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# New cyclizations via catalytic ruthenium vinylidenes*

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*Abstract*: New carbocyclizations that proceed via catalytic metal-vinylidenes are presented. Metal-vinylidene catalytic species, which are easily accessible from terminal alkynes and catalytic amounts of transition-metal complexes, can be involved either in pericyclic reactions or in tandem processes triggered by nucleophilic attack at the electrophilic position of the vinylidene. In both cases, a wide variety of valuable cyclic compounds are easily accessible. Some recent carbocyclizations will be described.

*Keywords*: cyclizations; metal-vinylidenes; pericyclic reactions; nucleophilic additions; carbocycles.

## INTRODUCTION

Many natural products and functionalized organic materials have carbocyclic structures. In particular, natural products containing medium-sized carbocycles continue to be important targets because of the synthetic challenges that they present and the potent biological activity that they frequently possess [1]. For this reason, the discovery of new reactions that allow the implementation of novel strategies for medium ring-sized carbocycles continues to be an important endeavor in organic synthesis [2]. Ideally, these strategies should conform to the atom-economy principle [3], occurring with high efficiency, selectivity, and in an environmentally benign fashion. In this sense, transition-metal catalysts continue to occupy a central role in modern organic reactions and have shown an increasing ability to accomplish these goals, both in improving existing processes and in the discovery of new ones. Among these systems, metal-vinylidene complexes, which are easily formed by activation of terminal alkynes with several transition metals [4], have emerged as very useful catalytic species in pericyclic reactions on the double bond of the vinylidene or through the exploration of the electrophilic nature of $C_\alpha$ of the metal-vinylidene with different nucleophiles [5].

A review of new and useful cyclization processes involving metal-vinylidenes is provided here.

## VINYLIDENES IN PERICYCLIC REACTIONS

Metal-vinylidenes can take part in electrocyclizations, cycloadditions, or sigmatropic rearrangements to give five- or six-membered carbocycles [5d].

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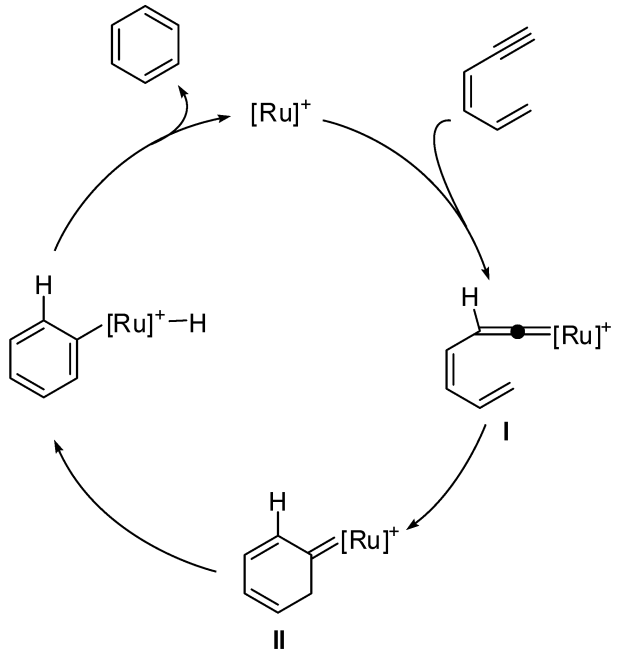
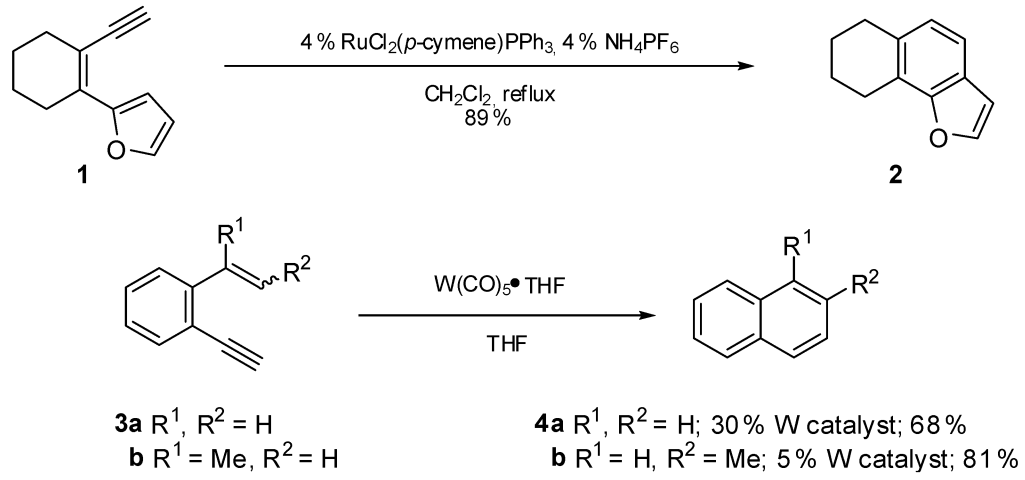
### Electrocyclizations involving catalytic metal-vinylidenes

Double bonds of Ru-vinylidenes of type **I**, obtained by the treatment of dienynes with available Ru(II)-complexes, can participate in a 6 $e^-$ π electrocyclization to Ru-carbene **II**. β-Hydride elimination from **II** followed by reductive elimination liberates benzene derivatives and the Ru-catalyst is regenerated (Scheme 1).



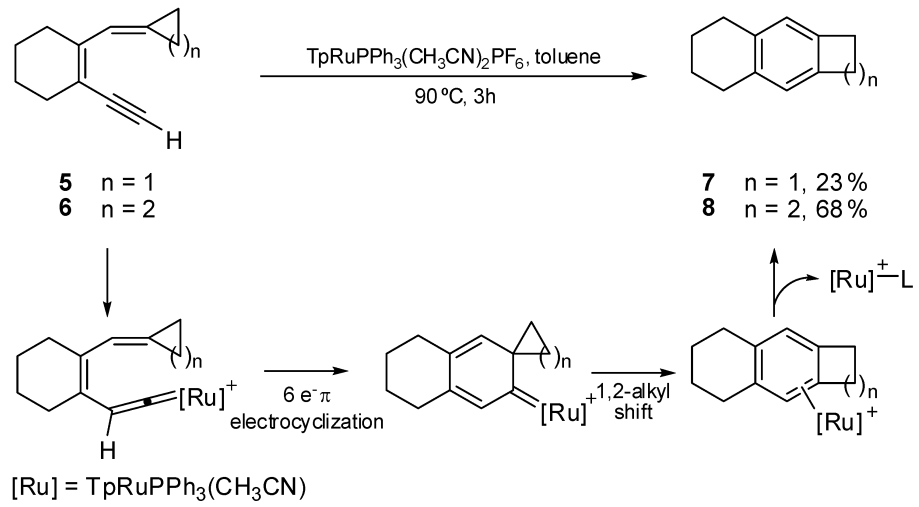

**Scheme 1** Proposed mechanism for the electrocyclization of Ru-vinylidenes.

Several examples of 6 $e^-$ π electrocyclizations involving metal-vinylidenes, such as Ru [6] or W [7], have been reported (Scheme 2).



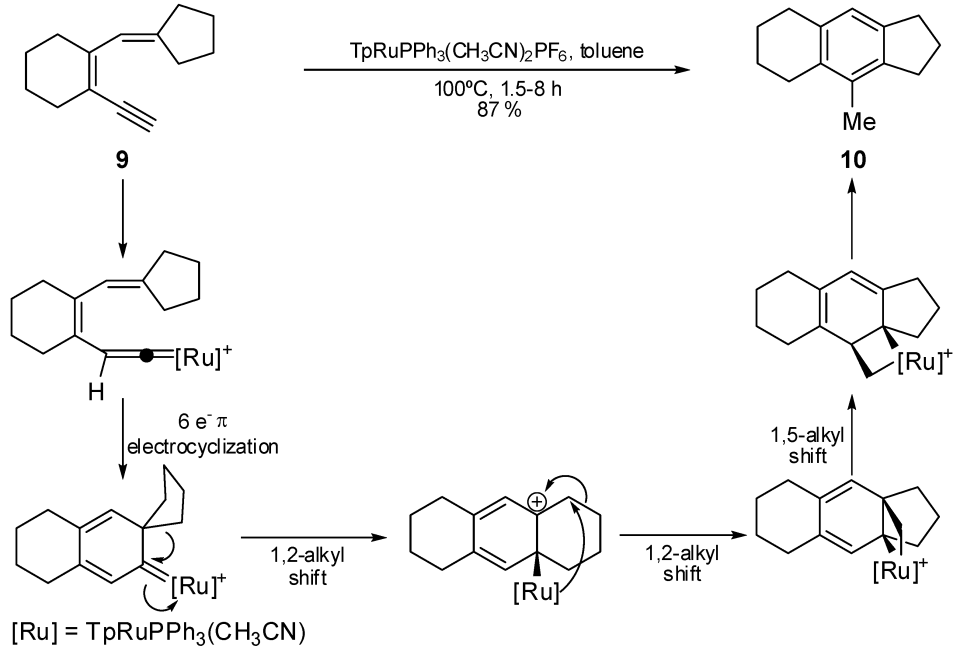

**Scheme 2** Ru- and W-catalyzed cycloisomerizations of dienynes to aromatic compounds.

More complex polycyclic structures can be achieved by regioselective 1,2-alkyl shift after the electrocyclization reaction of cyclopropylidenyl and cyclobutylidenyl derivatives **5** and **6** (Scheme 3) [8].




**Scheme 3** Cyclization of 3,5-dien-1-ynes with 1,2-alkyl shift.

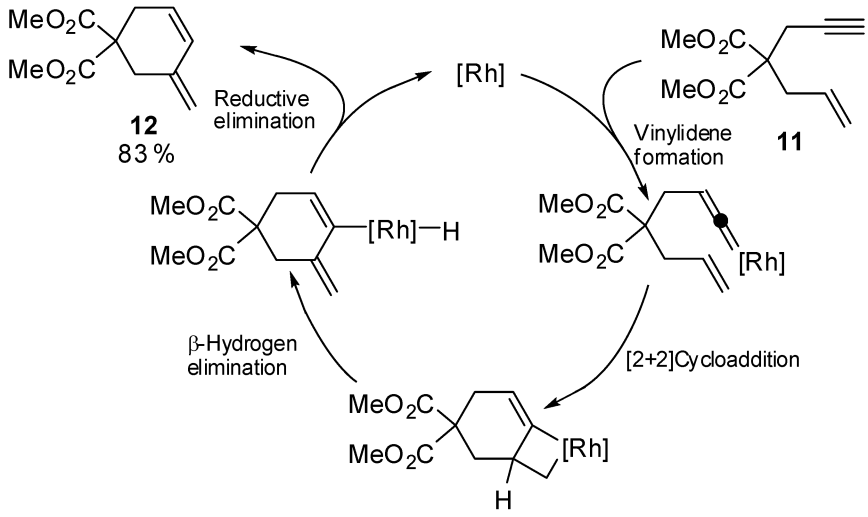
Surprisingly, when cyclopentylidene derivative **9** was used, polycyclic benzene **10** with an unexpected methyl group was obtained [8]. This transformation probably involves an initial 6 $e^{-}$ π electrocyclization followed by a regioselective 1,2-alkyl shift and the transfer of a methylene group (Scheme 4).




**Scheme 4** Ru-catalyzed methylene transfer reaction.

### [2+2] Cycloadditions involving catalytic metal-vinylidenes

Double bonds of metal-vinylidenes can also be involved in [2+2] cycloaddition reactions with unsaturated compounds, either inter- or intramolecularly. For example, treatment of 1,6-enyne **11** with $[Rh(cod)Cl]_2$ catalyst in the presence of a 10 mol % of $P(4\text{-}FC_6H_4)_3$ in DMF at 85 °C for 24 h afforded the cyclohexene **12** in excellent yield (Scheme 5) [9]. The proposed mechanism involves the initial formation of a Rh-vinylidene species and this undergoes a [2+2] cycloaddition with the pendant alkene followed by ring-opening of the rhodacyclobutane.

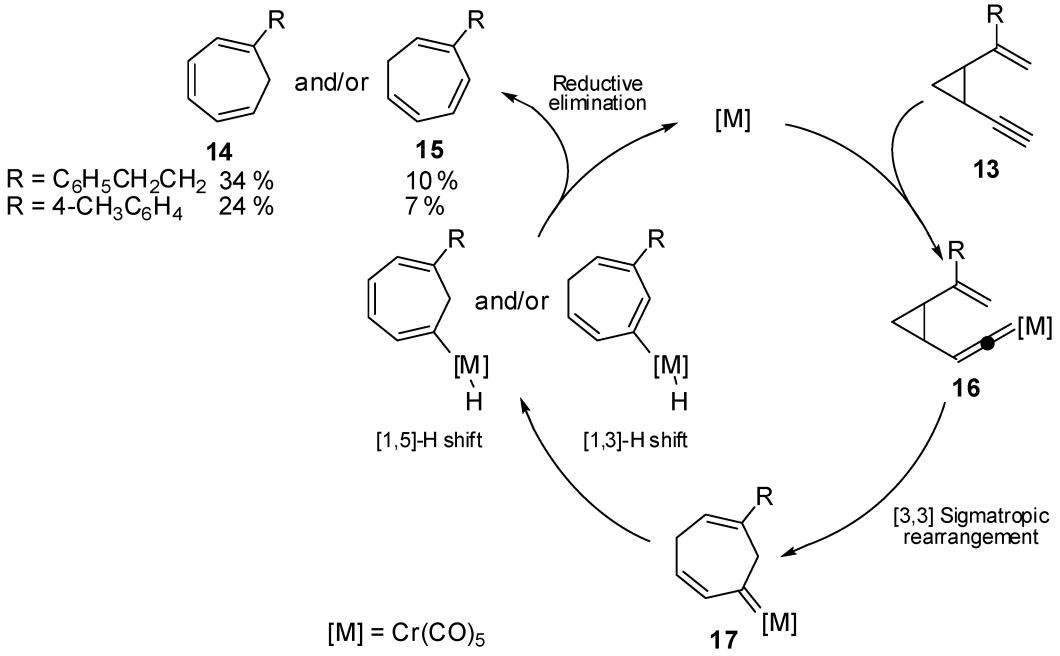



**Scheme 5** Proposed mechanism for [2+2] cycloadditions of Rh-vinylidenes.

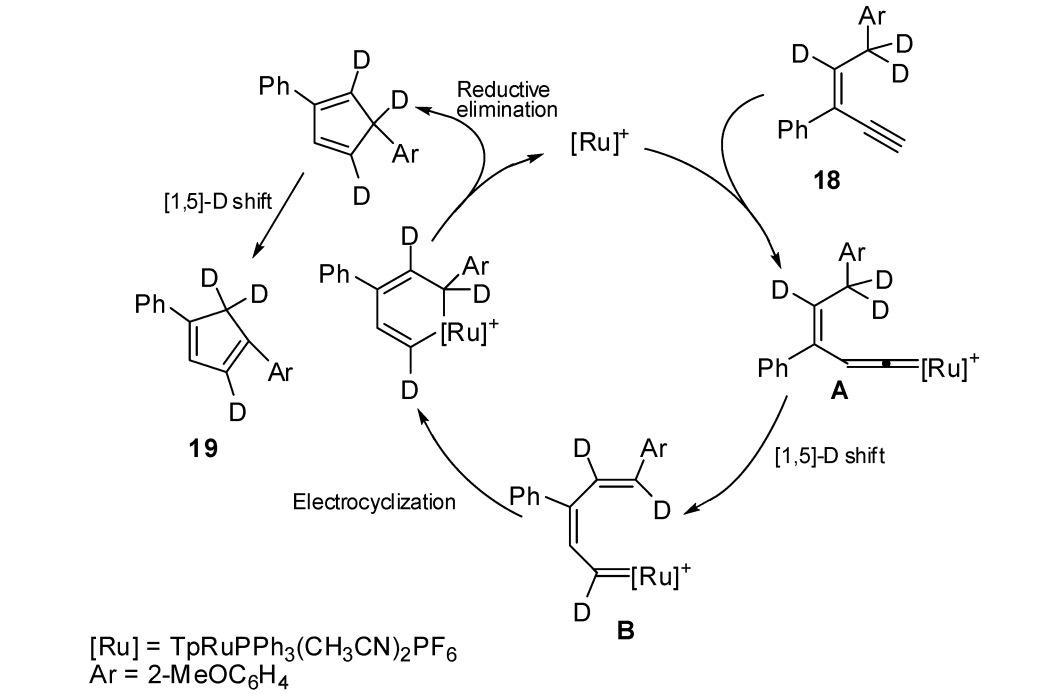
### Sigmatropic rearrangements involving catalytic metal-vinylidenes

Metal-vinylidene complexes can also participate in sigmatropic rearrangements to give carbocyclic compounds. For example, reaction of *cis*-vicinal vinyl-ethynylcyclopropanes **13** with catalytic amounts of group 6 transition-metal complexes affords a mixture of cycloheptatrienes **14** and **15** (Scheme 6) [10]. The formation of cycloheptatrienes can be explained in terms of a [3,3]-sigmatropic reaction of the initially formed vinylcyclopropylvinylidene **16** to give a seven-membered carbene complex **17**. Formation of the two isomeric 1,3,5-cycloheptatrienes can be explained by assuming the subsequent [1,5]- and [1,3]-hydrogen shifts in complex **17** followed by reductive elimination (Scheme 6).

[1,5]-Sigmatropic rearrangements of Ru-vinylidenes **A** derived from *cis*-enynes **18** followed by electrocyclization and reductive elimination of the intermediate Ru-carbene **B** to give cyclopentadienes **19** have also been reported (Scheme 7) [11].




**Scheme 6** Proposed mechanism for Cr-catalyzed [3,3]-sigmatropic rearrangement of metal-vinylidenes.



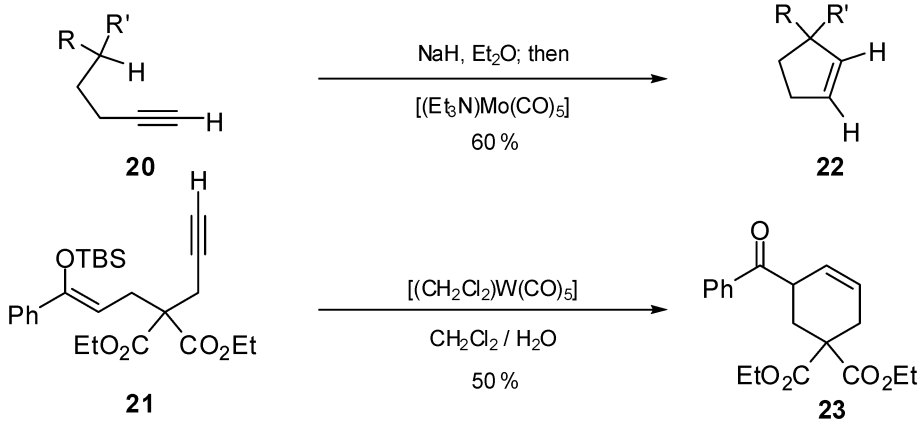

**Scheme 7** Proposed mechanism for the cycloisomerization of enynes through [1,5]-sigmatropic rearrangements.

## NUCLEOPHILIC ADDITION TO VINYLIDENES

The electrophilic nature of the $C_\alpha$ of metal-vinylidenes makes these species very reactive toward different types of nucleophiles to give Fisher-type carbene complexes, which can ultimately evolve to give useful functionalized carbocycles [5,12].

### Addition of *C*-nucleophiles

A variety of *C*-nucleophiles have been added to metal-vinylidenes to give five- or six-membered carbocycles (Scheme 8). For example, intramolecular attack of activated methylenes **20** or silyl-enol ethers **22** to Mo-vinylidenes [13] or W-vinylidenes [14] affords cyclopentenes **22** and cyclohexenes **23**, respectively.

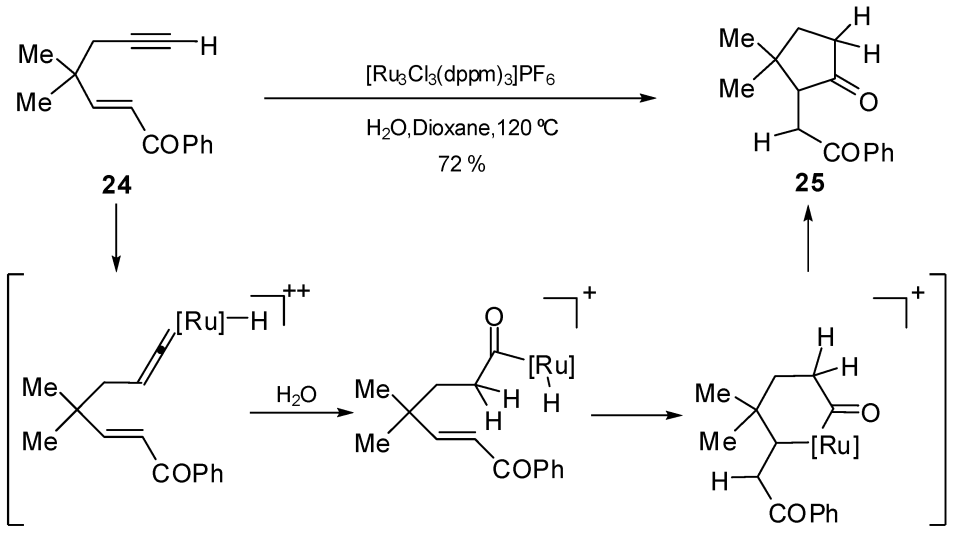



**Scheme 8** Carbocycloisomerizations of alkynyl-carbon nucleophiles.

### Addition of hetero-nucleophiles to catalytic metal-vinylidenes

#### *Addition of $H_2O$*

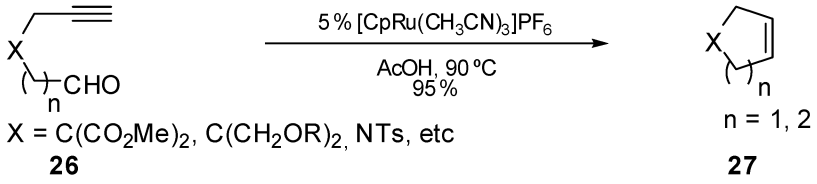
An efficient, substituent-tolerant and highly regioselective *anti*-Markovnikov hydration of terminal alkynes to aldehydes takes place by addition of water to the electrophilic $C_\alpha$ of Ru-vinylidenes [15]. Recently, a tandem hydration/cyclization reaction of 1,5-enynes **24** to afford cyclopentanones **25** has been described (Scheme 9) [16]. The reaction begins with the *anti*-Markovnikov hydration of the terminal alkyne via a Ru-vinylidene followed by the cyclization of an acylmetal species onto the conjugated alkene.




**Scheme 9** Hydration/cyclization of 1,5-enynes.

### *Addition of AcOH*

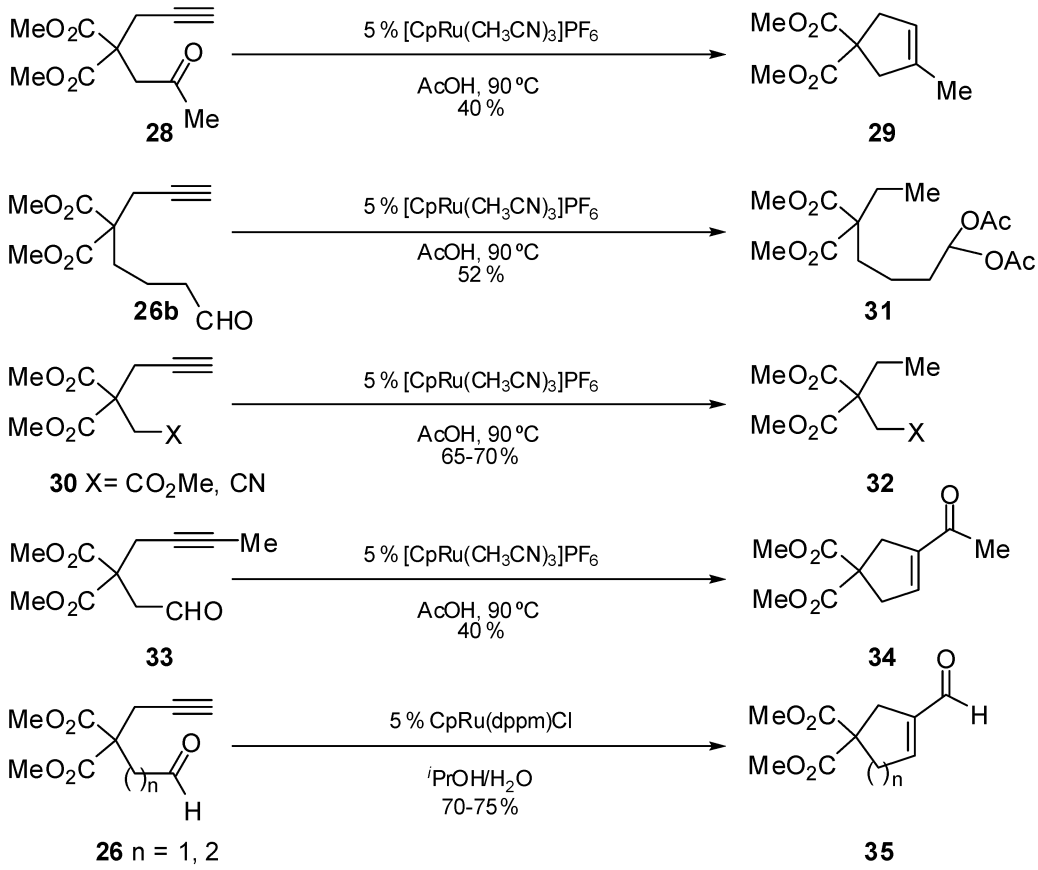
Reaction of terminal alkynals **26** in the presence of catalytic amounts of $[CpRu(CH_3CN)_3]PF_6$ in acetic acid at 90 °C affords cycloalkenes **27**, with the loss of one carbon, in excellent yields (Scheme 10) [17].




**Scheme 10** Ru-catalyzed cyclization of terminal alkynals.

A series of experiments was carried out in an effort to clarify the scope and limitations of this transformation (Scheme 11):

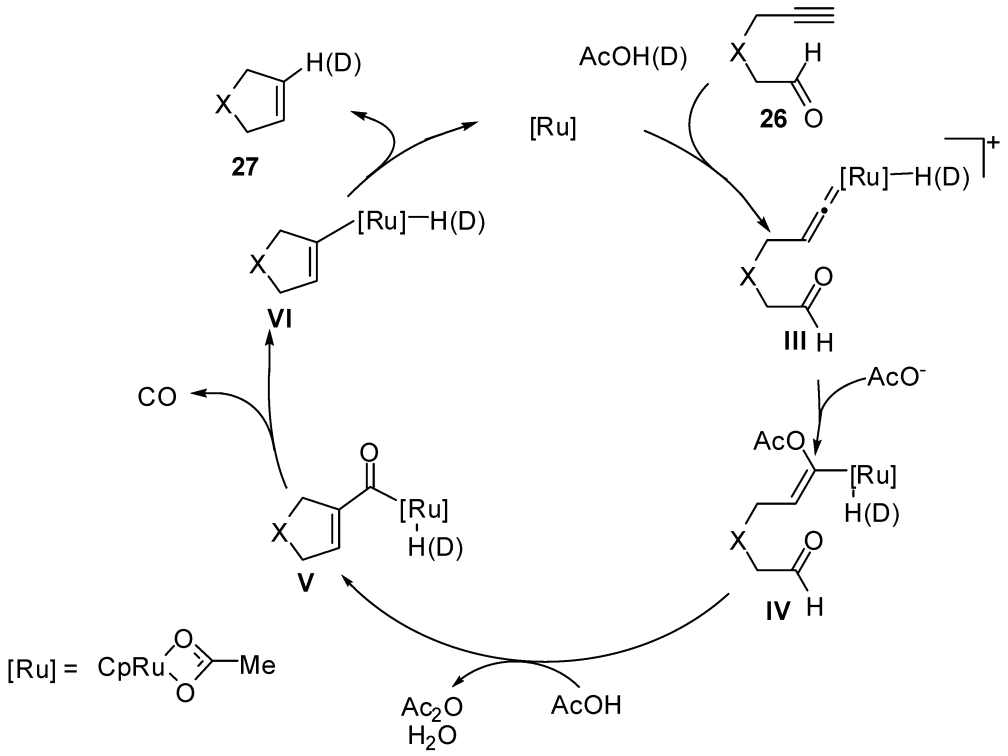
- Alkynone **28** afforded the corresponding cyclopentene **29**, indicating that an oxidative addition of the Ru to the aldehyde C–H bond is unlikely.
- Both 1,8-alkynals **26b** ($n = 3$, Scheme 10) and alkynes without the aldehyde group (**30**) gave rise to noncyclized acetals **31** and **32**, respectively, with the loss of one carbon. This suggests that the terminal carbon of the alkyne is the one lost during the reaction.
- When nonterminal alkynal **33** was used, a cycloisomerization occurred to give ketone **34**.
- Interestingly, terminal 1,6- and 1,7-alkynals were able to cycloisomerize to conjugated aldehydes (all of the carbons from the starting material remained) on using only CpRu(dppm)Cl as the catalyst in *i*PrOH/$H_2O$ as solvent.



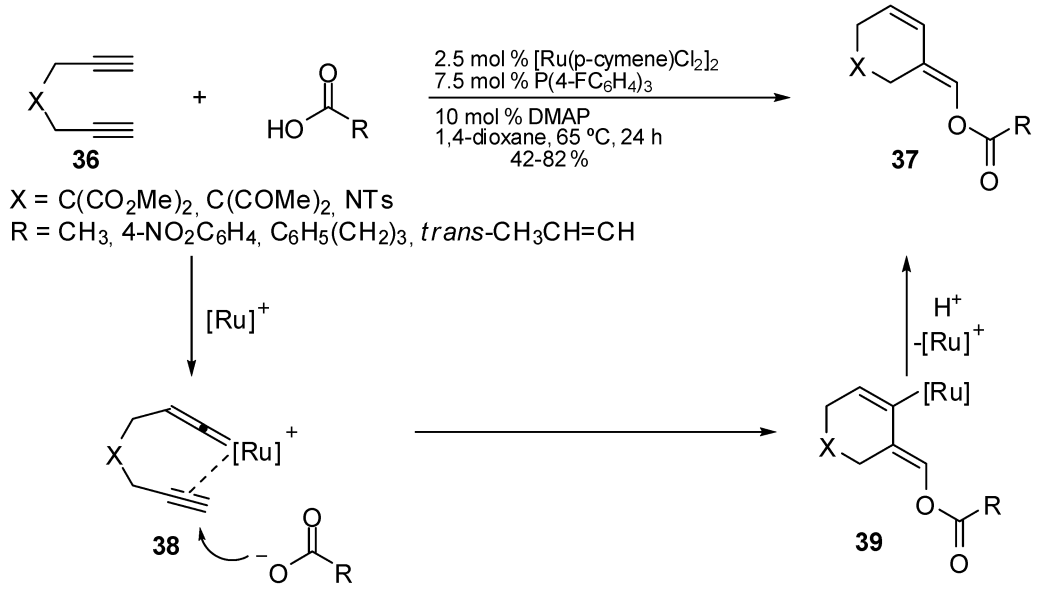

**Scheme 11** Scope and limitations of the Ru-catalyzed reaction of terminal alkynals.

A plausible mechanism for the Ru-catalyzed cyclization of terminal alkynals is depicted in Scheme 12. After the initial formation of Ru(II) vinylidene species **III**, nucleophilic addition of the acetic acid would afford the vinyl Ru species **IV**. A subsequent aldol-type condensation would give the acyl Ru hydride **V**. Reductive elimination products derived from intermediates **IV** (vinyl acetate) or **V** (aldehyde) did not afford the observed cycloalkene **27** after heating their solutions in AcOH at 90 °C in the presence of the Ru catalyst, showing that such a process is unlikely to occur. Finally, decarbonylation (*in which the terminal carbon of the alkyne is lost as CO*) followed by reductive elimination would afford the observed cycloalkenes **27**. When CpRu(dppm)Cl was used as a catalyst, the conjugated aldehydes **35** were obtained by reductive elimination from **V** (decarbonylation did not take place in this case due to the bidentate nature of the dppm ligand).

Very recently, a new Ru-catalyzed tandem addition/cyclization of 1,6-diynes **36** and carboxylic acids has been reported and gives six-membered-carbocyclic systems **37** (Scheme 13) [18]. A mechanistic proposal for this transformation involves the initial formation of the Ru-vinylidene **38** with the pendant alkyne coordinated to the metal center. Addition of the carboxylic acid to the alkyne moiety would afford vinylruthenium species **39**. The final protiodemetallation then furnishes the product and turns the catalyst over.




**Scheme 12** Plausible mechanism for the decarbonylative Ru-catalyzed cyclization of terminal alkynals.




**Scheme 13** Proposed mechanism for carboxylative diyne cyclization.

## CONCLUSIONS

In summary, the use of catalytic-metal vinylidenes is emerging as one of the most powerful methodologies for the activation of functionalized compounds bearing terminal alkynes. Pericyclic reactions involving the metal-vinylidene double bonds or tandem reactions triggered by nucleophilic attack at the electrophilic $C_\alpha$ of the vinylidene give rise to functionalized carbocyclic compounds in a very efficient manner.

## ACKNOWLEDGMENTS

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