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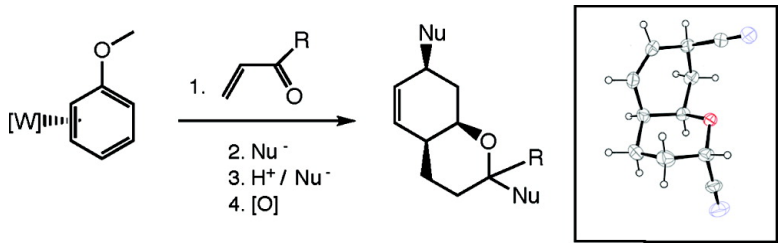

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Synthesis of 1-Oxadecalins from Anisole Promoted by Tungsten

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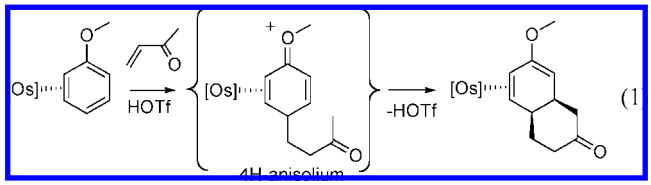
Abstract: The complex TpW(NO)(PMe_3)(η^2-anisole) is combined with acrolein or methyl vinyl ketone and various nucleophiles to generate novel chromen complexes. These complexes may be further elaborated by protonation and nucleophilic addition to generate chroman analogues with increased saturation and stereocenters. Treatment with various oxidants effects the decomplexation of the chromen.

Introduction

The chromen core is a prominent feature of several biologically active molecules, including forskolin, scutorientalin D, and phomactin A.[1] The impetus of the present study is to construct this oxadecalin system directly from a benzene nucleus.[2,3] Previously, we demonstrated that functionalized decalins could be synthesized from anisole by way of a Michael-aldol reaction sequence. This process relied on the ability of a π-basic transition metal complex, $[Os(NH_3)_5]^{2+}$, to stabilize the 4*H*-anisolium intermediate shown in eq 1.[4]



We envisioned a similar reaction sequence in which a heterobicycle was formed through an intramolecular 1,4 addition of an enone or enal to a benzene ring, as shown in Figure 1. With the aromatic character of the carbocycle removed, the resulting methoxydiene complex could be further elaborated into several potentially useful precursors to more complex chromens.

The previously described decalin synthesis utilizing pentaammineosmium(II) relied on a strong Brønsted acid (HOTf/CH_3CN) to promote the Michael addition. Unfortunately, the resulting 4*H*-anisolium is highly acidic and therefore incompatible with the proposed enolate or alkoxide intermediates in Figure 1. However, with the development of the more π-basic metal fragment {TpW(NO)(PMe_3)}, we hoped that the Michael addition and subsequent transformations could be carried out under neutral or basic conditions, thus allowing for the possibility of an anionic oxygen ring closure. The following account describes this process and subsequent elaboration of these bicyclic complexes into functionalized *cis*-1-oxadecalin cores.

Results and Discussion

The complex TpW(NO)(PMe_3)(η^2-*5,6*-anisole), **1**, prepared from anisole, PMe_3, and TpW(NO)Br_2,[5] was stirred in a solution of DMF and acrolein in an effort to directly form a dihydro-4*H*-chromen core (see Figure 1, path A). Unfortunately, the only complex isolated from this procedure was TpW(NO)(PMe_3)(η^2-DMF), resulting from displacement of the arene.[6] Repeating this experiment with other solvents, higher concentrations of acrolein, Lewis acids, or other Michael acceptors also failed to deliver the intended oxadecalin product.

Our second approach was to prepare and isolate a 4*H*-anisolium complex derived from acrolein or MVK, which could then be treated with an exogenous anionic nucleophile (see Figure 1, path B). We first attempted to prepare the 4H-anisolium complex directly from anisole **1**, a Michael acceptor, and a Brønsted acid. Ultimately, we found that combining the 2*H*-anisolium, **2**,[7] directly with the Michael acceptor was more efficient (Scheme 1). Complex **2** can be prepared from **1** and diphenylammonium triflate (DPhAT) as a single coordination diastereomer, where the oxygen is oriented away from the PMe_3 group.[5] Stirring a DMF solution of **2** with either acrolein or MVK resulted in a deep red solution. Subsequent volume reduction and addition to an excess of ether yielded the alkylated 4*H*-anisolium complexes as bright orange precipitates (>90%). The air-stable anisolium complexes **3** and **4** are formed both regio- and stereoselectively. Judging from NOE correlations and ^{31}P coupling constants,[5] alkylation occurs anti to the metal fragment and exclusively at the 4-position (Scheme 1).

[†] University of Virginia.
[‡] University of Richmond.

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(2) Brooks, B. C.; Gunnoe, T. B.; Harman, W. D. *Coord. Chem. Rev.* **2000**, *206−207*, 3–61.
(3) Keane, J. M.; Harman, W. D. *Organometallics* **2005**, *24*, 1786–1798.
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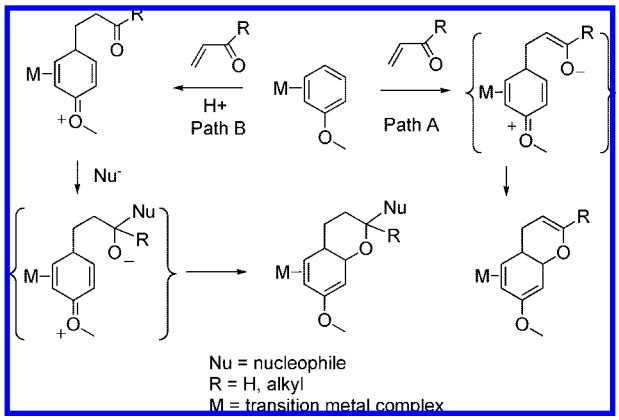
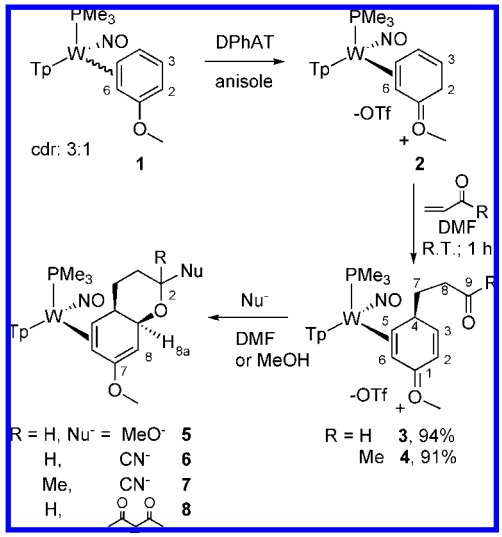


Figure 1. Proposed syntheses of the 1-oxadecalin cores.

Scheme 1. Synthesis of the Hexahydrochromen Complexes **5**−**8**

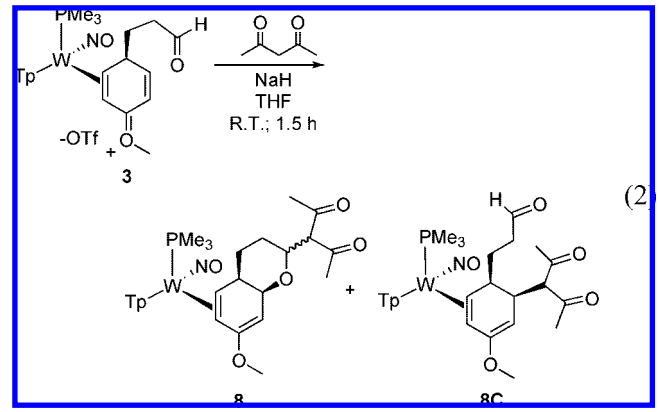


Spectroscopic features of the adducts **3** and **4** are similar to Os(II) or Re(I) 4*H*-anisolium complexes we have characterized.[4,8] Proton signals for **3** are located at 6.35 and 6.93 ppm, corresponding to the uncoordinated olefinic protons H2 and H3. Two upfield signals at 4.23 ppm (J_{PH} = 14 Hz) and 3.07 ppm correspond to those protons associated with the bound carbons. The ^{13}C NMR spectrum of **3** reveals a signal at 187.5 ppm for the oxonium carbon (C1). This value is more upfield than for organic enones (ca. 200 ppm) and indicates significant donation of electron density from the tungsten into the oxonium π system. The infrared absorption spectrum features a nitrosyl stretching frequency that is blue-shifted from the anisole complex (1614 cm^{-1} (**3**), cf. 1564 cm^{-1} (**1**)). Further, a cyclic voltammogram of this material shows its first oxidation wave near +1.4 V (NHE, 100 mV/s; cf. −0.30 V for **1**). Both of these features indicate a substantial loss of electron-density at tungsten in **3**, as compared to its neutral precursor (**1**).

Anionic nucleophiles reacted rapidly with either the acrolein- or MVK-derived anisolium complexes (**3** or **4**), their reactions being signaled by a solution color change from red to yellow and the appearance of product signals in the ^{31}P NMR spectrum. After passing the reaction mixtures through Celite to remove the unreacted nucleophiles, the solutions were added to pentane. As a general rule, precipitation of these neutral hexahydrochromen complexes was incomplete, resulting in low recovery of material. Hence, complexes **5**−**7** were typically converted to oxonium complexes (**9**−**11**) prior to their isolation (vide infra). These complexes are less soluble in hexanes and more resistant to decomposition in air.

Spectral features of the cyanide-derived chromen complex **6** (dr = 1:1) are typical of the chromen complexes **5**−**7**. The proton resonances at 4.21 ppm and 5.07 (H8) and carbon signals at 166.9 and 164.57 ppm (C7) indicate the presence of the vinyl ether functionality in each isomer. In addition, the nitrosyl stretching frequency for **6** is shifted to 1561 cm^{-1}, indicating a neutral organic ligand.

Judging from ^{1}H NMR data of crude reaction mixtures, the nucleophiles pentane-2,4-dione, dimethyl malonate, (1-methoxy-2-methylprop-1-enyloxy)trimethylsilane, trimethylphosphine, and pentanethiol, also react with **3** to form chromen complexes, but these experiments yielded impractical reaction mixtures. For example, the reaction of pentane-2,4-dione and anisolium **3** resulted in a 4:1:1 mixture of products after precipitation from pentane. While the chromen **8** is present as a 1:1 mixture of coordination diastereomers, the major product (**8C**) has ^{1}H NMR features, (CHO, 9.86 ppm; H3, 3.10 ppm; H6, 1.53 ppm; CH_3, 2.10; CH_3, 2.30 ppm) that are consistent with a C4,C3 tandem addition reaction sequence (eq 2). The filtrate of the reaction mixture yielded a small amount of chromen **8** that was free of **8C**. This sample was used for characterization purposes, but its chemistry was not explored further.



Treatment of **3** with triphenylphosphine, sodium phenoxide, sodium benzoate, sodium azide, propylamine, or aniline either led to recovery of **3**, the anisole complex **1**, or indeterminate decomposition. Finally, as we discuss below, the reaction of **3** with NaSPh leads to an entirely different polycyclic system.

Attempts to oxidatively demetallate the organic methoxydiene chromens of **5** or **6** using mCPBA, AgOTf, or $CuBr_2$ resulted in a retrocyclization sequence; ^{1}H NMR or GC−MS analysis of these reaction mixtures found anisole as the only recognizable organic product. To prevent the purported alcohol elimination, a process facilitated by rearomatization, further manipulation of the C7−C8 bond was required. Protonation of chromens **5**−**7** (prepared in situ) with DPhAT readily produced the oxonium analogues **9**−**11** in overall 75−93% yield starting from anisolium **3** or **4** (Table 1).[9] These species show a NO stretching

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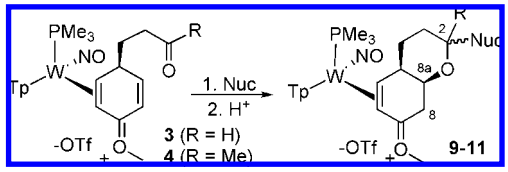
(9) Attempts to vary the substitution at C8 with carbon electrophiles such as Michael acceptors or aldehydes led to the isolation of the protonated species, even under anhydrous conditions.

Table 1. Formation of the Oxadecalin Core

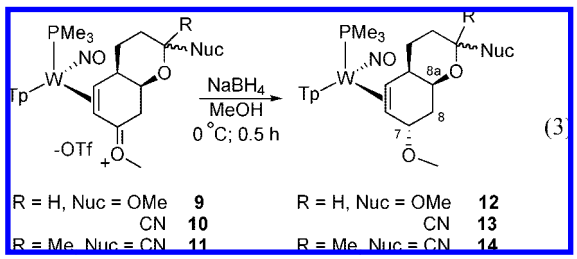


product	R	nucleophile	dr (C^2)	yield[a]
9	H	OMe	2:1	78
10	H	CN	1:1	93
11	Me	CN	4:1	75

[a] Reported yields (%) of **9**−**11** are from **3** or **4** (two steps).

feature (1617 cm^{-1}) consistent with a cationic ligand, and ^{13}C NMR signals indicating one carbonyl group for each diastereomer.

The enonium complexes **9**−**11** can be stereoselectively reduced by $NaBH_4$ in MeOH to form allyl ethers **12**−**14** (eq 3). Similar to the methoxydiene complexes **5**−**7**, hexahydrochromens **12**−**14** were not easily purified by chromatography or precipitation from solution, and therefore were not routinely isolated, other than for purposes of spectroscopic characterization. For these complexes, the nitrosyl stretch feature in the infrared spectrum shifts by ~50 cm^{-1} to lower energy indicating the return to a neutral organic ligand. The H7 methine resonance for each of the allyl ether complexes (**12**−**14**) is near 5.5 ppm. The addition of the hydride to the methylated carbonyl predictably occurs at the face of the carbocycle anti to the metal fragment. The stereochemistry of this addition (C7 in eq 3) is based on comparisons of coupling data for **12**−**14** with those of the independently prepared complex *syn*-TpW(NO)(PMe_3)-(1,2-dihydroanisole).[10] The reaction of oxonium complex **10** with other nucleophiles (e.g., sodium cyanide or thiophenol) led to the recovery of the vinyl ether complex **7** or unidentified decomposition products.



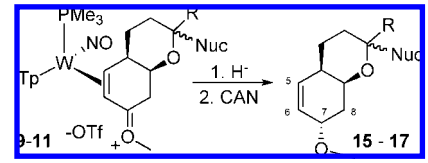
(3)

Treatment of complexes **12**−**14** (prepared in situ) with CAN in $CHCl_3$ liberates the functionalized 1-oxadecalins (Table 2). In a typical procedure, the air-stable enonium precursors **9**−**11** are reduced with $NaBH_4$, then directly treated with the oxidant (CAN). The oxadecalins **15**−**17** were isolated in 41−60% yields as yellow oils. While these materials are isolated as C2 epimer mixtures, individual diastereomers can be separated by column chromatography. Key spectroscopic features for the oxadecalin **17** include proton and carbon resonances at 5.66/132.1, 5.87/127.3, and 3.91/74.0 ppm, which are attributed to H5/C5, H6/C6, and H7/C7, respectively.

Further functionalization of the allyl ether complexes was explored using the cyanomethoxy chromen complex **13**. Elimination of the methoxy group with acid cleanly generates the π-allyl complex **18** in 74% yield. This species, like its precursor

(10) The stereochemistry of this complex is known from a crystal structure determination. Data to be published separately.

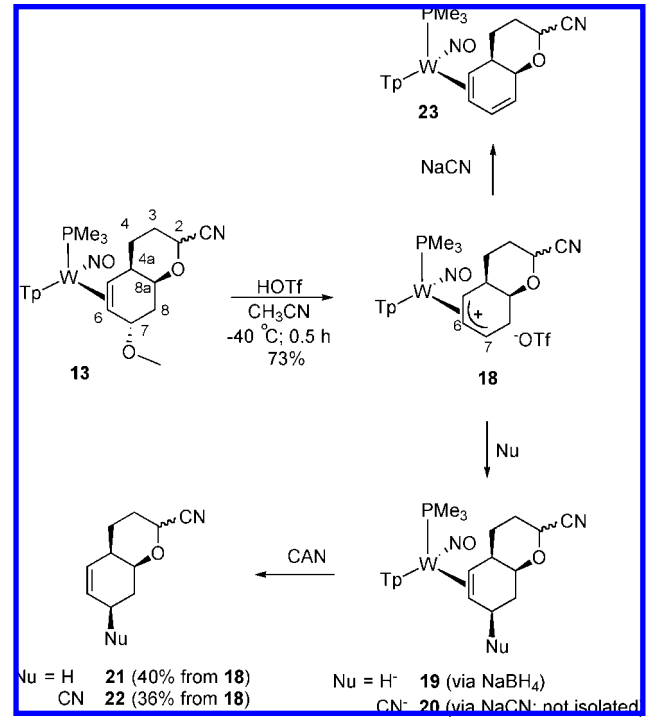
Table 2. Allyl Ether Oxadecalin Organic Molecules Isolated



product	R	nucleophile	dr (C2)	yield[a]
15	H	OMe	2:1	41
16	H	CN	1:1	60
17	Me	CN	4:1	60

[a] Isolated yield for the mixture of isomers.

Scheme 2. Synthesis of Octahydrochromen Cores



13, is isolated as a 1:1 ratio of C2 epimers. Spectroscopic features of this allyl complex indicates a highly asymmetric binding pattern. For example, one diastereomer displays resonances in the ^1H NMR spectrum at 6.12 (H7), and 4.50 (H5) for the terminal allyl positions with corresponding ^{13}C signals at 122.2 (C7) and 72.4 (C5) ppm. The other diastereomer shows similar signals. These data suggest an increase of positive charge at C7 for both diastereomers. This type of "η^2-allyl" character has been previously documented for both Mo and W nitrosyl systems.[11−13]

Stirring the allyl complex **18** with a nucleophile ($NaBH_4$ or NaCN) at 0 °C affords the addition products **19** and **20** (Scheme 2). Nucleophilic addition occurs exclusively at C7 resulting in a single isomer of these oxadecalin products. On the basis of precedent (vide infra), we suspect that the addition occurs to

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(13) Villanueva, L. A.; Ward, Y. A.; Lachicotte, R.; Liebeskind, L. S. *Organometallics* **1996**, *15*, 4190–4200.

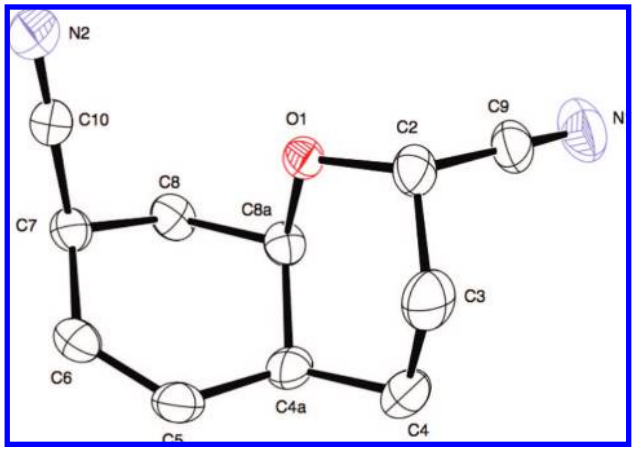
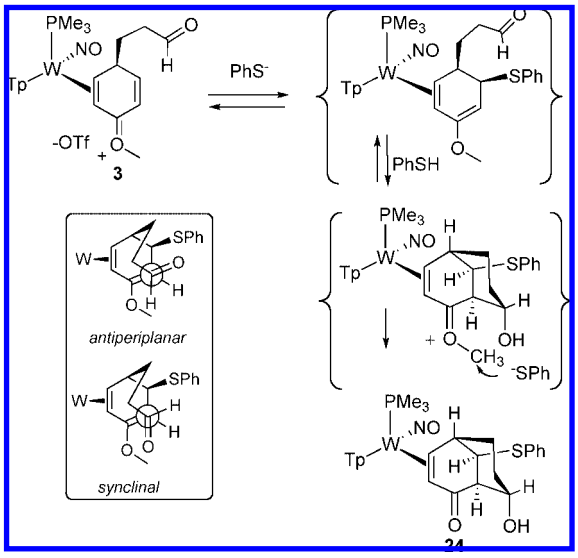


Figure 2. ORTEP of *cis*-oxadecalin **22**.

Scheme 3. Synthesis of Bicyclo[3.3.1]non-en-ones



the face of the carbocyclic ring anti to the metal fragment. However, we could not confirm this through H6 and H7 coupling data because of overlapping peaks in the ^{1}H NMR spectrum. The recovery of the oxadecalin, **21** was prepared from **18** by generating **19** in situ followed by the addition of CAN. In a similar manner, the cyano derivative **22** was prepared from **18** (via **20**) in 36% yield, and a crystal structure determination confirms the proposed stereochemical assignments of C4a, C7, and C8a (Figure 2). Presumably, **22** is formed via complex **20** (Scheme 2), but when we attempted to prepare and isolate this complex, a 1:1:1:1 mixture of four products resulted. We suspect that two of these products are the result of elimination, forming complex **23**. However, extensive overlap of peaks in the ^{1}H NMR spectrum and the inability to isolate these products prevented their confirmation. Efforts to decrease the formation of **23** by lowering the reaction temperature were unproductive as were our attempts to purify **20** by chromatography.

Interestingly, the pendant carbonyl of anisolium complex **3** can also undergo an *intramolecular* reaction with a suitable nucleophile. For example, in an attempt to generate a chromen complex analogous to complexes **5**−**8**, sodium thiophenoxide was combined with the acrolein-derived anisolium complex **3**. Rather than the anticipated chromen complex, an α,β-unsaturated enone complex (**24**) was isolated. This species showed a

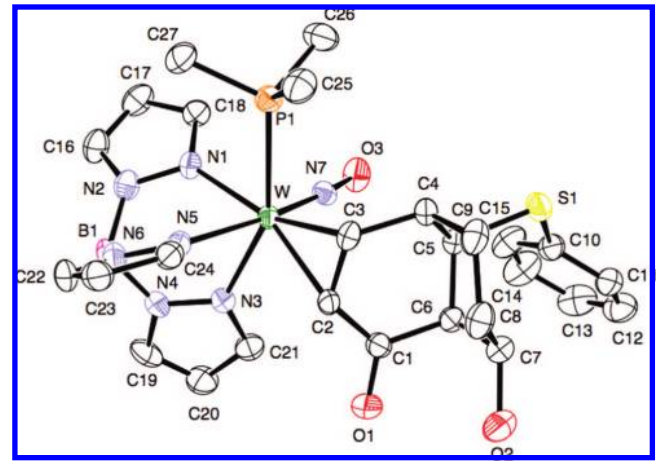
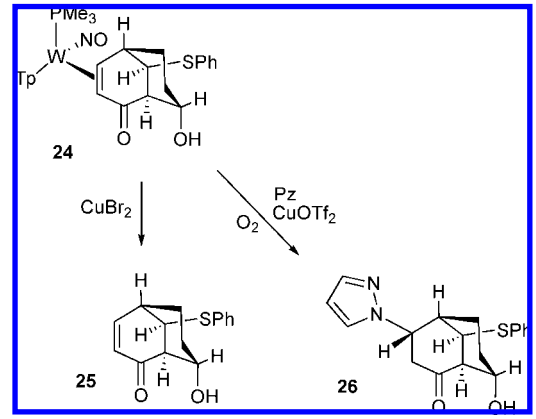


Figure 3. ORTEP of [3.3.1]bicyclononane complex **24**.

Scheme 4. Formation of Bicyclo[3.3.1]non-en-one Core



carbonyl stretching frequency at 1600 cm^{-1} similar to that of TpW(NO)(PMe$_3$)(η^2-2*H*-phenol).[14] Further, proton and carbon data for **24** indicated the loss of the methoxy group, and incorporation of the thiophenol moiety. HSQC and HMBC data led to the hypothesis that **24** was formed via thiophenol addition across C3 and C4. This was followed by the electrophilic addition of the aldehyde carbonyl to C2 of the originating arene and subsequent demethylation (Scheme 3). Ultimately, a crystal structure determination confirmed this hypothesis. Note from the ORTEP in Figure 3 that the initial Michael addition, the thiolate addition, and aldol reaction all occur anti to metal coordination. In addition, we note that the stereochemistry at C8 is consistent with a dipole-directed synclinal approach of the aldehyde to the purported vinyl ether intermediate (see Scheme 3).

What makes the reaction outcome with thiophenol and **3** different from those with other nucleophiles could be the exceptional ability of the thiophenolate ion to demethylate the purported oxonium intermediate (see Scheme 3) through an S$_N$2-type substitution mechanism. Through this demethylation, the retro-aldol and thiophenol elimination that would be required to restore **3** cannot take place.

The oxidation of **24** with CuBr$_2$ in CH$_3$CN led to the recovery of the bicyclic enone **25** in 50% yield (Scheme 4). The presence of air during the oxidation was found to cause a significant

(14) Todd, M. A.; Grachan, M. L.; Sabat, M.; Myers, W. H.; Harman, W. D. *Organometallics* **2006**, *25*, 3948–3954.

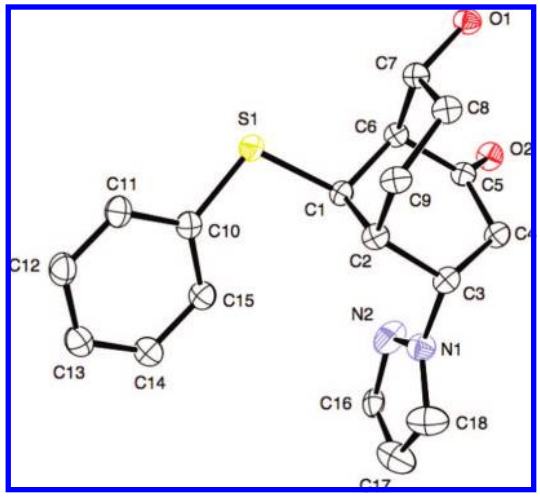
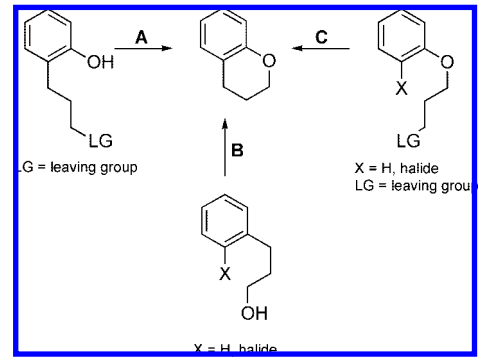


Figure 4. Crystal structure of pyrazolyl derivative **26**.

reduction in yield of **25** and the formation of new product, **26**. X-ray quality crystals of **26** were grown from methylene chloride, and a structure (ORTEP in Figure 4) determination indicated that **26** was the product of hydroamination of the once-bound alkene fragment of the bicyclononenone with pyrazole, which originates from fragmentation of the Tp ligand. The addition of excess pyrazole to the reaction mixture prior to addition of the oxidant and the use of $Cu(OTf)_2$ (still under an air atmosphere) in place of $CuBr_2$ increased the yield of the NH insertion product in solution to >95% (NMR). Unfortunately, the product was difficult to separate from the excess pyrazole, requiring fractional recrystallization to isolate **26** in pure form (11%). Of note, a control reaction of **25**, an excess of pyrazole, and $Cu(OTf)_2$ carried out in air failed to deliver even a trace of **26**. These observations along with the fact that the pyrazole added to the ring-face originally occupied by the tungsten suggests that the metal plays a central role in hydroamination. This decomplexation/hydroamination sequence is being further investigated.

The preparation of a chromen from an arene appears to be without precedent, but the aromatic chroman system is routinely synthesized from phenol[15−20] or other substituted benzene [21,22] precursors as outlined in Scheme 5.[23−30] Chromans have also

Scheme 5. Pathways to Chromans That Utilize Substituted Benzene Precursors



been prepared from fluorobenzenes using $\{Cr(CO)_3\}$[31] and $[Rh(C_5EtMe_4)Cl_2]_2$[32] to promote the aromatic substitution.

Conclusion

Anisole is activated by the metal fragment $\{TpW(NO)(PMe_3)\}$ allowing facile alkylations to the anisole ring that are both regio- and stereoselective. Addition of nucleophiles to the carbonyl of the resulting product has led to the formation of both chromen and bicyclo[3.3.1]nonen-2-one cores, controlling up to three and four stereocenters, respectively. Further manipulation to the vinyl ether of the chromen core has led to the isolation of the allyl ether scaffolds. Elimination of the methoxy and nucleophilic addition to the resulting allyl has led to novel chromen cores containing up to five new stereocenters. Taken together, the reaction sequences described herein demonstrate that with the aid of a single application of a tungsten dearomatization agent, all six of the benzene ring carbons can be chemically modified under mild reaction conditions and with predictable stereocontrol.

Acknowledgment. The authors gratefully acknowledge Beatrice Grasu for help characterizing compound **26**. This work was supported by the NSF (CHE-0111558 (UVA), 9974875 (UVA), 0116492 (UR), and 0320669(UR)).

Supporting Information Available: Full synthetic details for the preparation of compounds, selected spectra of these compounds, and crystallographic information for compounds **22**, **24**, and **26**. This material is available free of charge via the Internet at http://pubs.acs.org.i.

JA803605M

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