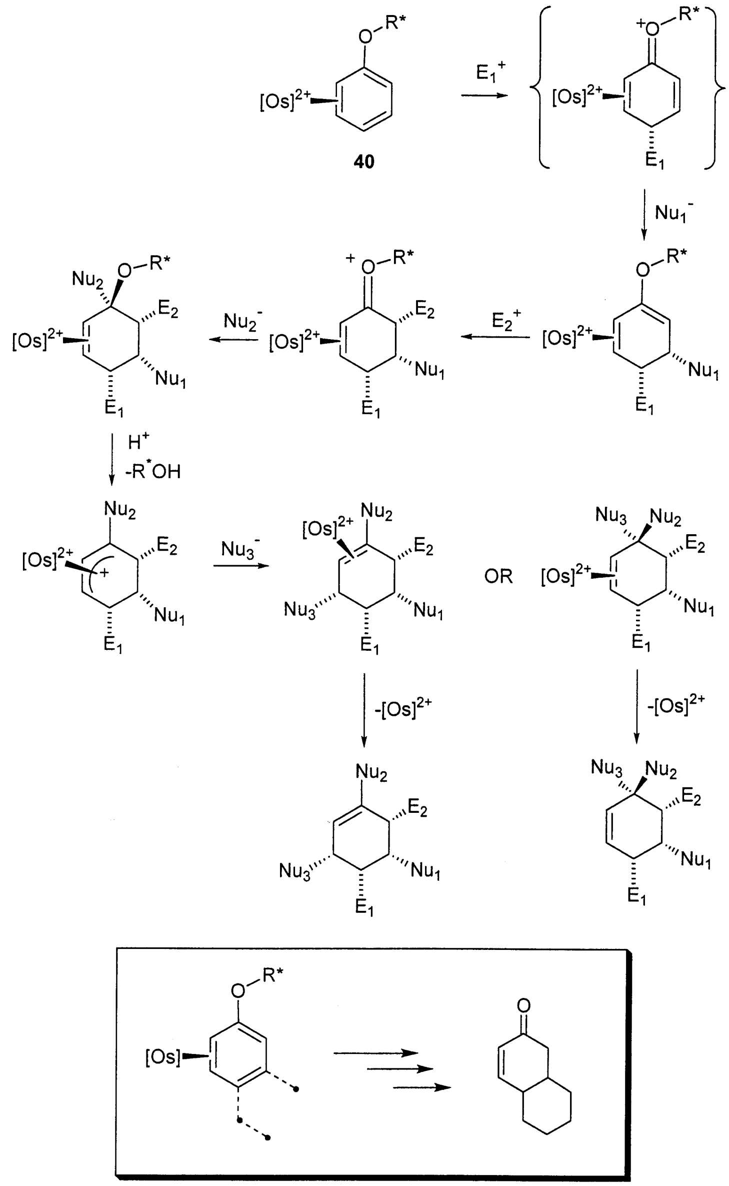


Figure 1. Nearly every position of anisole, including the benzylic and homobenzylic carbons, may be elaborated through either tandem electrophilic/nucleophilic addition reactions or Diels–Alder cycloaddition. R^*=Me or chiral auxiliary.

spectroscopic data that was collected. Accordingly, demetallation afforded a single product, either **31** or **32**, in 30% yield from naphthalene.[34]

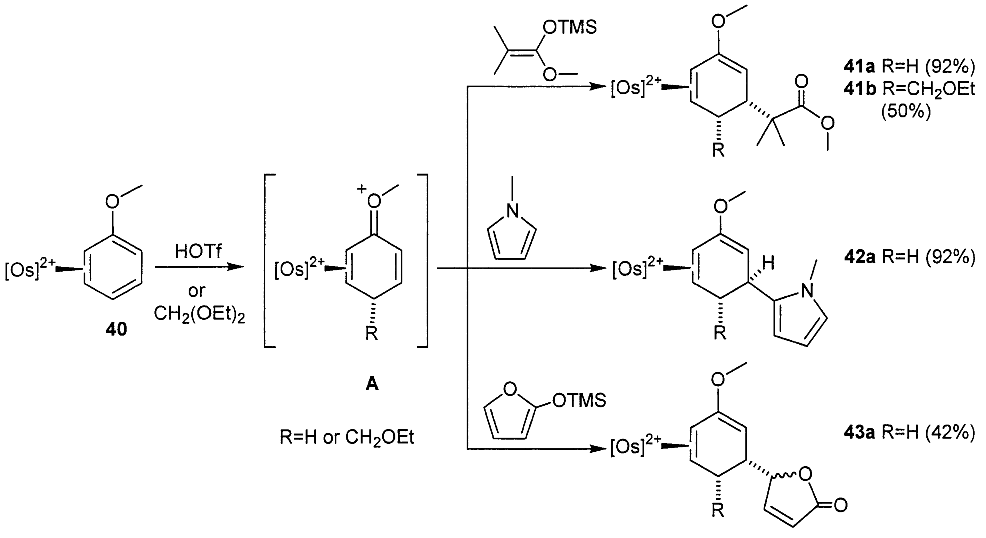
4.4. Phenols

Pentaammineosmium(II) complexes of phenol and substituted phenols display pronounced reactivity toward electrophiles under exceptionally mild conditions (Scheme 8).[35] When an amine base (DIEA) alone is employed as a promoter and the reaction is performed under kinetic conditions (−40°C, the *p*-cresol complex **33** undergoes a Michael addition with MVK to yield the complexed dienone **34** with concomitant formation of the quarternary center at C(4). However, when the reaction is performed under thermodynamic conditions [20°C or with the addition of the co-catalyst $Zn(OTf_2)$], the regioselectivity changes so that only the *ortho*-substituted product **37** is recovered. Decomplexation (AgOTf or O_2) provides the metal-free products in moderate overall yield. This strategy was employed in the stereoselective C(10) alkylation of β-estradiol to provide **39**.[36]

Performing a tandem electrophilic/nucleophilic addition sequence on complexed phenols, however, has proven to be difficult. The coordinated dienone that results after addition of the electrophile is much less reactive than organic dienones (vide infra). This deactivation results from the significant electron donation from the metal into the π^* orbital of the enone, analogous to the decreased reactivity of acrylamide as an electrophile when compared with MVK.

4.5. Anisoles

The η^2-anisole complexes of pentaammineosmium(II)



Scheme 9.

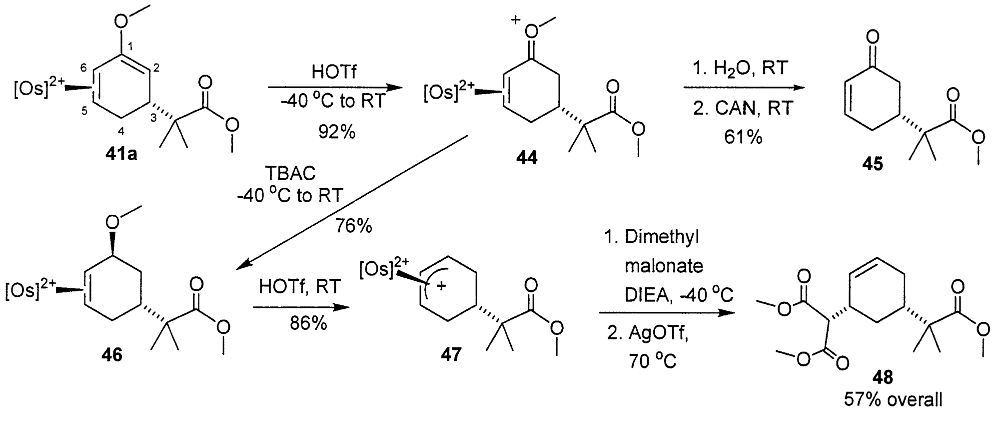
have been the most extensively investigated of the dihapto-coordinated arene complexes owing to the rich variety of transformations that are facilitated by complexation. Through tandem electrophilic/nucleophilic additions and Diels–Alder cycloadditions, up to 5 carbons of the original aromatic ring as well as the benzylic and homobenzylic positions may be activated toward reaction. Fig. 1 depicts the activation and subsequent elaboration steps in the functionalization of the anisole nucleus through tandem electrophilic/nucleophilic additions. The complex is significantly more electron-rich than the complexes of toluene and xylene and therefore undergoes addition reactions with a much broader range of electrophiles. Likewise, the anisolium complex that is formed following electrophilic addition is significantly more amenable to nucleophilic attack than the corresponding phenol-derived dienone complexes.

The anisole complex reacts with a variety of electrophiles, including H$^+$ (HOTf), acetals, ketals, Michael acceptors, and carboxylic anhydrides. These complexes are also highly robust and tolerate a variety of Lewis acids including BF$_3$·OEt$_2$, silyl-triflates, and various metal salts [Sn(II), Sn(IV), Zn(II), Sc(III), Li(I)].

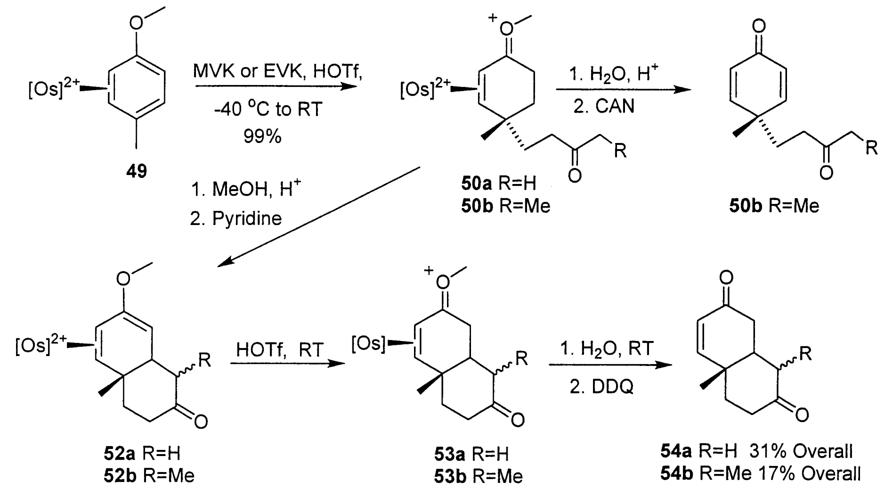
A variety of stereodefined cyclohexene and cyclohexenone derivatives may be prepared rapidly and efficiently from the anisole complex through a sequence of tandem electrophilic/nucleophilic additions. The anisolium complex (**A** in Scheme 9) is generated following protonation or acetal addition, which occurs exclusively to the anisole face opposite metal coordination. The complex is unstable at ambient temperature but may be manipulated at −40°C and has been characterized by low temperature ^{1}H- and ^{13}C NMR spectroscopy.[37]

Although the anisolium is stabilized by π-donation from both the electron-rich metal fragment and from the methoxy substituent, the complex is sufficiently reactive so that a variety of nucleophiles may be added. These include hydride or carbon nucleophiles such as SKA, siloxyfuran, and *N*-methylpyrrole (Scheme 9). The additions occur stereoselectively to the face of the anisolium opposite metal coordination and regioselectively to the meta position C(3) when carbon nucleophiles are employed. Hard nucleophiles such as hydride (NaBH$_4$ or Li9BBNH) add preferentially to the oxonium carbon C(1).[38] Nucleophiles that fail to react with the anisolium complex include furans, β-diketones, allylsilanes, and allylstannanes.

Cyclohexene or cyclohexenone derivatives may be

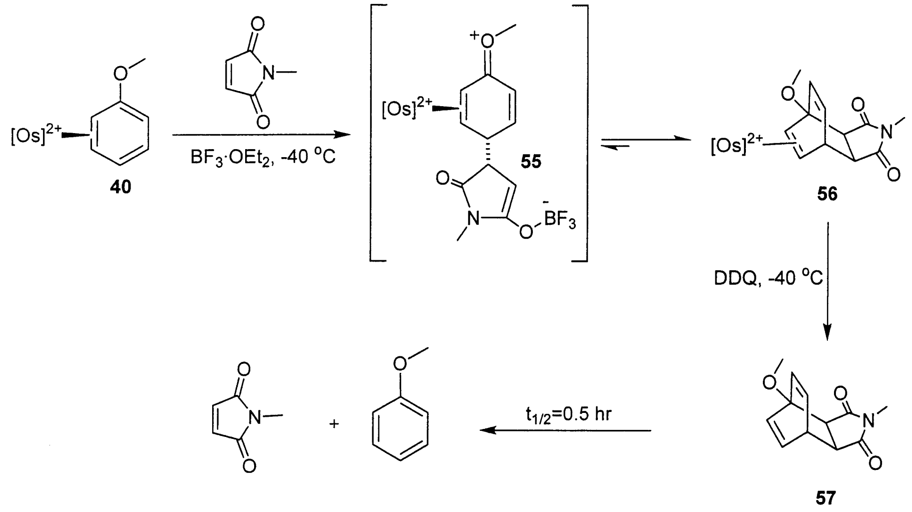


Scheme 10.



Scheme 11.

synthesized through further chemical manipulations of the vinyl ether complexes **41–43**. These compounds are reactive toward acid (HOTf), generating the relatively stable 2*H*-oxonium intermediates which may be isolated as triflate salts (Scheme 10). 2*H*-Oxonium complexes such as **44** are unreactive toward carbon nucleophiles but are susceptible to hydride addition to yield complexed allyl ethers (such as **46**) or to hydrolysis to afford substituted cyclohexenones (e.g. **45**, isolated after demetallation). The allyl ether complexes are unstable to acid and undergo elimination of the methoxy substituent to afford η^3-allyl species such as **47**. This complex is susceptible to



Scheme 12.

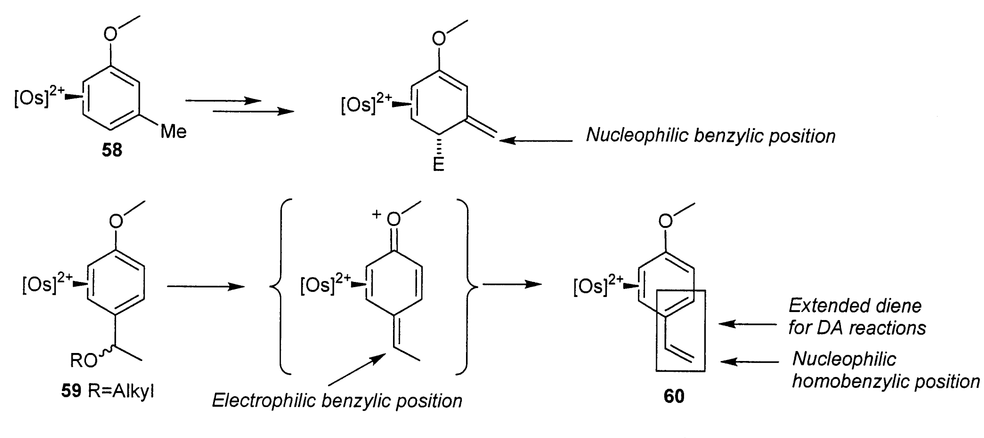
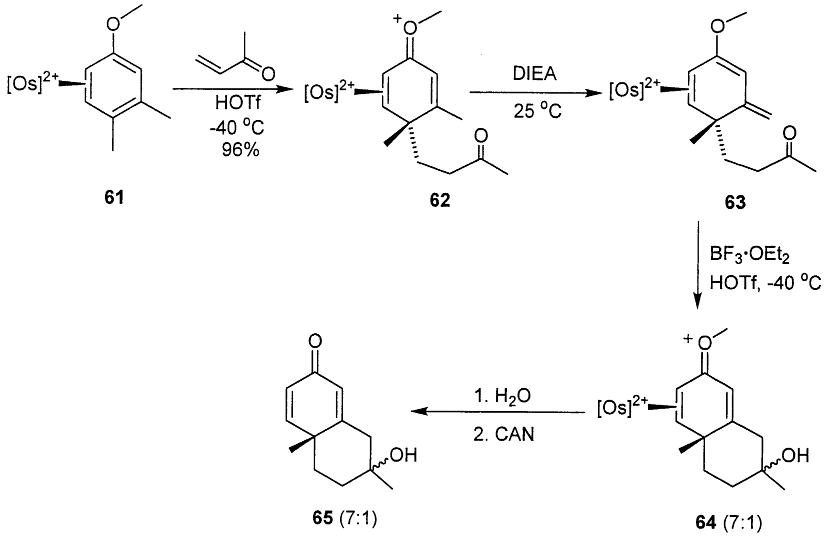
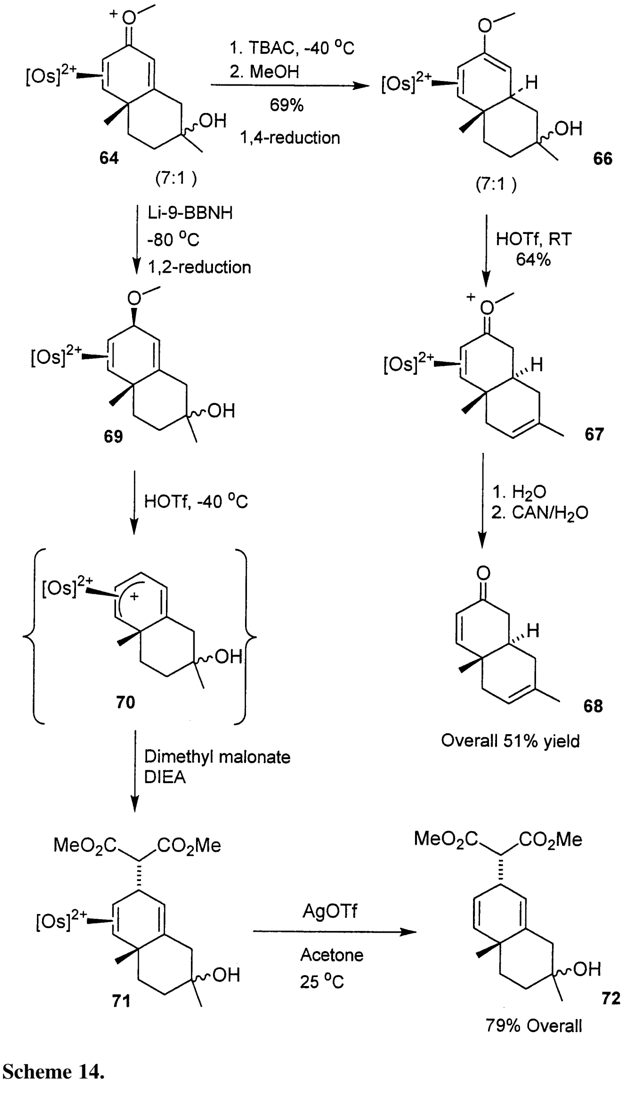


Figure 2. The benzylic and homobenzylic positions of substituted anisoles are activated through η^2-coordination by pentaammineosmium(II).



Scheme 13.

nucleophilic attack affording the *cis*-1,3-disubstituted cyclohexene product **48** in moderate overall yield. As an application of this methodology, enediones **54a** and **54b** have been prepared from *p*-methylanisole and MVK or MEK, respectively, through a tandem Michael–Michael ring closure sequence (Scheme 11).[37]



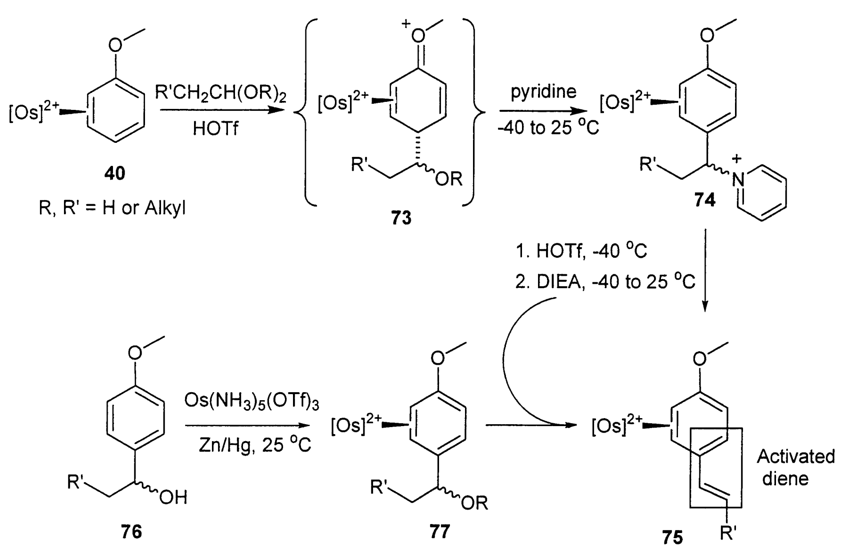
Scheme 14.

The η^2-anisole complex **40** will also undergo a formal [4+2] cycloaddition with *N*-methylmaleimide (Scheme 12) at low temperature in the presence of $BF_3{\cdot}OEt_2$ to form the complexed bicyclo[2.2.2]octadiene product **56** as a single diastereomer. Although it was discovered that the reaction proceeds through an initial Michael addition followed by nucleophilic ring closure, the high stereoselectivity was attributed to a Diels–Alder-like transition state yielding the product with exclusively *endo*-selectivity with respect to the unbound diene portion of the anisole. Decomplexation with DDQ at low temperature (−40°C) initially yields the methoxy-bicyclo[2.2.2]octadiene **57** which undergoes retrocycloaddition to afford only anisole and NMM.

The benzylic and homobenzylic positions of substituted anisole are also activated through complexation with pentaammineosmium(II). The observed reactivity is depicted in Fig. 2. These extended modes of reactivity have been exploited in the synthesis of complex polycyclic ring systems through Diels–Alder reactions and Michael–Michael or Michael–aldol ring closure sequences.[39]

For example, the *m*-methylanisolium complex **62**, prepared through initial Michael addition of **61** with MVK, may be regioselectively deprotonated at the benzylic *m*-methyl substituent, generating **63** which contains the exocyclic methylene functionality (Scheme 13). The benzylic methylene reacts chemically as an extended vinyl ether and subsequently cyclizes with the pendant oxobutyl group in aldol fashion in the presence of $BF_3{\cdot}OEt_2$ at low temperature. Subsequent hydrolysis followed by decomplexation (CAN) yields the functionalized bicyclic dienone **65**.[39]

Complex decalin systems have been prepared through further chemical manipulation of the complexed oxonium intermediate **64** (Scheme 14). During these studies, an interesting selectivity in reduction was observed. When the relatively weak hydride reagent TBAC was employed,

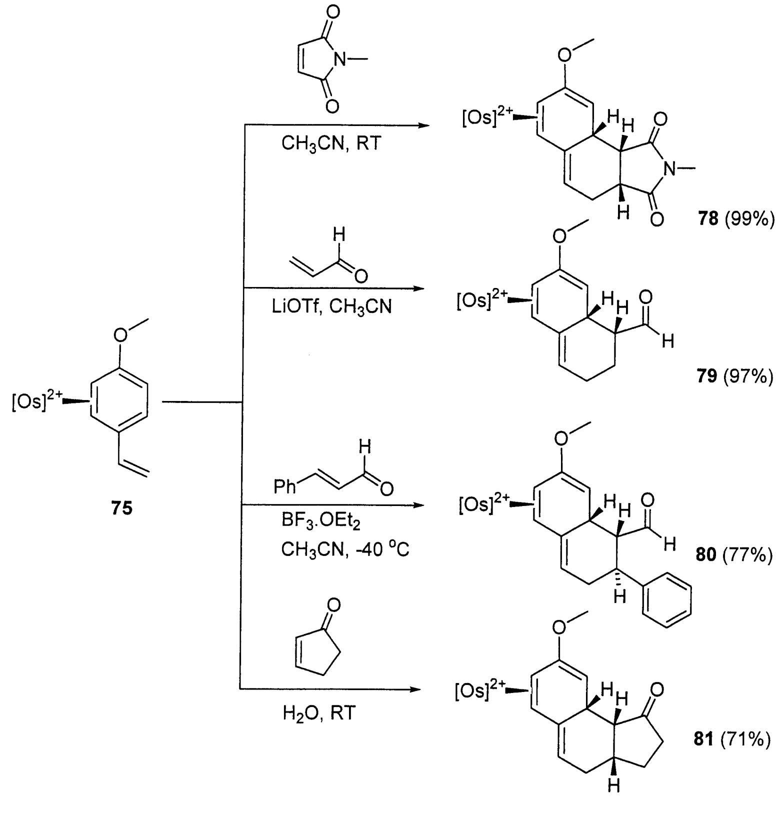


Scheme 15.

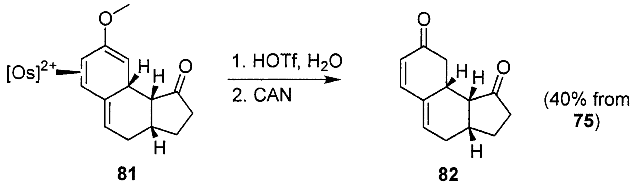
the oxonium was reduced to the *trans*-decalin product **66** through regioselective 1,4-addition. Subsequent protonation (**67**) and hydrolysis followed by oxidation of the metal center afforded the functionalized *trans*-decalone **68** in 51% overall yield. Likewise, when lithium-9-BBN was used as a hydride source, the reduction occurred in an exclusively 1,2-fashion, providing access to the allyl-ether complex **69**. Acid induced formation of the η^3-allyl complex (**70**), addition of dimethyl malonate (**71**), and decomplexation (AgOTf) provided **72** in overall 79% yield.[39]

4.6. 4-Methoxystyrenes

A complementary approach to synthesizing decalins from η^2-arenes is through a Diels–Alder reaction of styrene and a dienophile. Although the direct complexation of styrene derivatives by pentaammineosmium(II) is not a useful synthetic procedure for preparing the η^2-arene complexes owing to the generally poor kinetic regioselectivity of binding, exclusively ring-bound η^2-styrene complexes have been prepared by building the pendant vinyl moiety onto the arene after complexation.[40]



Scheme 16.



Scheme 17.

Scheme 15 outlines the two approaches that have been developed for the preparation of the 4-methoxystyrene complex **75**. Direct elaboration of the anisole complex **40** through a sequence of acetal addition (**73**), deprotonation/pyridine addition (**74**), and elimination/rearomatization yields **75**. Alternatively, the benzyl alcohol derivative **76** may be directly complexed (**77**) and then subjected to the elimination/rearomatization conditions.[40]

The styrene complex **75** displays unprecedented reactivity when employed as the diene component in Diels–Alder reactions (Scheme 16). The cycloadditions proceed under mild conditions with a variety of dienophiles, including NMM (**78**), acrolein (**79**), 4-phenylbutenone (**80**), and cyclopentenone (**81**). The cycloadduct complexes are stable in solution at ambient temperature and may be isolated by simple precipitation into stirring Et_2O/CH_2Cl_2. Additionally, neither cycloreversion nor double Diels–Alder products are observed, indicative of the stabilizing effects imparted through coordination of the pentaammineosmium(II) fragment to the resulting methoxydiene moiety of the cycloadducts. The stereochemistry for these reactions was assigned based on NOE studies and is consistent with the cycloadditions occurring to the styrene face opposite metal coordination and with exclusively *endo*-selectivity (de>95%).

Although direct oxidation of the cycloadduct complexes led to hydrolysis and rearomatization producing benzyl alcohol derivatives, metal-free dearomatized cycloadducts may be isolated if the vinyl ether is first transformed to a more acid-stable functionality. For example, protonation of **81** with HOTf followed by hydrolysis allows for the preparation of the dienone **82** (Scheme 17).[40]

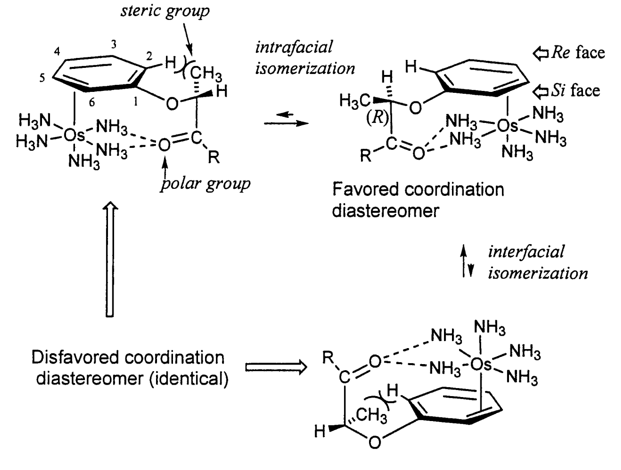
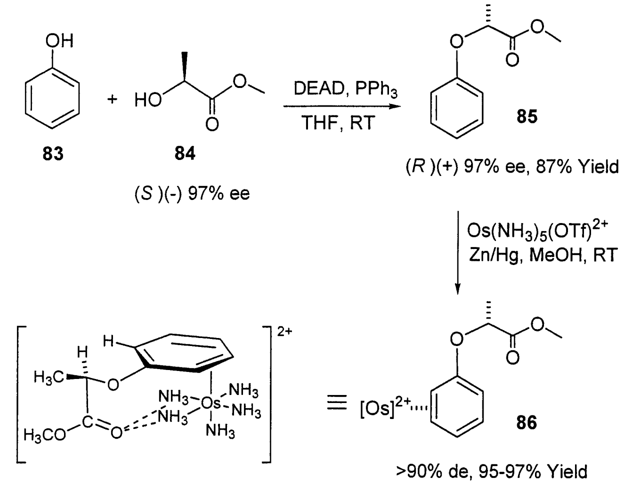


Figure 3. The key interactions considered in preparing asymmetric anisole derivatives.



Scheme 18.

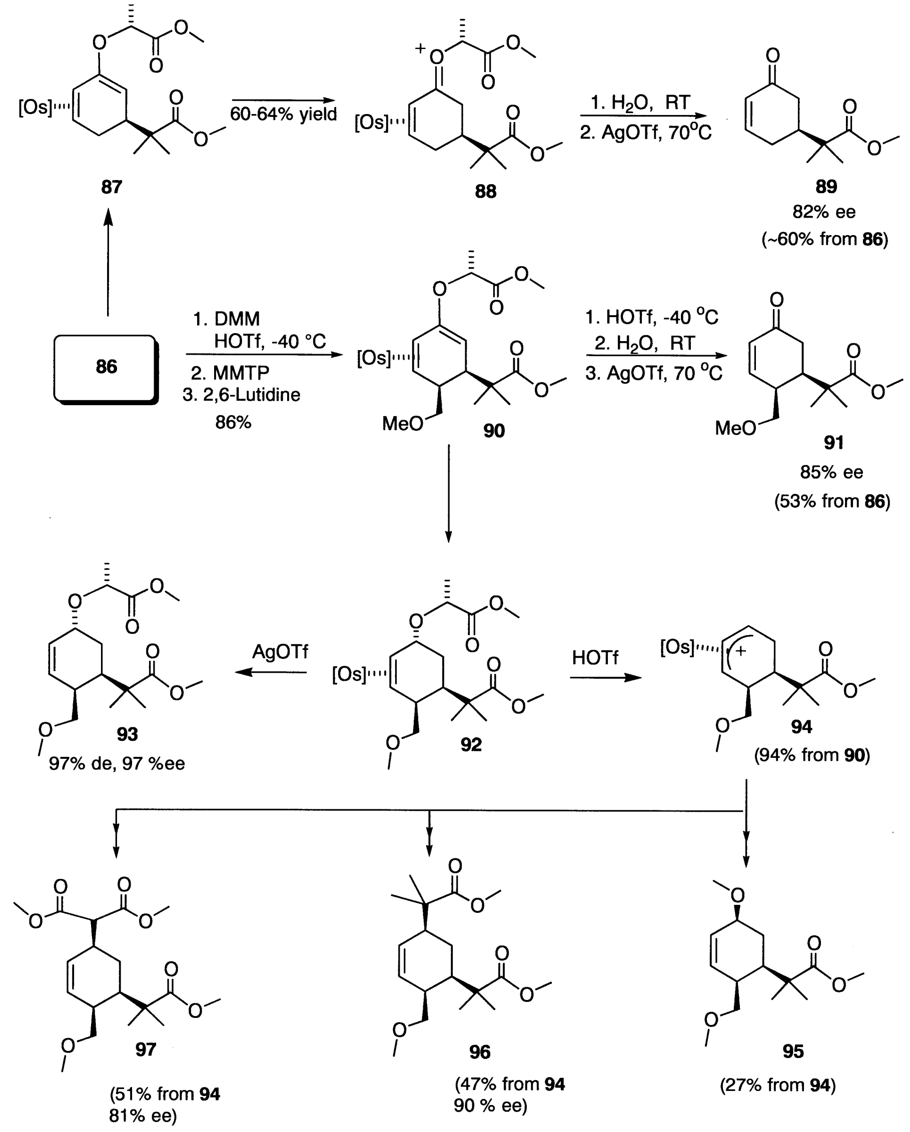
4.7. Chiral anisole derivatives

Recently, asymmetric dearomatization reactions have been achieved through the employment of a chiral auxiliary onto anisole derivatives. Initial attempts to introduce asymmetry into the metal fragment through altering the ligand set were unsuccessful, rendering the metal fragment incapable of binding aromatics in an η^2-fashion.[24,41] However, enantioselective transformations have been accomplished through the preparation of asymmetric anisole derivatives.[42]

The rational for introducing chirality into these systems was based on four key factors depicted in Fig. 3. First, the pentaammineosmium(II) binds anisole regioselectively across C(5)–C(6). Second, the coordination diastereomers interconvert by both intra- and interfacial isomerization to provide the thermodynamically favored coordination diastereomer. Third, the methoxy substituent remains primarily in the plane of the aromatic ring in order to maximize interaction of an oxygen lone pair with the conjugated anisole π-system. And fourth, the ammine protons of the metal fragment are acidic and are capable of forming H-bonds with appropriate acceptors. Thus, the chiral complex **86** was prepared in >90% de (95–97% yield) employing methyl lactate (**84**) as the chiral auxiliary.[43]

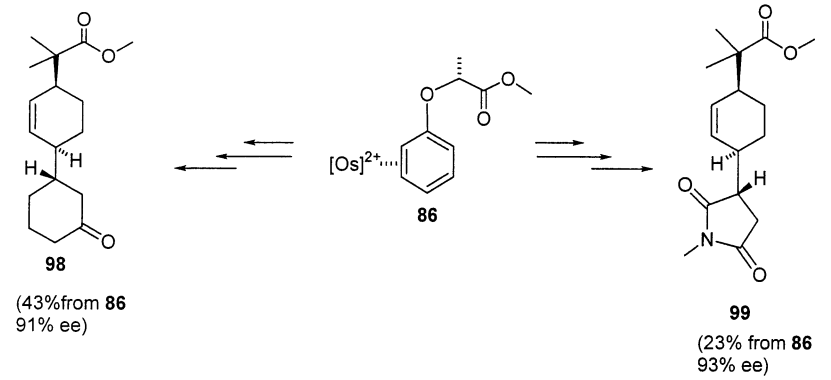
As depicted in Scheme 18, the auxiliary contains a chiral center in close proximity to the anisole oxygen atom, one hydrogen bond acceptor group, and a sterically demanding alkyl substituent. The high coordination diastereoselectivity results from a combination of hydrogen bond interactions between the ammine ligands and the ester functionality and minimization of steric interactions of the bulky alkyl group with an *ortho* hydrogen.

Tandem electrophilic addition/nucleophilic addition reactions to the chiral complex **86** were performed to afford the stereodefined cyclohexenes and cyclohexenone derivatives in moderate to high ee's, indicating that a substantial chiral induction had occurred from the remote chiral auxiliary (Scheme 19). Perhaps most significant about these findings is the way in which the chiral auxiliary is used. Whereas the most common employment of chiral

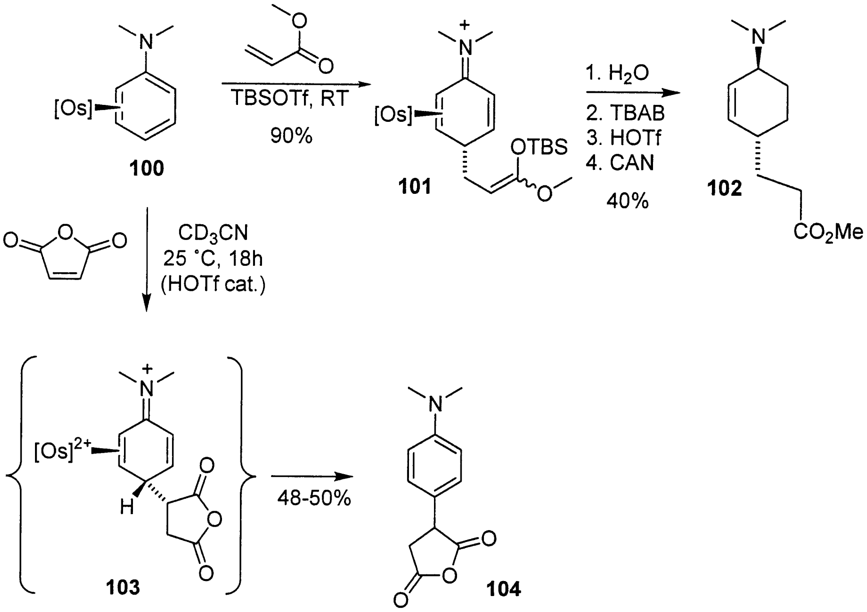


Scheme 19.

auxiliaries is to shield one of two prochiral faces from addition, the chiral auxiliary in these studies was used only to direct the diastereoselective coordination of the pentaammineosmium(II) fragment, which, in turn, directs the subsequent addition reactions to the arene face opposite metal coordination. Through tandem electrophilic addition/nucleophilic addition sequences, the substituted cyclohexenes **95–99** were prepared in high enantiomeric excess and in moderate to high overall yield from **86**.[42] (Schemes 19 and 20)



Scheme 20.



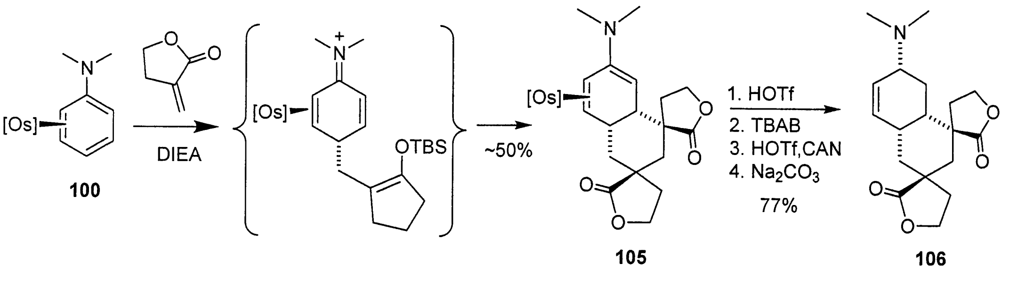
Scheme 21.

4.8. Anilines

Aniline complexes of pentaammineosmium(II) are more reactive toward electrophiles than their anisole counterparts. Accordingly, the complexes show increased reactivity toward relatively mild electrophiles. However, the addition of nucleophiles to the resulting anilinium complexes has proved more problematic, thus limiting the utility of aniline dearomatization.

As observed with anisole, electrophilic additions occur to the arene face opposite metal coordination and exclusively at C(4) to afford *p*-substituted anilinium complexes. For example, the *N*,*N*-dimethyl aniline complex **100** reacts with methyl acrylate in the presence of TBSOTf to afford the iminium silyl ketene acetal **101**. Subsequent reduction with borohydride and decomplexation (CAN) affords the 4-substituted aminocyclohexene **102** in moderate yield (Scheme 21).[44]

For more reactive electrophiles, no promoter is necessary and reaction ensues upon combining the reagents. For instance, complex **100** reacts with maleic anhydride to afford **104** in 25–30% yield as a result of a sequential Michael addition, rearomatization, and ligand substitution. However, the addition of a catalytic amount of HOTf improves the yield to 50%. When combined with α-methylene-γ-butyrolactone, complex **100** also undergoes a Michael–Michael-ring closure (MMRC) sequence to afford **105**. Protonation and reduction of the enamine followed by demetallation (CAN) provides the spirolactone product in high yield (Scheme 22).[44]



Scheme 22.

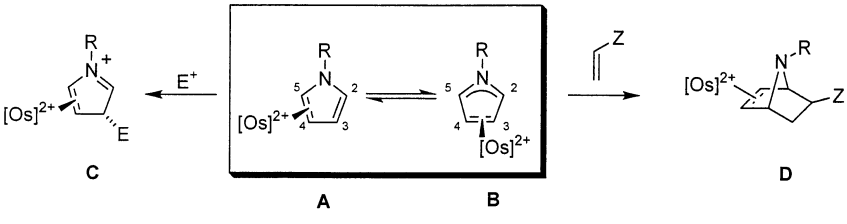
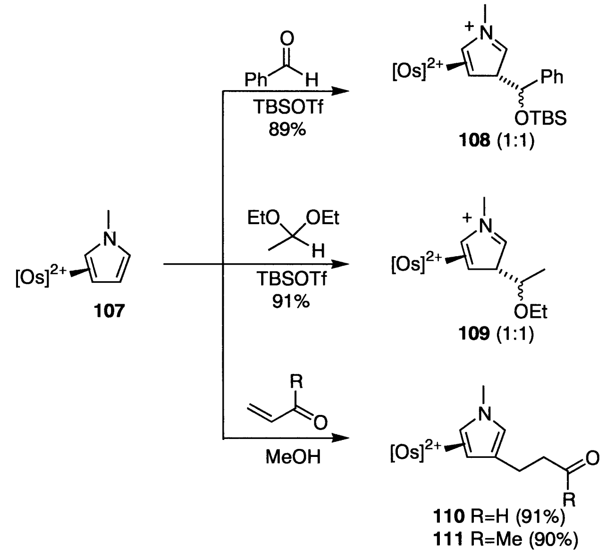


Figure 4. The general reactivity observed with η^2-pyrrole complexes: β-addition or substitution and dipolar cycloaddition.



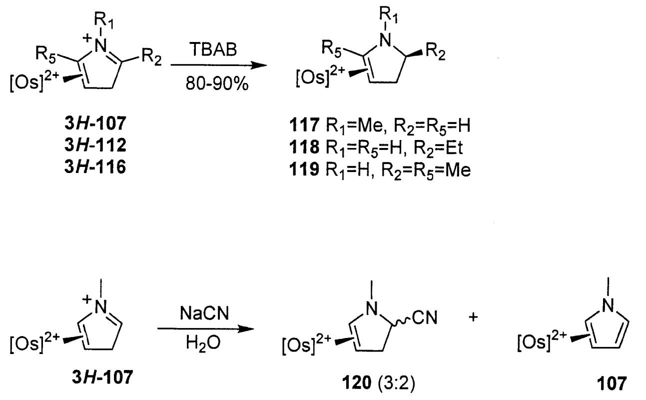
Scheme 23.

5. Aromatic heterocycles

5.1. Pyrroles

5.1.1. Overview. Pentaammineosmium(II) binds to pyrroles primarily across C(4)–C(5) (**A**), rendering the uncoordinated portion of the heterocycle enamine-like in reactivity (Fig. 4).[45] Soft electrophilies, such as Michael acceptors, generally add to the β-position whereas hard electrophiles (H^+, acetic anhydride, silyl triflates, methyl triflate) add primarily at nitrogen.[46] The metal fragment, however, is not static and migrates across the face of the pyrrole π-system through linkage isomerization to generate small quantities of the highly reactive C(3)–C(4) bound tautomer (**B**). This species behaves chemically as an azomethine ylide and undergoes 1,3-dipolar cycloaddition with electron deficient olefins. Although the two isomers **A** and **B** are in dynamic equilibrium in solution, adjusting the reaction conditions may control the reaction pathway. Thus, β-substituted pyrroles, α-substituted pyrroles, 3-pyrrolines, and substituted indole products may be obtained from the original aromatic heterocycle.[47]

5.1.2. β-Electrophilic additions. There are only a limited number of approaches that have been developed to date to prepare β-substituted pyrroles from pyrrolic precursors given the preference for electrophilic additions or substitutions to occur primarily at the α-position.[48] The two most common approaches are (a) placement of sterically bulky substituents or electron withdrawing groups at the α-positions to direct addition to the β-position and (b) isomerization of an α-substituted pyrrole to the corresponding β-substituted isomer. Pyrrole complexes of pentaammineosmium(II) show a dramatic reversal of selectivity compared to uncomplexed pyrroles, tending to react with soft electrophiles almost exclusively at the β-position when Lewis acids or protic solvents are used.[45,46,49] Additionally, the electron-donating metal fragment serves to stabilize the resulting pyrrolium intermediates from undergoing rearomatization, multiple additions, polymerization, or retro-addition.

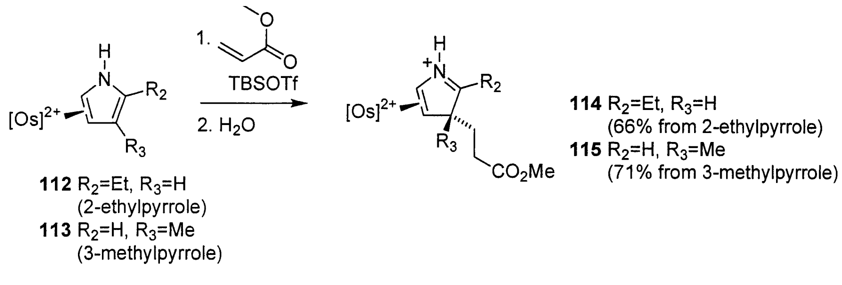


Scheme 25.

The *N*-methylpyrrole complexe **107** reacts with aromatic aldehydes, acetals, and Michael acceptors to generate the addition products **108**–**111** (Scheme 23). The products result from stereoselective electrophilic addition to the pyrrole face opposite metal coordination.[46]

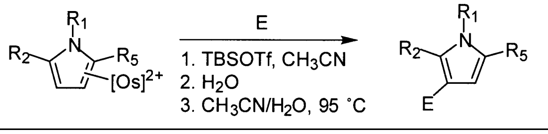
For asymmetric pyrroles, the pentaammineosmium(II) preferentially binds the less substituted double bond (Scheme 24). Accordingly, electrophilic additions result in the generation of vicinally substituted products. For example, conjugate addition of the 2-ethylpyrrole complex with methyl acrylate in the presence of TBSOTf affords the 2,3-disubstituted 3*H*-pyrrolium **114** in 66% yield.[46] Similarly, when 3-methylpyrrole is employed as the substrate, the Michael addition results in the 3,3-disubstituted product **115** in 71% yield.

The 3*H*-pyrrolium complexes of *N*-methylpyrrole (3*H*-**107**), 2-ethylpyrrole (3*H*-**112**), and 2,5-dimethylpyrrole (3*H*-**116**), prepared through treatment of these complexes with HOTf, are susceptible to borohydride reduction to afford the



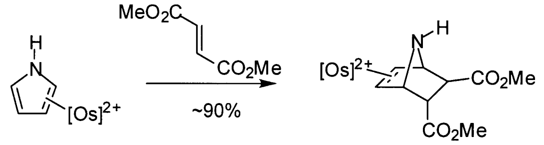
Scheme 24.

Table 1. The synthesis of β-substituted pyrroles through electrophilic addition, rearomatization, and decomplexation[46]



R_1	R_2	R_5	E	Yield (%)
Me	H	H	Ac	80
Me	H	H	$(CH_2)_2CO_2Me$	>95
H	Me	Me	$(CH_2)_2CO_2Me$	95
Me	H	H	$(CH_2)_2CO_2Me$	75

Table 2. Empirical reaction half-lives as a function of solvent in the synthesis of **122** from **121** (0.10±0.01 M) and dimethyl fumarate (0.30±0.03 M)[50]



121 **122**

	Solvent	$t_{1/2}$ (min)
1	Acetonitrile	185
2	Acetone	111
3	2 M LiOTf, DME	25
4	MeOH	22
5	DMF	15
6	DMA	9
7	DMSO	5
8	5 M LiOTf, DME	5

2-pyrrolines **117–119** (Scheme 25). The stereochemistry of the addition results from the delivery of hydride to the iminium face *anti* to metal coordination. The addition of carbon nucleophiles has proved more problematic, primarily owing to the relatively high acidity of the ammine ligands. However, cyanide ion adds to the 3*H*-pyrrolium to give **120** as a 3:2 mixture of diastereomers isolated with ~30% of the rearomatized compound.

The demetallation of 2-pyrroline complexes has proven difficult owing, perhaps, to the high reactivity of the enamine products. However, substituted 1*H*-pyrroles may be prepared through a sequence of complexation, electrophilic addition, rearomatization, and ligand dissociation. Table 1 lists a representative series of β-substituted pyrroles prepared employing this methodology.[46]

5.1.3. 7-Azanorbornanes.

The 3,4-η^2-pyrrole isomer **B** reacts as an azomethine ylide and undergoes 1,3-dipolar cycloaddition with a variety of electron-deficient olefins to yield complexed 7-azanorbornenes (Fig. 5).[50] The coordinated metal stabilizes the product thereby allowing further transformations to be performed while maintaining the integrity of the bicyclic framework. This approach complements the two major non-organometallic routes to preparing 7-azanorbornanes which are (a) Diels–Alder cycloaddition of pyrroles with electron-deficient alkynes followed by hydrogenation of the resulting azanorbornadienes, and (b) intramolecular nucleophilic ring-closure of aminocyclohexanes.[51,52]

The osmium-mediated dipolar cycloaddition reactivity has been shown to be a versatile route to the preparation of analogues of the natural product epibatidine,[53,54] a powerful non-opiod analgesic with a potency 200 times that of morphine, and has led to the discovery of the muscarinic receptor ligands CMI-936 and CMI-1145 in our laboratory (Fig. 5).[55]

The reactivity of the pyrrole complexes may be directed toward cycloaddition over β-addition through the employment of polar, aprotic solvents (Table 2). The origin of this rate enhancement for cycloaddition over β-addition has been ascribed to an increased electron donation from the metal fragment into the HOMO of the azomethine ylide arising from better hydrogen-bonding interactions between the solvent and the ammine ligands.[50]

Table 3 shows a representative number of cycloadduct complexes and corresponding demetallated 7-azanorbornanes. The stereochemistry of the adducts was initially elucidated through NOE studies in which *exo* cycloadducts bearing an *N*-methyl substituent show strong interaction with the ring protons.

The outcome of the stereoselectivity of the cycloadditions was rationalized based on minimization of steric interactions between the newly formed bridge and either the

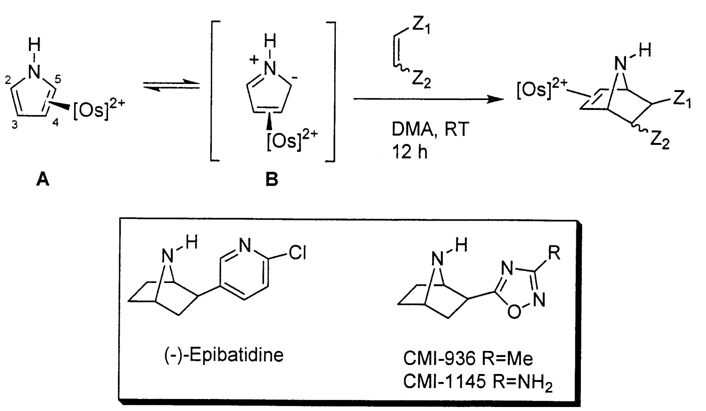
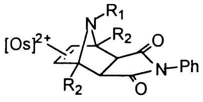
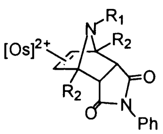
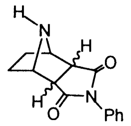
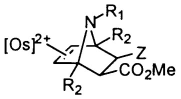
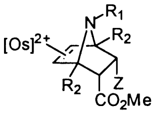
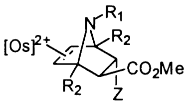
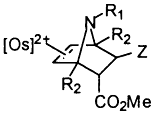
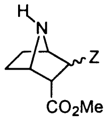
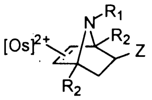
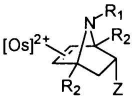
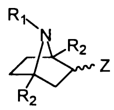
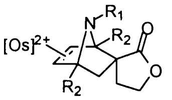
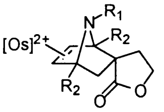
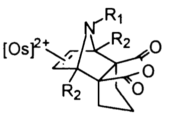
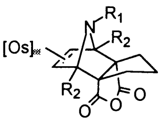


Figure 5. The general route to the 7-azabicyclo[2.2.1]heptane core of the natural product epibatidine employing the cycloaddition reactivity of η^2-bound pyrroles.

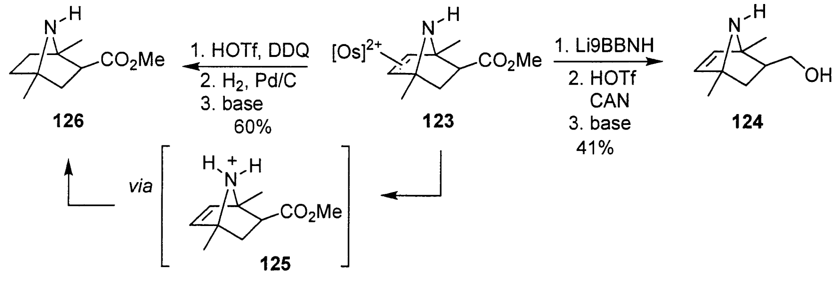
Table 3. Cycloadduct complexes and 7-azanorbornanes prepared from pyrroless[50]

A (exo)	b (endo)	R_1	R_2	Z	a/b	Yield (%)	Representative organic product	Yield a/b (%)
		H	H		6:1	85		39/41
		Me	H		1:6	85		
		H	Me		5:1	89		
		Me	Me		1:1	77		
		TMS	H		<1:20	89		
		H	Me	CO_2Me	2:1	82		
		H	Me	3-pyridyl	9:1	83		
		H	H	CO_2Me	-	78		42
		H	Me	CO_2Me	-	86		
		H	Me	3-pyridyl	16:1	93		46/69
		H	Me	CO_2Me	12:1	97		60(a+b)
		H	Me	CN	5:1	83		
		Me	H	CO_2Me	1:1	84		65(a+b)
		Me	H	CN	1:1	98		67(a+b)
		H	Me		>20:1	96		
		H	Me		>10:1	84		

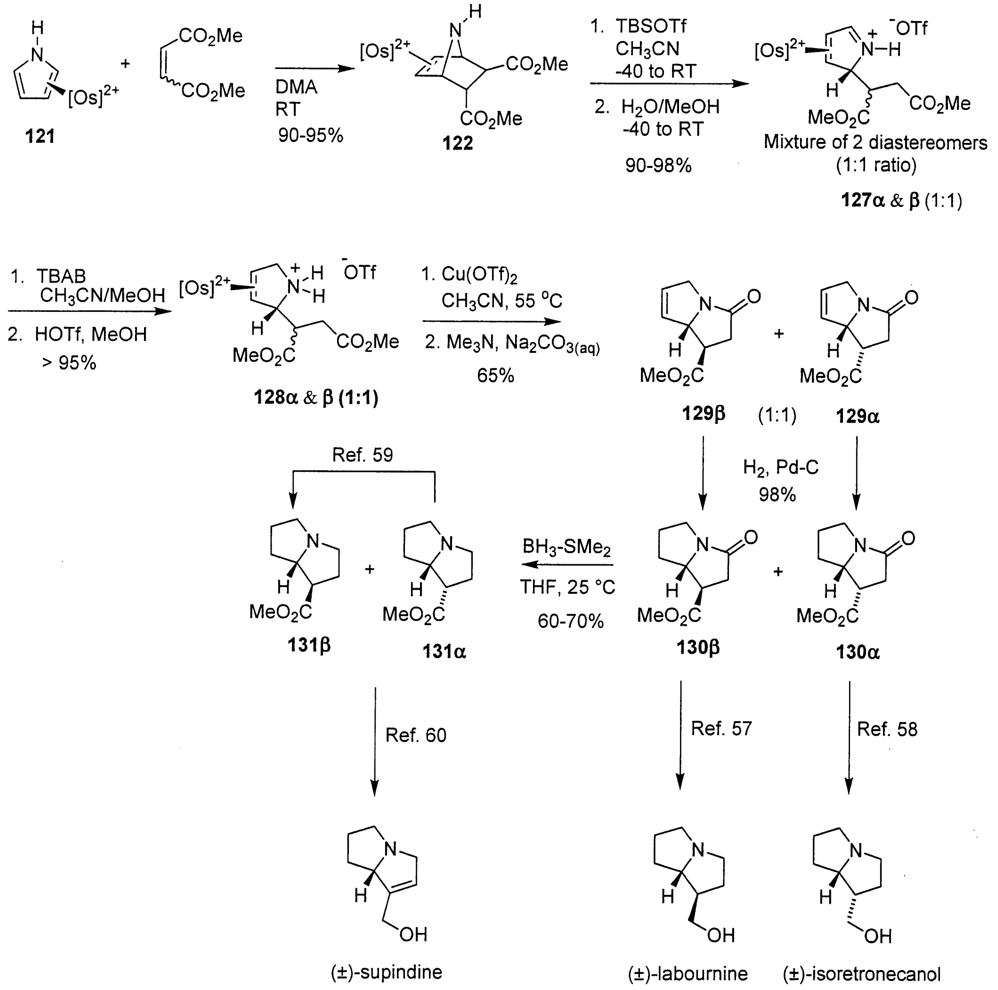
nitrogen substituent or the bridgehead substituents. The *exo* selectivities are most pronounced when the bridgehead positions are substituted and the nitrogen is unsubstituted, such as with 2,5-dimethylpyrrole. Likewise, *endo* selectivities are most pronounced when the reverse is true. For instance, the cycloaddition of *N*-TMS pyrrole with *N*-phenylmaleimide yields an *exo*/*endo* ratio of <1:20 but with 2,5-dimethylpyrrole, the ratio is 5:1.

Decomplexation and isolation of the metal-free cycloadduct products requires protonation of the bridging nitrogen with strong acid (HOTf) followed by oxidation (DDQ) of the metal to liberate the 7-azanorbornenes (Scheme 26). The intermediates, such as **125**, are susceptible to retro-cycloaddition upon deprotonation and must therefore be hydrogenated prior to isolation. Alternatively, 7-azanorbornenes such as **124** may be isolated if the electron-withdrawing substituents are reduced prior to removal of the metal fragment.

5.1.4. Pyrrolizidines. The electron-rich pentaammineosmium(II) fragment may serve a dual purpose of initially activating the pyrrole ligand toward cycloaddition and then rendering the cycloadduct complex labile toward retro-Mannich ring opening through stabilization of the resulting 2*H*-pyrrolium intermediates such as **127** (Scheme 27). Although 2*H*-pyrrolium complexes may be directly decomplexed by heating to generate α-substituted pyrrole products,[47] reduction with TBAB followed by decomplexation and ring closure yields pyrrolizinone products in moderate overall yield (40–60% from the pyrrole precursor).[50,56]



Scheme 26.

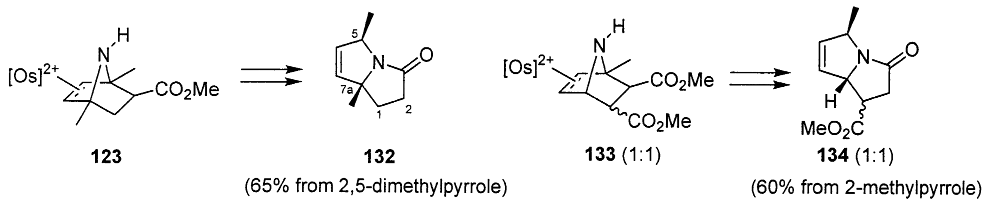


Scheme 27.

The high functionality of the pyrrolizinones **129**, prepared from pyrrole and dimethyl fumarate, make them versatile as advanced intermediates for the synthesis of a number of pyrrolizidine natural products.[56] Intermediates **130β** and **130α**, readily prepared via hydrogenation of **129**, have been converted to (±)-labournine[57,58] and (±)-isoretronecanol,[58] respectively. The *endo* substituted product **131α** which has also been used to prepare isoretronecanol, may be converted to **131β** through base induced epimerization.[59] As a mixture of isomers, **131** has been used to prepare (±)-supindine.[60]

α-Substituted pyrroles may be used to generate the corresponding alkylated pyrrolizinones (Scheme 28). For example, **132** was prepared from 2,5-dimethylpyrrole and methyl acrylate. The stereochemistry of C(7a) in the final product results from the stereoselective dipolar cycloaddition of the dienophile to the pyrrole face opposite metal coordination. Similarly, the stereochemistry at C(5) arises from stereoselective addition of hydride *anti-* to the metal fragment to the iminium generated upon ring opening. Interestingly, when 2-methylpyrrole is employed as the starting material (**133**→**134**), the ring-opening step occurs regioselectively such that the alkyl substituent can stabilize the resulting iminium (2*H*-pyrrolium) carbon via hyperconjugation. Hydride reduction followed by decomplexation and ring-closure leads to the β-orientation of the C(5) methyl group in **134**.

5.1.5. Indoles. A variety of substituted indoles have been prepared employing a Diels–Alder cycloaddition strategy of η^2-β-vinylpyrrole complexes with electron-deficient olefins



Scheme 28.

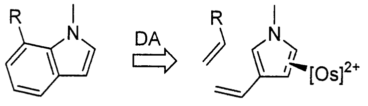
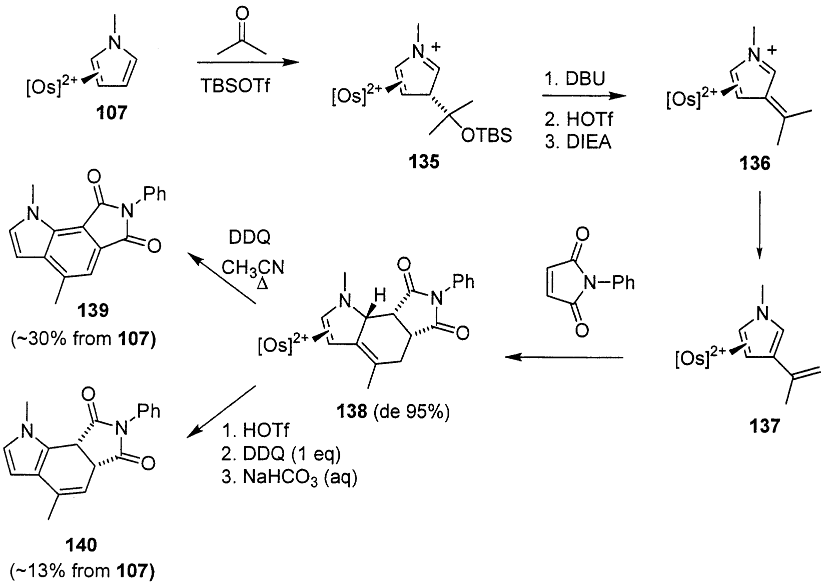


Figure 6. The tetrahydroindole ring system may be synthesized through a Diels–Alder cycloaddition of complexed β-vinyl pyrroles and electron deficient dienophiles.

(Fig. 6). In contrast to more traditional strategies, such as the Fischer process, in which the indole is prepared from a carbocycle, this strategy builds the carbocycle onto the pyrrolic precursor. Although this cycloaddition approach is not novel,[61,62] complexation of the metal fragment offers a number of advantages over the non-metal mediated approaches. Primarily, β-vinylpyrroles are difficult to prepare and manipulate, and are highly susceptible to polymerization. These reactive species, however, may be generated under controlled conditions through metal coordination resulting in high yields (typically >85%) of β-vinylpyrrole complexes.[49]

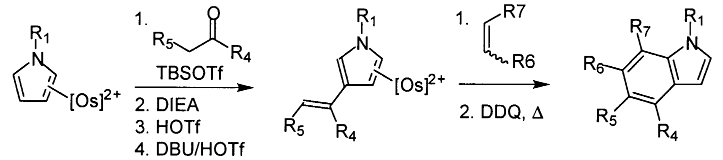
A representative synthesis of indoles **139** and dihydroindole **140** is shown in Scheme 29. The general strategy involves initial complexation of the pyrrole followed by β-electrophilic addition with a suitable electrophile (to yield **135**) so that subsequent treatment with base, acid, then base again generates the β-vinylpyrrole complex **137**. These complexes react with electron deficient olefins in Diels–Alder fashion to yield complexed indoles such as **138**, which may be demetallated upon treatment with an oxidant.

The procedure is amenable to the preparation of indoles



Scheme 29.

Table 4. Preparation of substituted indoles through Diels–Alder addition of β-vinylpyrroles with electron deficient dienophiles[49]



R$_1$	R$_4$	R$_5$	R$_6$	R$_7$	Yield (%)
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$_2$Me	CO$_2$Me	35(42)
Me	Ph	H	CO$_2$Me	CO$_2$Me	48(55)
Me	Ph	H	H	CO$_2$Me	39(49)
Me	H	H	–C(O)N(Ph)C(O)–		7(12)
Me	OMe	H	–C(O)N(Ph)C(O)–		29(37)
Me	OMe	H	H	CO$_2$Me	12(17)
Me	H	Ac	–C(O)N(Ph)C(O)–		46(52)
Me	H	CO$_2$Me	–C(O)N(Ph)C(O)–		14(17)
Me	CO$_2$Me	CO$_2$Me	–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)

Yields are for the overall isolated yield of the purified indole products. Values in parentheses are the yields for the decomplexation step alone.

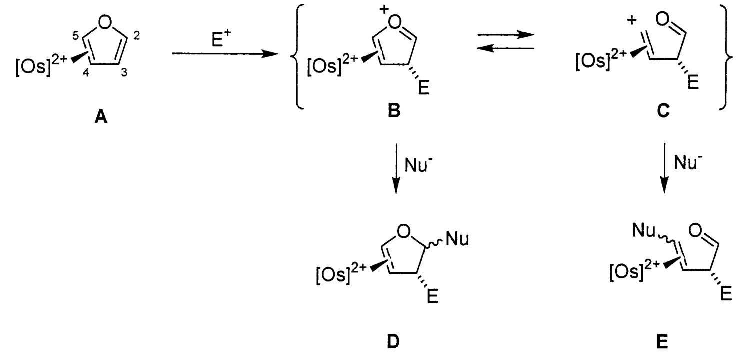


Figure 7. The general reactivity patterns observed for η^2-furan complexes.

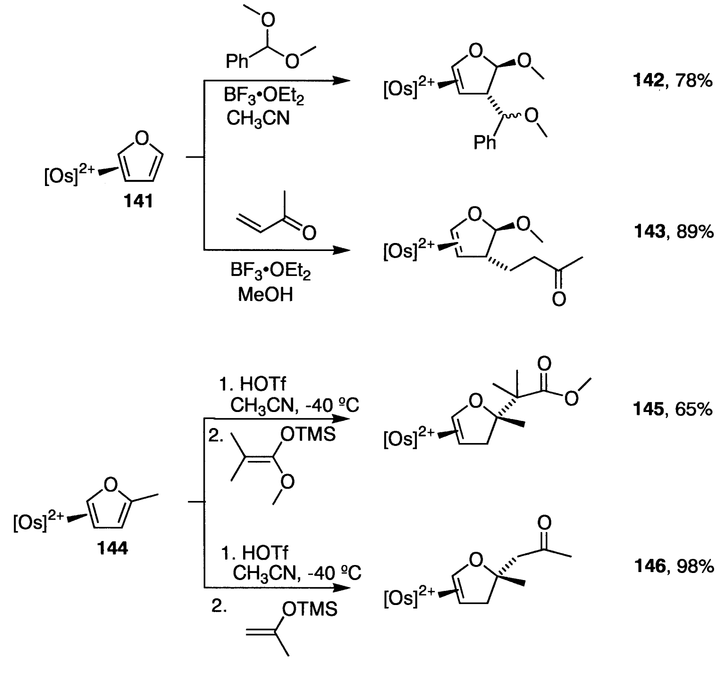
(Table 4) containing substituents at positions C(4), C(5), C(6), and C(7). Through this strategy, the substituent at C(4) and C(5) of the final indole product originate from the electrophile and the substituents at C(6) and C(7) originate from the dienophile. A variety of electrophiles have been employed to include ketones (those capable of aldol addition), acetals (e.g. acetaldehyde diethylacetal), carboxylic anhydrides (acetic anhydride), and alkynyl esters (methylpropiolate). This approach appears to be limited to the synthesis of *N*-alkylated indoles.

5.2. Furans

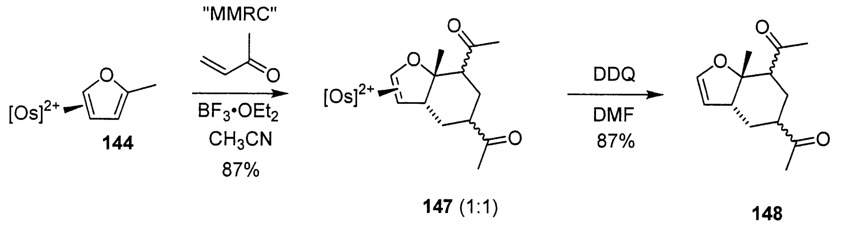
5.2.1. Overview. The normal chemistry of furan is dominated by electrophilic substitution reactions at the α-carbons. Such reactivity has been rationalized by the greater thermodynamic stability of the 2*H*-furanium ion compared to its 3*H*-furanium isomer and the strong driving force for the furanium ion to rearomatize.[48] The complexation of furan by pentaammineosmium(II) dramatically alters the heterocycle's normal mode of reactivity. The metal fragment binds predominantly across C(4)–C(5) such that the uncoordinated portion of the heterocycle resembles a vinyl ether (Fig. 7). Electrophiles, therefore, add to the unbound β-carbon, C(3), to produce a 3*H*-furanium complex **B** which is thought to be in equilibrium with its ring opened form **C**. Accordingly, these complexes are susceptible to nucleophilic addition at C(2), generating the vicinally substituted dihydrofuran **D**, and at C(5), affording the β,γ-unsaturated carbonyl product **E**.[63]

A number of strategies have been developed to prepare a host of stereodefined heterocyclic cores from furan that exploits this novel reactivity. Particularly, the employment of tethered electrophile–nucleophile combinations demonstrates the potential for the synthesis of new annulated products.

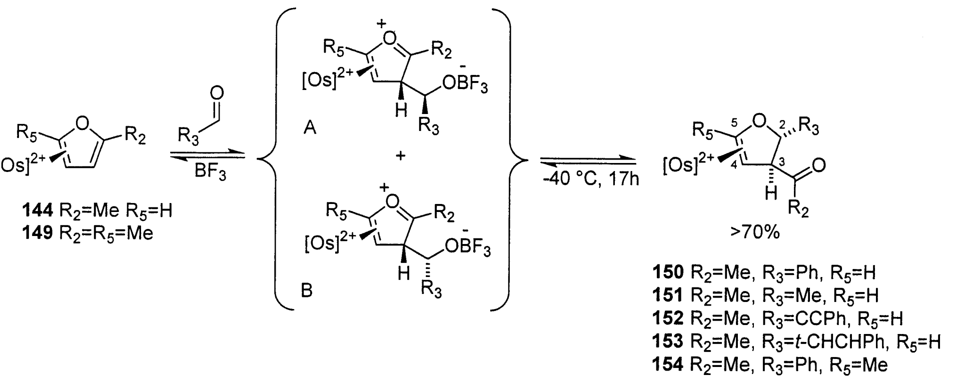
5.2.2. Dihydrofurans. Vicinally functionalized 2,3-dihydrofurans have been prepared through tandem electrophilic/nucleophilic addition sequences to the complexes of furan (**141**) and 2-methylfuran (**144**) (Scheme 30).[63,64] For example, complex **141** reacts with benzaldehyde dimethylacetal in the presence of $BF_3{\cdot}OEt_2$ to afford a mixture of two



Scheme 30.



Scheme 31.



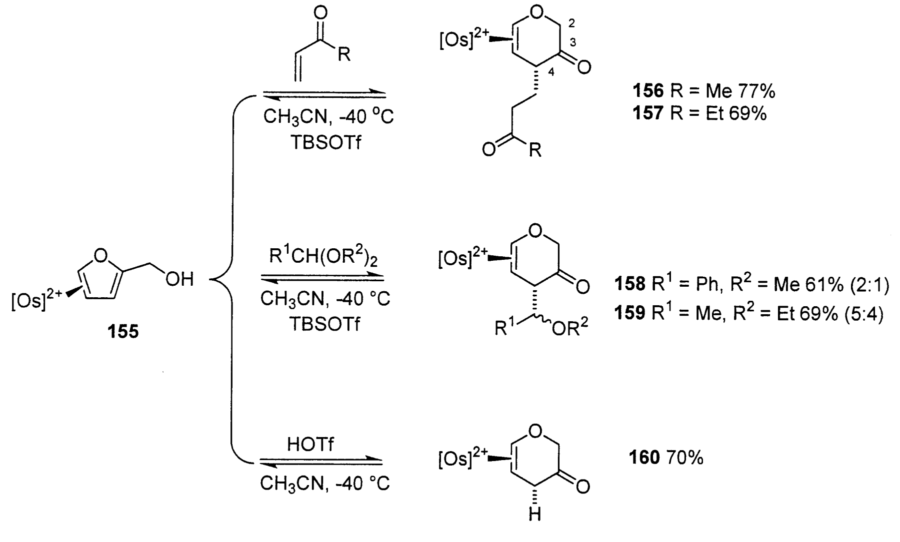
Scheme 32.

diastereomers **142**. Similarly, the furan complex reacts with MVK in methanol to yield **143** as a result of initial Michael addition followed by nucleophilic addition of methanol. When 2-methylfuran is employed as the starting material, a proton (HOTf) may be used as the electrophile followed by the addition of SKA or trimethylsiloxypropene to afford **145** and **146**, respectively. In each of these reactions, the addition of electrophile occurs *anti* to metal coordination. In cases where the nucleophile may participate in hydrogen bonding interactions with the ammine ligands of the metal fragment, such as with methanol, the addition occurs *syn* to the metal. Otherwise, the nucleophile also adds *anti* to the metal.

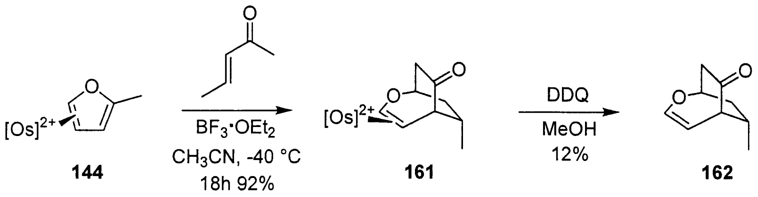
The hexahydrobenzofuran complex **147**, isolated as a mixture of two diastereomers, was prepared through a tandem Michael–Michael-aldol sequence and demetallated to yield the organic product **148** in high yield (Scheme 31).

5.2.3. 3-Acetyl-2,3-dihydrofurans.

The aldol reaction of the 4,5-η^2-furan complexes **144** and **149** with aldehydes results in the formation of 3-acetyl dihydrofurans through an unprecedented rearrangement where the resulting 3*H*-furanium undergoes subsequent nucleophilic displacement at C(5) by the internal alkoxide to afford a new dihydrofuran ring (Scheme 32).[65] The stereochemistry at C(3) in the isolated products is determined by the aldol addition occurring to the furan face opposite metal coordination. However, the stereochemistry at C(2) arises through the formation of the thermodynamically favored isomer in which the more



Scheme 33.



Scheme 34.

bulky alkyl substituent is oriented *anti* to the coordinated metal. Shorter reaction times lead to isolation of both *cis*- and *trans* products. A variety of aldehydes have been used including acetaldehyde, benzaldehyde, cinnamaldehyde, and phenylpropargylaldehyde to generate the *trans*-2,3-disubstituted dihydrofurans **150–155**. Interestingly, this reactivity is not observed with the analogous Os–pyrrole complexes in which β-electrophilic addition results in the relatively stable 3*H*-pyrrolium complexes that add nucleophiles only at the unbound α-carbon.

5.2.4. 2*H*-Pyranones. A variety of 2*H*-pyranones, such as **156–160**, may be prepared from the 2-hydroxymethylfuran complex **155** via a tandem electrophilic/nucleophilic addition sequence (Scheme 33). The initial electrophilic addition of acetal, α,β-unsaturated aldehyde, or H^+ (HOTf) occurs stereoselectively to the furan face opposite metal coordination. The hydroxymethyl group subsequently reacts as the latent nucleophile, adding to the bound α-carbon following the electrophilic addition step to close the new pyranone ring. Thus, the oxygen atom of the original furan becomes the 3-oxo substituent in the final product.

This reactivity was highlighted in the preparation of the bicyclic oxepin **162**, prepared from 2-methylfuran and penten-2-one (Scheme 34).[65] This ring system is integral to the core of the Seiricardines, compounds which are moderate fungal growth inhibitors. The mechanism of the rearrangement is believed to involve a cascade Michael/aldol/aldol sequence.

6. Concluding remarks

Using an electron-rich, $16e^-$ metal fragment, aromatic molecules may be coordinated through a single π-bond. Such coordination acts to disrupt the π-system and activates the aromatic toward electrophilic addition reactions. The resulting arenium, allyl, and 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 the activation of unsaturated molecules. This approach is complementary to the more established chemistry of nucleophilic addition to metal-coordinated π-systems. Until recently, this methodology has been limited to the pentaammineosmium(II) system, a reagent which, though remarkably versatile, has practical limitations such as cost and toxicity. On the horizon, however, is the next generation of dearomatization agents of the type {ReTp(CO)(L)}.[24,66] These materials, in addition to being substantially less expensive and more safe than osmium, are chiral at metal, and electronically and sterically tunable. Thus, they can be tailored to optimize a particular reaction sequence.

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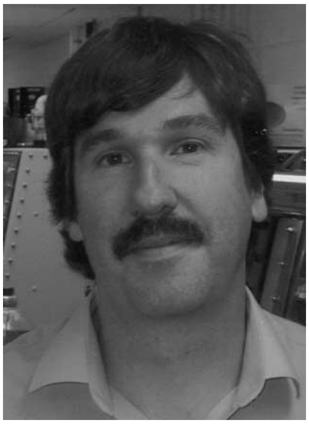
Biographical sketch

Philip L. Smith was born in Eugene, Oregon on June 25, 1968. He attended the College of William and Mary, Williamsburg, VA where he received a BSc in Chemistry in 1990 and was commissioned as a 2nd lieutenant in the United States Army, Medical Service Corps. He continued his chemistry studies at William and Mary, working with Professor W. Gary Hollis, Jr. (now at Roanoke College) and received an MA in 1991. He spent the following 6 years at duty assignments for the Army including tours at the US Army Center for Health Promotion and Preventive Medicine, Edgewood, MD and at the US Army Pacific Environmental Health Engineering Agency, Sagamihara, Japan. In 1997, he entered the PhD program at the University of Virginia and has since worked under the guidance of Professor W. Dean Harman developing synthetic methodology employing Re(I) and Os(II) dearomatization agents. Currently a Major in the US Army, he will be assigned to the Walter Reed Army Institute of Research (WRAIR), Silver Spring, MD upon completion of his doctoral degree.

Mahendra D. Chordia was born in Pune, India. He received his BSc (1983) and MS (1995) from the University of Poona, Pune. In 1992, he received his PhD in chemistry under the supervision of Professor N. S. Narasimhan at the University of Pune. He worked at the National Chemical Laboratory, Pune, for one year (1991–92) prior to coming to coming to the United States. He worked as a post-doctoral research associate at Virginia Polytechnic Institute and State University, Blacksburg, VA with Professor D. G. I. Kingston (1992–96). He then moved to his current position as a research scientist with Professor W. Dean Harman at the University of Virginia, Charlottesville, VA. His research interests include the development of new synthetic methods, organometallic reactions, asymmetric synthesis, and the design and synthesis of medicinally and biologically important small molecules with a focus on understanding their interactions with living systems.



W. Dean Harman was born in 1960 in Stanford, California. He received his BSc 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 PhD 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 awarded the Cavalier Distinguished Teaching Chair. Harman has been named as a Camille and Henry Dreyfus Teacher–Scholar (1992–1995), an NSF Young Investigator (1993–1998), an Alfred P. Sloan Research Fellow (1994–1996) and has been the recipient of several University teaching awards. He is the co-author of approximately 85 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, Virginia, at the edge of the Blue Ridge Mountains with his wife Lisa, and two children, Alorah and Dustin.