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Ruthenium-Mediated Cycloaromatization of Acyclic Enediynes and Dienynes at Ambient Temperature

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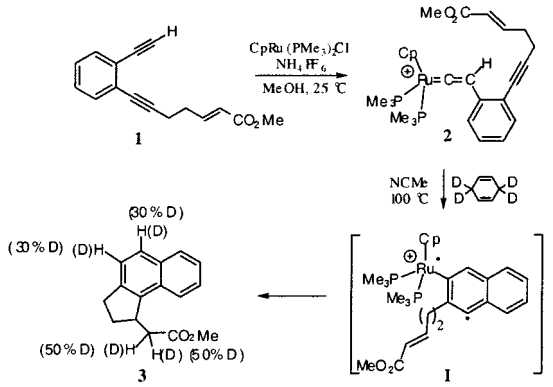
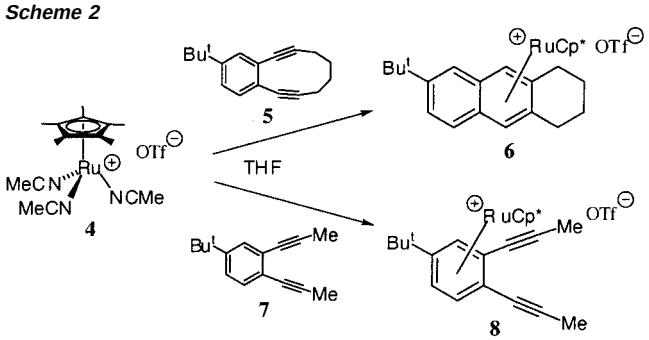
Potential applications of the Bergman[1] cycloaromatization in synthetic[2] and medicinal chemistry[3] have stimulated research into methods for promoting enediyne cycloaromatization under mild conditions.[4−7] This is particularly desirable in the case of non-strained acyclic 3-ene-1,5-diyne substrates which often require elevated temperatures for onset of thermal cycloaromatization. Of particular note in this regard is Finn's report on the conversion of diyne **1** to vinylidene **2**, which undergoes cycloaromatization at 100 °C in the presence of 1,4-cyclohexadiene to give **3** (Scheme 1).[6a] When 1,4-cyclohexadiene-d_4 was used as a D-atom donor, 30% deuterium incorporation was observed at both the C4- and C5-hydrogen positions of the benz[*e*]indene product, leading the authors to propose a Myers−Saito-type mechanism[7] involving the diradical intermediate **I**.

Scheme 1



We previously reported that [(η^5-C_5Me_5)Ru(CH_3CN)$_3$]OTf (**4**)[8] mediates the room-temperature cycloaromatization of *strained-ring* benzoenediynes, such as the conversion of enediyne **5** to **6** (Scheme 2).[9] We were disappointed to find that the strain-free acyclic enediyne **7** failed to cyclize, but instead gave only the uncyclized η^6-arene complex **8**.

Scheme 2



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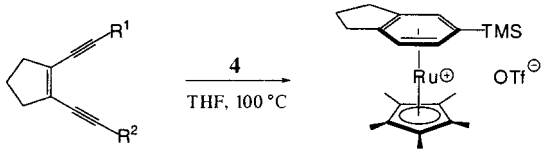
We now report that complex **4** does indeed mediate the cycloaromatization reaction of *acyclic*[10] enediynes, as well as the cycloaromatization of conjugated dienynes.

When a THF-d_8 solution of **9**-TMS and 1,4-cyclohexadiene was heated at 150 °C for 14 d, there was no evidence for the formation of a dihydroindene derivative by ^{1}H NMR spectroscopic analysis of the sample. However, reaction of **9**-TMS (103 mg, 0.4 mmol) and the ruthenium complex **4** (0.4 mmol) in THF (10 mL) at 100 °C led to isolation of the η^6-[(2,3-diyhdro-1H-inden-5-yl)-trimethylsilane] complex **10** in 69% yield (Scheme 3). Under similar conditions the enediynes with bulky alkyne substituents, **9**-Bu^t, **9**-TIPS, and **9**-Me, failed to undergo a detectable (by NMR spectroscopy) cycloaromatization reaction.

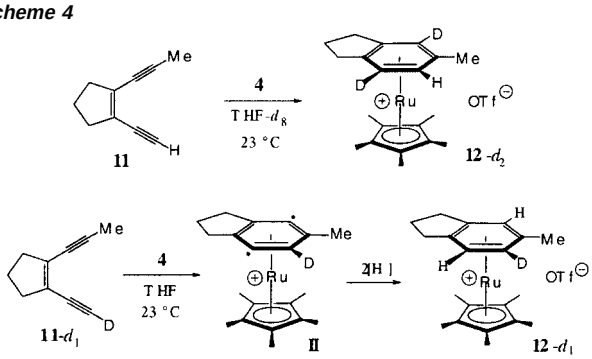
Scheme 3



9-TMS, $R^1 = R^2$ = TMS
9-Bu^t, $R^1 = R^2$ = Bu^t
9-TIPS, $R^1 = R^2$ = TIPS
9-Me, R^1 = Me, R^2 = TIPS

The work of Finn suggested that loss of a TMS substituent in the conversion of **9**-TMS to **10** may have generated a terminal alkyne capable of cycloaromatization via a vinylidene mechanism. We therefore examined the reaction of 1-ethynyl-2-(1-propynyl)-cyclopentene (**11**; 0.048 mmol, 4.8 mM) with **4** (0.047 mmol) in THF solvent and observed the *room-temperature* formation of **12** in 92% isolated yield (Scheme 4). When the reaction was carried

Scheme 4



out in THF-d_8 and monitored by ^{1}H NMR spectroscopy, the deuterium-enriched arene **12**-d_2 was formed within 10 min at room temperature. Integration of the ^{1}H NMR signals for **12**-d_2 indicated ca. 90% deuterium enrichment at both the C4- and C7-hydrogen positions. Furthermore, reaction of the deuterium-labeled analogue

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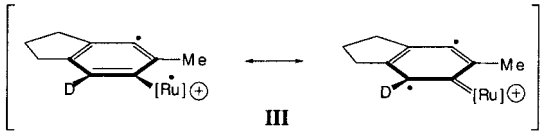
11-d_1 (83% deuterium enrichment at the ethynyl hydrogen) and **4** led to the formation of **12**-d_1 with 63% deuterium incorporation at the C6-hydrogen position and no isotopic enrichment at either the C4- or C7-hydrogen sites.

These isotopic labeling results are consistent with the formation of a *p*-benzyne intermediate, possibly arene complex **II**, in the conversion of **11** to **12**. The absence of deuterium incorporation at the C7-hydrogen position of **12**-d_1 rules out a vinylidene-based mechanism proceeding via diradical **III** (Chart 1).

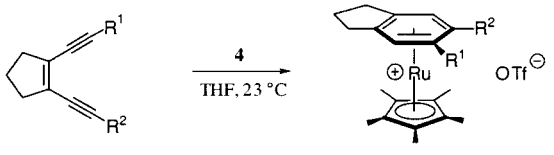
Chart 1



III

Encouraged by the results with enediyne **11**, the reactions of internal enediynes **13**-Me, **13**-Pr^n, **13**-Bu^i, and **14** with **4** were examined (Scheme 5). In all cases, a rapid reaction with **4** occurred within minutes at room temperature to give good yields of the η^6-dihydroindene complexes **15** and **16**.

Scheme 5

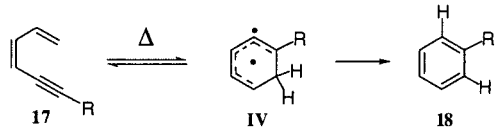


13-Me, $R^1 = R^2 =$ Me
13-Pr^n, $R^1 = R^2 =$ Pr^n
13-Bu^i, $R^1 = R^2 =$ Bu^i
14, R^1 = Me, R^2 = TMS

15-Me, $R^1 = R^2$ = Me; (64% yield)
15-Pr^n, $R^1 = R^2$ = Pr^n; (73% yield)
15-Bu^i, $R^1 = R^2$ = Bu^i; (88% yield)
16, R^1 = Me, R^2 = TMS; (77% yield)

The substantial driving force exhibited by the [Cp*Ru] cation for enediyne cycloaromatization suggested that conjugated dienynes may be susceptible to a ruthenium-mediated Hopf cyclization.[11] As shown in Scheme 6, the Hopf cyclization involves the high temperature (200−250 °C) conversion of hexadienynes, **17**, to benzene derivatives **18**. As is the case for the thermal Bergman cycloaromatization, the Hopf cyclization proceeds via a cyclic intermediate of diradical character (**IV**).

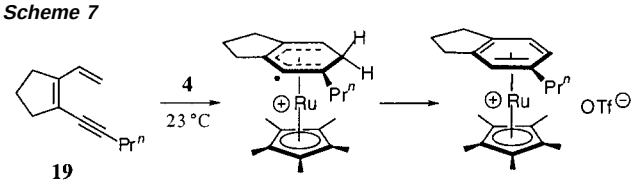
Scheme 6



17 **IV** **18**

In a preliminary experiment, treatment of dienyne **19** (0.029 mmol) with **4** (0.029 mmol) in THF-d_8 solvent (0.23 mL) at room temperature led to the formation of the η^6-dihydroindene complex **20** within 10 min (52% NMR yield; Scheme 7). In contrast to the

Scheme 7



19 **V** **20**

reactions of **4** with enediynes in THF-d_8, there is no deuterium enrichment (<5% by ^{1}H NMR analysis) at any dihydroindene hydrogen position in **20**. The location of the *n*-propyl substituent at C5 excludes a vinylidene intermediate in the formation of **20**.[12,13] The lack of significant D-atom abstraction from THF-d_8 and the rapid rate of reaction suggested that $CDCl_3$ may also serve as a solvent.[14] Indeed, reaction of **19** (0.023 mmol) and **4** (0.023 mmol) in $CDCl_3$ (0.44 mL) at room temperature (50 min) resulted in the formation of **20** in 96% NMR yield, with no significant deuterium enrichment. By analogy with intermediates **II** and **IV**, the Ru(III) cyclohexadienyl cation **V** must be considered as a *potential* intermediate in the conversion of **19** to **20**. However, intermediate **V** requires a H-atom transfer, possibly intramolecular, which is rapid relative to the rate of D-atom abstraction from solvent

Finally, we note that the lack of cycloaromatization of enediyne **7** may be the result of a more rapid Ru-arene formation, which is not possible with the cyclopentene substrates reported herein. Studies are currently underway to determine the detailed mechanism and scope of these new metal-mediated cycloaromatization reactions.

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Supporting Information Available: Characterization data for compounds **13**−**16**, **19**, **20** and tables of crystallographic data for **10** and **15**-Pr^n (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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