Inhibition and Acceleration of the Bergman Cycloaromatization Reaction by the Pentamethylcyclopentadienyl Ruthenium Cation

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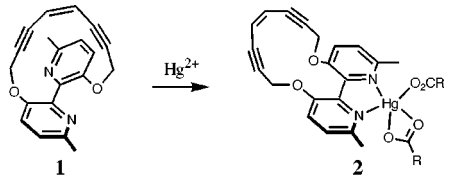
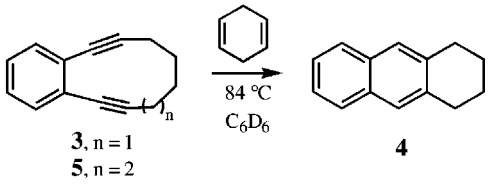
The fascinating mode of action exhibited by enediyne antitumor antibiotics has stimulated research into methods for controlling cycloaromatization of enediynes to 1,4-aryldiradicals (Bergman cycloaromatization[1]).[2] Among the ingenious methods developed for activation of cyclic enediynes is metal ion coordination.[3,4] In this approach, the activation energy for cyclization is lowered by metal ion coordination to heteroatoms judiciously situated within the enediyne framework. For example, complexation of $Hg(OCOCF_3)_2$ to the 2,2′-bipyridine unit within cyclic enediyne **1** leads to a conformational change in the enediyne core **2** and lowers the cyclization temperature by ∼100 °C.[3b] Here we report (1) the first conclusive evidence that metal coordination to the ene function of enediynes retards the rate of Bergman cycloaromatization,[5,6] and (2) a new organometallic trigger for the cycloaromatization of cyclic enediynes, one which does not require heteroatoms for metal ligation.[7]



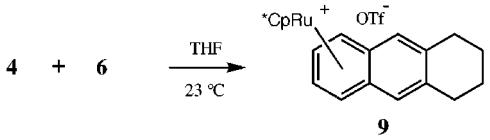
Semmelhack previously reported that heating benzene-d_6 solutions of 3,4-benzo-cyclodec-3-ene-1,5-diyne **(3)** and 1,4-cyclohexadiene (0.5 M) at 84 °C gave tetrahydroanthracene (**4)** with a half-life of 24 h.[8] The 11-membered ring analogue **5** failed to undergo a thermal Bergman cyclization.



In an effort to prepare a robust η^6-arene complex of **3** we employed the "super-areneophile" $[(\eta^5\text{-}C_5Me_5)Ru(NCMe)_3][OTf]$ (**6**).[9−11] When a THF solution of **3** (50 mg, 54 mM) and **6** (140 mg, 54 mM) was stirred under a nitrogen atmosphere at 23 °C (12 h), the arene complex $[(\eta^5\text{-}C_5Me_5)Ru(\eta^6\text{-}3,4\text{-benzocyclodec-3-ene-1,5-diyne})][OTf]$ (**7**) precipitated from solution as white flakes in 47% unoptimized yield (Scheme 1).

When the reaction of **3** and **6** was monitored by ^1H NMR spectroscopy (CD_2Cl_2 or THF-d_8), a set of minor resonances was observed in addition to those that arise from **7**. In particular, a singlet at δ 6.79 (THF-d_8) was attributed to the aromatic hydrogens (residual protio resonances) on the ruthenium-bound central ring of cyclization product **8**.

When THF-d_8 or NO_2CD_3/CH_3CN solutions of **7** were heated at 60 °C (72 h), no conversion to **8** was observed by ^1H NMR spectroscopy. Furthermore, the reaction of tetrahydroanthracene (**4**) and **6** in THF (rt, 12 h) gave an 83% isolated yield of arene complex **9**,[15c] which proved to be stable in THF-d_8 at 60 °C (72 h). Thus, complex **8** does not arise from either **7** or **9** via ruthenium migration, nor does it arise from in situ formation of **4** and subsequent ruthenium complexation.



To improve the yield of cycloaromatization product and substantiate the occurrence of a metal-accelerated Bergman cycloaromatization, the substituted enediynes **10** and **11** were examined in reactions with **6**. In the absence of **6**, neither **10** nor **11** undergo a cycloaromatization in THF at room temperature.

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(15) (a) Crystal data for **7**: $C_{25}H_{27}F_3O_3RuS$, orthorhombic, *Fdd*2, a = 25.1032(6) Å, b = 51.8895(12) Å, c = 7.3805(2) Å, V = 9613.8(6) Å^3, Z = 16, T = 173 K, 4968 reflections and 298 parameters, $R(F)$ = 0.0465, $wR(F^2)$ = 0.1319. (b) Crystal data for **3**: $C_{14}H_{22}$, tetragonal, $P4_12_12$, a = 7.916(2) Å, b = 7.916(2) Å, c = 16.556(6) Å, V = 1037.3(6) Å^3, Z = 4, T = −87 °C, 818 reflections and 64 parameters, $R(F)$ = 0.0469, $wR(F^2)$ = 0.1120. A less precise X-ray structural analysis of **3** has been reported: Bennett, M. J.; Smith, R. A. *Acta Crystallogr.* **1977**, *B33*, 1123. (c) Crystal data for **9**: $C_{25}H_{29}F_3O_3$-RuS, orthorhombic, *Pnma*, a = 29.2978(8) Å, b = 11.4140(3) Å, c = 7.4888-(2) Å, V = 2504.30(18) Å^3, Z = 4, T = 223 K, 1759 reflections and 173 parameters, $R(F)$ = 0.0915, $wR(F'^2)$ = 0.2920. The triflate counterion is both rotationally and end-for-end disordered. Both ions reside on a crystallographic mirror plane.

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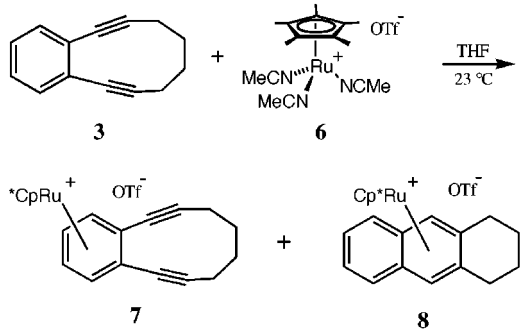
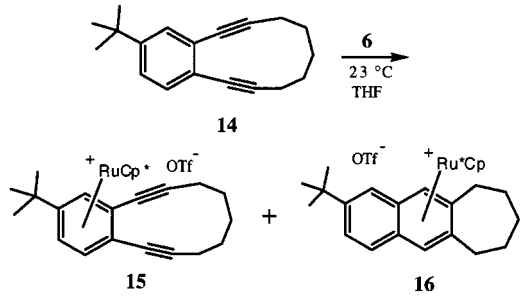
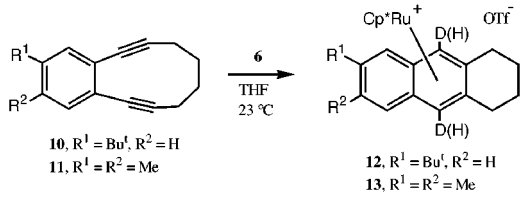
Scheme 1



Scheme 2



However, when a THF solution of **10** (17 mg, 8.4 mM) and **6** (32 mg, 8.4 mM) was maintained at room temperature for 5 h, the cyclized product **12** was formed and isolated as a yellow solid in 71% yield. In a similar fashion, reaction of enediyne **11** with **6** in THF at room temperature led to isolation of ruthenium arene **13** as yellow solid in 63% yield. Consistent with the formation of a 1,4-diradical intermediate, the reaction of **10** with **6** in THF-d_8 gave the cyclized product **12**-*d* with 79% deuterium incorporation at the aromatic hydrogen positions in the complexed ring.



In an effort to extend this new cycloaromatization reaction to a less strained cyclic enediyne, we examined the reaction of the 11-membered ring enediyne **14** with **6** (Scheme 2). In THF solution **6** (84 mg, 33 mM) and **14** (45 mg, 32 mM) underwent a slow reaction at room temperature over the course of 65 h to give ~42% yield of two C_5Me_5 containing products in a 2.7:1 ratio. Although the mixture was not separated, on the basis of ^{1}H NMR spectroscopic data ($CDCl_3$), we assign structure **15** [δ 5.71 (s, 1H), 5.96 (d, 1H), 6.31 (dd, 1H)] to the minor product, and cyclized structure **16** [δ 6.41 (s, 1H), 6.44 (s, 1H), 7.33 (d, 1H), 7.52 (d, 1H), 7.71 (dd, 1H)] to the major product. The acyclic enediyne, 4-*tert*-butyl-1,2-di(1-propynyl)benzene, also underwent reaction with **6** over the course of 48 h in THF but gave only the uncyclized arene complex in 71% yield.

The mechanism of this new metal-accelerated Bergman cycloaromatization remains to be established; however, the above results indicate that 1,4-diradicals are involved and point to ruthenium−alkyne interactions as a key feature of the triggering process for cycloaromatization. The increased yield of cycloaromatized product from substituted enediynes **10** and **11**, relative to unsubstituted **3**, is presumably related to steric inhibition of ruthenium coordination to the arene in **10** and **11**, which in turn shifts a partitioning between uncyclized and cyclized product toward the cyclized form.

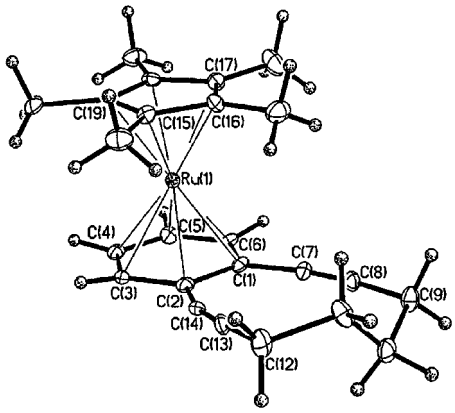


Figure 1. ORTEP diagram (30% thermal ellipsoid probabilities) for (**7**). Selected bond lengths (Å) and angles (deg) are given for (**7**) with the corresponding value for the free enediyne (**3**) in brackets: C1−C2 1.448-(10) [1.414(5)], C1−C7 1.431(9) [1.437(3)], C2−C14 1.431(10) [1.437-(3)], C7−C8 1.219(9) [1.187(4)], C14−C13 1.207(9) [1.187(4)]; C1−C2−C14 118.1(6) [117.04(14)], C2−C1−C7 116.8(6) [117.04(14)], C1−C7−C8 164.2(7) [166.4(3)], C2−C14−C13 166.5(6) [166.4(3)], C7−C8−C9 174.3(7) [174.7(3)], C12−C13−C14 174.9 (6) [174.7(3)].

Access to **3** and **7** permitted a determination of the effect that metal−ene coordination has on the rate of a Bergman cycloaromatization reaction. In nitromethane-d_3 (1,4-cyclohexadiene, 0.21 M), enediyne **3** (0.056 M) underwent a clean cycloaromatization to give **4** over the course of 18 days at 100 °C. In marked contrast, the ruthenium complex **7** was stable under essentially identical reaction conditions. Whereas **3** undergoes a photochemical Bergman cycloaromatization in the presence of 1,4-cyclohexadiene,[12,13] photolysis (Hanovia 450 W, 48 h) of **7** in CD_2Cl_2 in the presence of 1,4-cyclohexadiene (0.25 M) failed to give an observable reaction by NMR spectroscopy.

The reluctance of **7** to undergo cycloaromatization (relative to **3)** is presumably related to decreased aromaticity in the incipient 1,4-diradical which would be generated from **7**. In the solid-state structure of **7** (Figure 1), the C8−C13 nonbonded distance of 3.32 Å is typical of 10-membered ring enediynes[14] and similar to the 3.27 Å distance observed in the solid-state structure of **3**.[15] Within experimental uncertainty, there is little difference in bond angles and distances between **3** and **7** (Figure 1, caption).

Efforts are currently underway to develop a catalytic version of this novel cycloaromatization chemistry, and extend the work reported here to nonaromatic acyclic enediyne and simple dieneyne substrates.

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Supporting Information Available: Characterization data for compounds **7**, **9**, **12**, **13**, the **15**/**16** mixture, and **17**; tables of crystallographic data for **3**, **7**, and **9** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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