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Oxidative Demetalation of Cyclohexadienyl Ruthenium(II) Complexes: A Net Ru-Mediated Dearomatization

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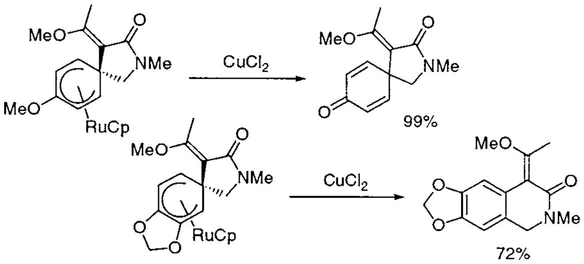
ABSTRACT



An experimentally simple method for the demetalation of spirocyclic cyclohexadienylruthenium(II) complexes has been developed. Treatment of an alkoxy-substituted cyclohexadienyl complex with $CuCl_2$ affords either azaspiro[4.5]decane derivatives or heavily functionalized tetrahydroisoquinolines. The former reaction manifold completes a net Ru-mediated dearomatization as the organometallic starting materials are prepared from (η^6-arene)Ru^{II} precursors. Both of these heterocyclic products are well suited for further synthetic elaboration.

The utility of (η^6-arene)metal complexes in synthetic organic and organometallic chemistry is well-documented, and numerous synthetic strategies that exploit the unique reaction manifolds available to these stable intermediates have been successfully implemented.[1] An avenue of investigation currently attracting considerable attention concerns the development of methods suitable for converting functionalized arene−metal complexes into nonaromatic metal-free cyclohexane derivatives.[2] The impetus for this work stems from the ready availability of aromatic (benzene-based) synthetic starting materials. Methods for manipulation of such building blocks, ideally in a stereocontrolled fashion, that result in formation of alicyclic compounds would provide new opportunities for construction of complex natural (and unnatural) products. Toward this end, metal-mediated dearomatization protocols involving η^6-arene complexes of Cr^0, Mo^0, and Mn^I are especially noteworthy, as are methods employing η^2-arene Os and Re complexes.[3,4]

In connection with efforts aimed at uncovering novel and concise synthetic routes suitable for the construction of polycyclic materials, we have begun to explore the potential of relatively simple (arene)Ru^{II} complexes to serve as versatile intermediates. Despite ease of preparation and favorable stability profiles, the synthetic utility of arene−Ru derivatives remains largely untapped.[5] In the course of

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(1) (a) Semmelhack, M. F. In *Comprehensive Organometallic Chemistry II*; Hegedus, L. S., Ed.; Elsevier Science, Ltd.: Oxford, 1995; Vol. 12, pp 979−1038. (b) Davies, S. G.; McCarthy, T. D. In *Comprehensive Organometallic Chemistry II*; Hegedus, L. S., Ed.: Elsevier Science, Ltd.: Oxford, 1995; Vol. 12, pp 1039−1070.

(2) Pape, A. R.; Kaliappan, K. P.; Kündig, E. P. *Chem. Rev.* **2000**, *100*, 2917.

(3) (a) Bernardinelli, G.; Gillet, S.; Kündig, E. P.; Liu, R.; Ripa, A.; Saudan, L. *Synthesis* **2001**, 2040. (b) Kündig, E. P.; Fabritius, C.-H.; Grossheimann, G.; Robvieux, F.; Romanens, P.; Bernardinelli, G. *Angew. Chem., Int. Ed.* **2002**, *41*, 4577. (c) Pearson, A. J.; Vickerman, R. J. *Tetrahedron Lett.* **1998**, *39*, 5931.

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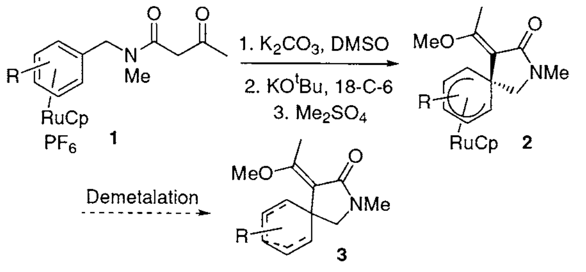
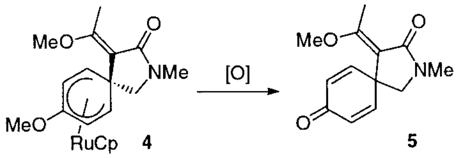
initial studies, we discovered a somewhat unexpected spirocyclization process operative in *N*-benzylacetoacetamide complexes bearing an η^6-coordinated CpRu^{II} fragment (**1**).[6] The reaction proceeds via regio- and stereoselective intramolecular nucleophilic aromatic addition followed by subsequent enolate O-alkylation. The product azaspiro cyclohexadienyl Ru^{II} complexes (**2**) are then isolated as stable materials in 44−86% yield (Scheme 1).[7] We recognized that successful removal of the CpRu^{II} fragment from **2** without disruption of the spirocyclic linkage would provide azaspiro[4.5]decane derivatives of the general structure **3** while at the same time completing an overall Ru-mediated dearomatization (i.e., **1** → **3**). This latter feature acquires added significance in that methods for the *efficient* transformation of arene−Ru (and Fe) complexes into functionalized nonaromatic alicyclic products have not been reported.[8]

Scheme 1



Initial attempts to effect demetalation of **2** (R = H) via protonolysis of the cyclohexadienyl ligand were unsuccessful, presumably due to the acid lability of the enol ether functionality.[7] We therefore decided to examine the viability of developing an oxidative demetalation process. A few reports describing the oxidative demetalation of various transition-metal fragments from allyl or dienyl ligands have appeared that are particularly relevant to our studies. Sutherland found that reaction of simple CpFe^{II} cyclohexadienyl complexes with DDQ results in loss of the CpFe moiety and re-aromatization of the ligand to afford substituted benzene products.[9] Pearson has reported a ceric ammonium nitrate (CAN) mediated oxygenation/cleavage of dienyl Mn^{I} complexes,[10] while CuCl$_2$ has been used to induce oxidative CO insertion/demetalation in Fe^{II} allyl alkyl complexes.[11] Copper^{II} chloride has also been successfully employed in the demetalation of certain (η^4-diene)Fe^0 complexes,[12] and CuCl$_2$ as well as CAN have been demonstrated to be effective demetalating agents for various substituted (η^3-allyl)Mo^{II} complexes.[10,13] For our studies, we chose to employ the methoxy-substituted complex **4** as the test substrate in anticipation of generating the "quinone-like" product **5** upon successful demetalation (Table 1). Gratifyingly, exposure of **4** to the oxidizing agents indicated did indeed afford **5** in each case, with CuCl$_2$ providing the best result. Dienone **5** is obtained as a single diastereomer whose structure was assigned on the basis of NMR spectroscopy and unambiguously confirmed through X-ray diffractometry (Figure 1). As **4** is derived from **1** (R = 4-OMe), the formation of **5** constitutes the first example of (η^6-arene)-Ru-mediated dearomatization leading to a functionalized cyclohexenone product.

Table 1. Oxidative Demetalation of Cyclohexadienyl−Ru Complex **4**[a]



[O]	conditions	% yield[b]
DDQ	3 equiv, CH_2Cl_2, rt	17
CAN	3 equiv, acetone, rt	7
$CuCl_2$	2 equiv, EtOH, rt	99

[a] Reactions performed using 0.12 mmol of **4**. [b] Isolated yield.

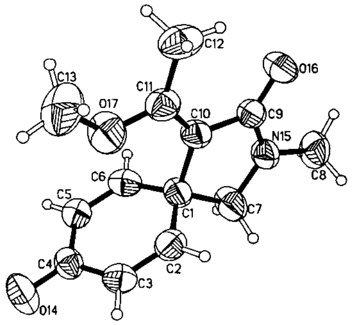


Figure 1. Molecular structure of **5** (ORTEP).

The applicability of this procedure for the demetalation of other spirocyclic cyclohexadienyl complexes was examined, and the results are summarized in Table 2. Further studies are required to elucidate the mechanistic features of this process (including the role of the Ru metal center); however, the origination of the products shown can be conveniently rationalized by invoking the intermediacy of a

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(12) Pearson, A. J. *J. Chem. Soc., Perkin Trans. 1* **1980**, 400.

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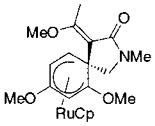
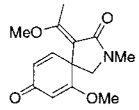
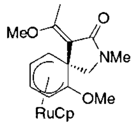
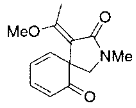
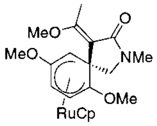
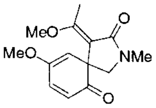
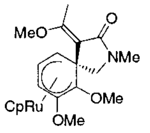
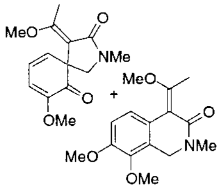
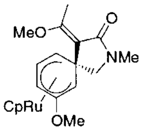
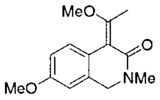
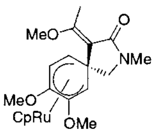
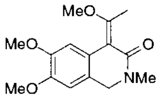
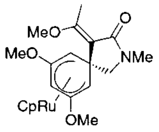
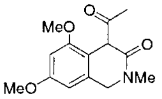
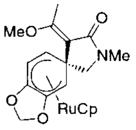
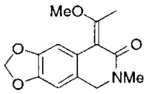
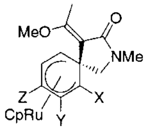
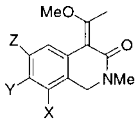
Table 2. $CuCl_2$-Mediated Demetalation[a]

Entry	Substrate	Product(s)	% Yield[b]
1			73
2			70[c]
3			92[c]
4			32 56
5			55
6			90
7			82[d]
8			72
9			
		X = Cl; Y = Z = H	22
		Y = Cl; X = Z = H	60
		Z = Cl; X = Y = H	84

[a] Conditions: substrate (~0.12 mmol), $CuCl_2$ (2 equiv), EtOH, rt, 30 min. [b] Isolated yield. [c] After treatment of crude product mixture with $P(OEt)_3$. [d] Hydrolyzed product was obtained.

cyclohexadienyl cation, perhaps generated via two single-electron oxidations (2 equiv of $CuCl_2$ is required for complete consumption of the substrates). Thus, demetalations in which a methoxy group is strategically located at the 2- or 4-position of the cyclohexadienyl substrate afford conjugated or cross-conjugated dienone products in good to excellent isolated yield (entries 1−3). In reactions leading to fully conjugated dienones (entries 2 and 3), ^1H NMR spectra of the crude products revealed the presence of the expected lactams as well as CpRu-containing species postulated to be the corresponding η^4-complexes. Accordingly, treatment of the crude product mixtures with $P(OEt)_3$ (2.2 equiv, THF, rt, 3 h) liberated the putative η^4 ligands from the CpRu fragments and dramatically improved the overall yield of the demetalation process. In addition, small amounts of $CpRuCl[P(OEt)_3]_2$ were also isolated from these reactions.[14]

The incorporation of an alkoxy substituent at the 3-position of the cyclohexadienyl ligand dramatically alters the outcome of oxidative demetalation. In these instances (entries 4−8), a skeletal rearrangement is observed that entails olefin migration and re-aromatization to produce heavily functionalized fused-ring tetrahydroisoquinoline derivatives exclusively (except for the reaction shown in entry 4). Cyclohexadienyl cation-like intermediates are also consistent with this fused-ring reaction manifold. The presence of a 3-alkoxy group facilitates vinyl cation migration (necessitating cleavage of the spirocyclic linkage) in a manner outwardly reminiscent of the well-known dienol−phenol rearrangement.[15] A comparison of the results shown in entries 3 and 4 seems to indicate that the rearrangement manifold is sensitive to steric effects as a tetrahydroisoquinoline product was not obtained in the former reaction. It is further noteworthy that the rearrangement pathway supersedes formation of a cross-conjugated dienone product as revealed in entry 6.

Interestingly, formation of tetrahydroisoquinoline products was also observed when chloro-substituted substrates were employed (entry 9). However, unsubstituted and methyl-substituted azaspiro cyclohexadienyl complexes failed to react cleanly with $CuCl_2$. Taken together, these results indicate that an electron-releasing substituent is required for controlled removal of the $CpRu^{II}$ fragment under these reaction conditions.

In conclusion, a mild and scalable method for demetalation of substituted cyclohexadienyl Ru^{II} complexes in high yield has been uncovered.[16] This procedure affords either nonaromatic spirocyclic dienones or novel tetrahydroisoquinoline derivatives, both of which are well suited for further synthetic elaboration. Indeed, the ring system present in **5** is directly related to the spirostaphylotrichin/triticone alkaloids (Figure 2).[17] Studies aimed at further expanding the scope of this demetalation process (particularly as it relates to dearomatization) and defining the synthetic utility of the heterocyclic products are underway.

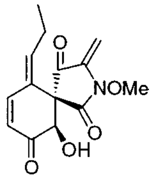


Figure 2. Spirostaphylotrichin C.

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Acknowledgment. We thank the NIH−NIGMS for financial support (1R15GM63529-01).

Supporting Information Available: Experimental procedures, compound characterization data, and X-ray structure of **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) Demetalation of **4** has been performed on a gram scale. **Experimental Procedure.** Ru-cyclohexadienyl substrate **4** (1.00 g, 2.4 mmol) and $CuCl_2$ (0.67 g, 5.0 mmol) were combined in 10 mL of EtOH, and the resulting mixture was stirred at room temperature for 30 min. During this time, a red solid precipitated from the reaction mixture. This solid was removed by filtration, and the filtrate was partitioned between CH_2Cl_2 and brine. The layers were separated, and the aqueous phase was re-extracted with CH_2Cl_2 (×2). The combined organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by radial chromatography (SiO_2, EtOAc) to afford **5** (0.46 g, 82%) as a yellow solid: mp 164 °C; $R_f = 0.40$ (EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ* 2.46 (s, 3H), 2.90 (s, 3H), 3.28 (s, 2H), 3.53 (s, 3H), 6.25 (d, $J = 9.9$ Hz, 2H), 6.78 (d, $J = 9.9$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.87, 30.08, 44.24, 54.35, 106.14, 127.84, 150.88, 164.38, 168.62, 186.30; IR (thin film) ν (cm^{-1}) 3030, 2952, 2913, 1660.8, 1622, 1402, 1262, 1061; HRMS (EI) calcd for $C_{13}H_{15}NO_3$ 233.1052 [M]$^+$, found 233.1053. Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.00. Found: C, 66.85; H, 6.39; N, 6.11.

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