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Construction of Novel Polycyclic Ring Systems by Transition-Metal-Catalyzed Cycloisomerization of Ene−Ene−Ynes. Interception of a Carbenoid Intermediate in Skeletal Reorganization of Enynes

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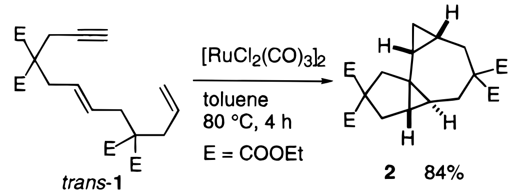
The synthesis of complex organic molecules from simple, readily available starting materials is one of the challenging projects in organic synthesis.[1] The transition-metal-catalyzed cycloisomerization of substrates containing two elements of unsaturation, such as ene−ene,[2] ene−diene,[3] ene−yne,[4−8] ene−allene,[9] diene−diene,[10,11] diene−yne,[12] and diene−allene,[13] offers an attractive pathway for the conversion of acyclic substrates to cyclic compounds which have been difficult to prepare by conventional methods thus far. Such reactions give cyclized products which retain functionalities that are useful for further synthetic transformations. Thus, it is clear that cycloisomerization reactions represent a powerful tool for the construction of a variety of cyclic systems. The cycloisomerization of substrates which contain three or more elements of unsaturation would be a further useful method for the construction of novel ring systems if a single product could be obtained. However such reactions are rare.[14]

Recently, we reported the $RuCl_2$- and $PtCl_2$-catalyzed cycloisomerization (skeletal reorganization) of 1,6-enynes to 1-vinylcyclopentenes.[4] Although Trost[5] and Mori[6a] independently discovered formally similar transformations, the mechanism of these reactions are different from one another. Trost proposed the intermediacy of the palladacyclopentene complex, a Pd(IV) complex, via the oxidative cyclization of enynes with Pd(II), and the reaction described by Mori clearly proceeds via a ruthenium−carbene mechanism. In addition, the first step in the catalytic reaction studied in this laboratory appears to be complexation of metal halides to an acetylene.[15] Although we have little information relative to the precise reaction mechanism, a carbenoid intermediate is proposed to play a key role. We reasoned that if the carbenoid complex is an intermediate in the reaction pathway, then it might be possible to trap in situ the carbenoid intermediate using trapping agents with appropriate species which are known to react with carbene complexes.[17] We found that this can be accomplished using an intramolecular olefin.[18] We wish to report a remarkable catalytic reaction in which interception of not only the first intermediate in the cycloisomerization but also the second intermediate has been achieved (eq 1). The reaction involves the formation of four carbon−carbon bonds. Although this multibond participating reaction seems rather complex, it is surprisingly general and provides a unique path to a polycyclic framework.



(1)

The reaction of dodeca-6,11-dien-1-yne derivative, *trans*-**1**, in toluene in the presence of 4 mol % $[RuCl_2(CO)_3]_2$ at 80 °C for 4

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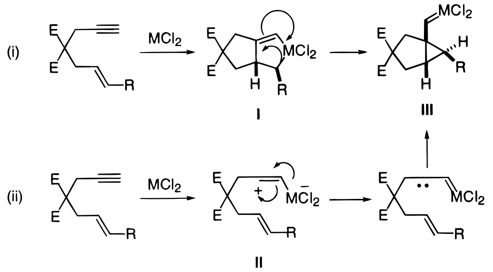
[15] Of the possibilities for the first step of the catalytic cycle, the following two pathways appear to be the most realistic: (i) via metalacyclopentene **I** and (ii) via a slipped, polarized η^1-alkyne complex bearing a positive charge at the β psition **II**. As we compare these two mechanisms, pathway (ii) appears to be more plausible on the basis of the following analysis. A complex closely related to **II** was proposed in the reaction of acetylenes with a ruthenium(II) complex by Dixneuf.[16] Although oxidative cyclization of enynes usually occurs with a low valent transition metal complex, it seems unlikely that this process would occur uniquely with such a diversity of metal complexes, such as Ru(II), Pt(II), Rh(II), Ir(I), and Re(I). Clearly, additional experiments will be required to completely understand the reaction mechanism.



Moreover, the mechanism of generation of the carbenoid complex **III** is not clear and must also await further studies.

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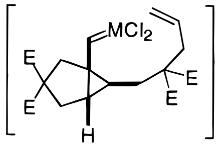
h under an atmosphere of N_2 gave rise to a stereocontrolled cycloisomerization to produce the tetracyclo[6.4.0.0.^{1,9}0^{2,4}]-undecane derivative **2**[19,20] in 84% isolated yield as a single stereoisomer (eq 1). The structure of **2** was established by ^{1}H and ^{13}C NMR spectroscopic investigations (including H−H, C−H, and C−C COSY and NOE), mass spectrometry, and combustion analysis. It is interesting to note that other transition-metal complexes, such as $PtCl_2$ (75% yield, 4 h), $[Rh(OOCCF_3)_2]_2$ (72%, 1 h), $[IrCl(CO)_3]_n$ (54%, 4 d), and $ReCl(CO)_5$ (74%, 1 d) also show catalytic activity for this very complex transformation. In all cases, the skeletal reorganization product, 1-(1,6-heptadien-1-yl)cyclopentene derivative, was not detected by GC in the crude reaction mixture, which is in contrast to our previous observation.[4] The reaction involves two cyclopropanation reactions where both acetylenic termini formally act as a carbene to react with olefins. The reaction is rationalized by the intermediacy of a carbenoid intermediate **3**, which undergoes intramolecular cyclopropanation to give **2**.

We next examined the reaction of *cis*-**1**. If the first cyclopropanation leading to a carbenoid complex takes place stereospecifically, the carbenoid complex **4** would be expected to be generated from *cis*-**1**. The carbenoid moiety in **3** is sufficiently close to react with the intramolecular olefin. On the other hand, the complex **4** would not be expected to undergo cyclopropanation because the carbenoid moiety is too distant to react with the olefin; this is true. The reaction of *cis*-**1** did not result in the formation of the corresponding tetracyclic compound, but rather, a complex reaction mixture was obtained.



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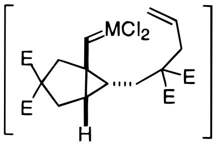
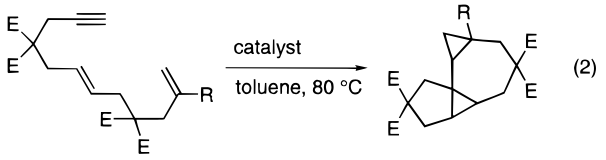


4

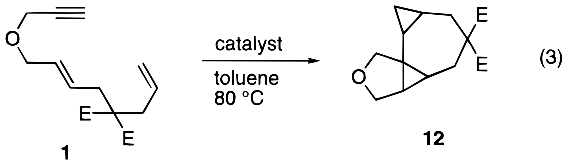
Following our findings that the successful synthesis of tetracyclic compounds depends on the stereochemistry of the olefin, we examined various *trans*-isomers of dodeca-6,11-diene-yne derivatives. Substitution of a methyl or phenyl group at the internal olefinic carbon of the terminal alkene moiety has little effect on the efficiency of the cycloisomerization (eq 2). Treatment of chloro-substituted substrate **9** with $[RuCl_2(CO)_3]_2$ or $PtCl_2$ gave complex mixtures. However, the use of $[Rh(OOCCF_3)_2]_2$ as a catalyst gave the corresponding polycyclic compound **10** in good yield. Although the stereochemistry of each product was not determined, it is assumed that all of the products have the same stereochemistry as **2**.

An interesting limitation, based on the structure of the substrates, was noted. Substrates bearing a substituent at the external terminus of the olefin and substrates having one-carbon longer in the tether did not afford the corresponding tetracyclic compounds, but rather, the usual skeletal reorganization took place in moderate yields. It is apparent that a steric effect in the vicinity of the carbenoid moiety is an important factor for the second cyclopropanation to proceed.



5 R = Me	$[RuCl_2(CO)_3]_2$	4 h	**6** R = Me	70%
	$PtCl_2$	1 h		61%
	$[Rh(OOCCF_3)_2]_2$	30 h		41%
7 R = Ph	$[RuCl_2(CO)_3]_2$	18 h	**8** R = Ph	62%
	$PtCl_2$	18 h		30%
	$[Rh(OOCCF_3)_2]_2$	1 h		69%
9 R = Cl	$[Rh(OOCCF_3)_2]_2$	1 h	**10** R = Cl	60%

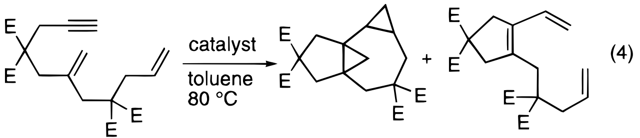
The present reaction can be extended to the use of an oxygen-containing tether. Subjecting the oxygen atom-containing substrate **11** to similar reaction conditions provides the oxatetracycloundecane derivative **12** (eq 3).



1 **12**

$PtCl_2$	2 days	33%
$[Rh(OOCCF_3)_2]_2$	1 day	34%

The juxtaposition of the unsaturation determines the ring system being formed. For example, the reaction of **13** creates a tetracyclo[6.6.1.0^{1,8}0^{2,4}]undecane system[20] although the usual skeletal reorganization reaction competed with this (eq 4).



13 **14** **15**

		14	**15**
$[RuCl_2(CO)_3]_2$	1 h	0%	75%
$PtCl_2$	1 h	0%	90%
$[Rh(OOCCF_3)_2]_2$	1 h	51%	34%

In summary, the reaction described herein demonstrates a novel, one-step entry to unprecedented polycylic ring systems from acyclic starting substrates. The starting materials are readily prepared, and the resulting fused tetracycles are an unprecedented framework which are difficult to prepare using reported methods. The procedure is quite simple. It is noteworthy that the formation of the tetracyclic compounds suggests the intervention of a carbenoid intermediate in the transition-metal-catalyzed skeletal reorganization of 1,6-enynes, which we have reported earlier.[4]

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Supporting Information Available: Lists of special data and elemental analyses of the products (5 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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(19) All new compounds were characterized by NMR, IR, and mass spectral data and by elemental analyses or high-resolution mass spectra. See the Supporting Information.

(20) This ring system could not be found in Chemical Abstracts by CAS ONLINE.