Ruthenium-Mediated Domino Sequence Forming Six-Membered Ring Diene from Ene-Yne and Alkene

Masahiro Murakami, Minoru Ubukata, and Yoshihiko Ito
Department of Synthetic Chemistry and Biological Chemistry, Graduate School of Engineering, Kyoto University, Yoshida, Kyoto 606-8501

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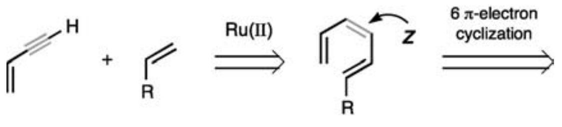
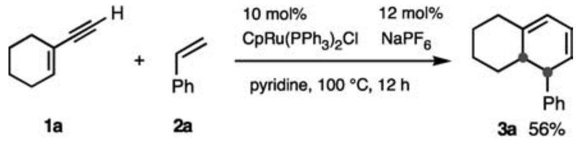
A new domino reaction is developed in which a six-membered ring diene is formed in a regio- and stereoselective manner from an ene-yne and an alkene through the mediation of a ruthenium complex.

The Diels-Alder [4 + 2]cycloaddition reaction is arguably the most important tool to build six-membered carbocycles.[1] Typically, an electron-rich 1,3-diene and an electron-deficient dienophile are employed. Strenuous reaction conditions, however, are required for the combination of substrates lacking electron-withdrawing or -donating substituents. Considerably wider substrate scope is provided by the use of transition metal complexes, which act as a template bringing the unsaturated substrates together in the right array to promote the cycloaddition reaction.[2] We now report a different type of transition metal-mediated process which constructs a six-membered cyclic conjugated diene in a regio- and stereoselective manner from an ene-yne and an alkene. The reacting partners which are not activated by electron-withdrawing or -releasing substituents undergo a formal [4 + 2]cycloaddition sequence consisting of two mechanistically distinct steps.

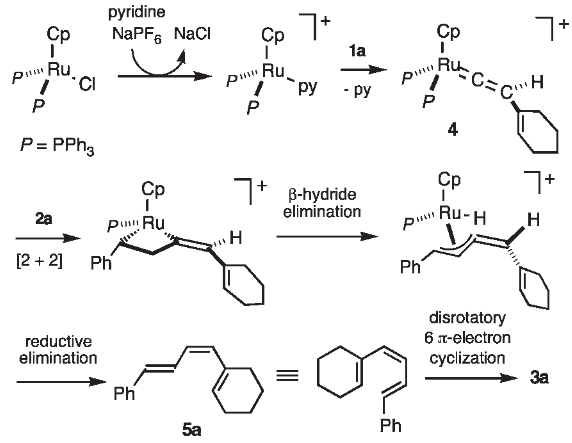
We have recently reported a ruthenium-catalyzed coupling reaction of an alkene with a terminal alkyne.[3] The ruthenium vinylidene complex initially formed from a terminal alkyne couples with the alkene, ultimately resulting in formal *trans* 1,2-addition of the C_{sp2}–H linkage of the alkene across the C–C triple bond. Of note is that the thermodynamically less stable *Z* geometry is laid on the C–C double bond developing from the alkyne. Although several other ruthenium-catalyzed processes which allow an olefin and an alkyne to be connected have been reported, they all outfit the produced double bond with *E* geometry.[4] The *trans* addition mode providing *Z* geometry attracted us in respect that application of this reaction to a terminal ene-yne would afford a conjugated triene geometrically fit for 6 π-electron electrocyclic reactions.



Thus, we examined the ruthenium-catalyzed reaction of ene-yne **1a** and styrene **2a**. A pyridine solution of **1a** and **2a** (10 equiv) was heated at 100 °C for 12 h in the presence of [CpRu(PPh_3)$_2$Cl] (10 mol%) and $NaPF_6$ (12 mol%). After chromatographic isolation, bicyclic conjugated diene **3a** was obtained stereoselectively[5] in 56% yield.



The stereoselective formation of diene **3a** is explained by assuming the following pathway. The *trans* addition of the terminal C_{sp2}–H linkage of styrene **2a** across the C–C triple bond of ene-yne **1a** occurs by the mechanism proposed previously to involve ruthenium vinylidene complex **4**.[3,6] As the result, conjugated triene **5a** is produced. The intervening double bond has *Z* geometry, and the phenyl-substituted double bond has *E* geometry. The *Z* geometry contained in **5a** permits a six-membered transition state for the subsequent electrocyclic ring-closing reaction to occur. Thermally allowed disrotatory motion of the substituents accounts for the stereospecific formation of **3a** from **5a**.



The above-mentioned mechanism consisting of two distinct steps was verified by the experiment using 4-phenyl-1-butene **2b**, which was less reactive than styrene **2a**. When ene-yne **1a** was reacted with **2b** under analogous conditions for 90 min, formation of triene **5b** having *Z* geometry for the internal double bond was observed in the ^{1}H NMR spectrum of the reaction mixture. On further heating in the absence of the ruthenium catalyst, triene **5b** was converted to the cyclohexadiene derivative **3b** by a thermal electrocyclic ring-closing reaction. The ruthenium-catalyzed reaction of **1a** with **2b** at 140 °C for 24 h directly afforded **3b** stereoselectively in 49% yield.

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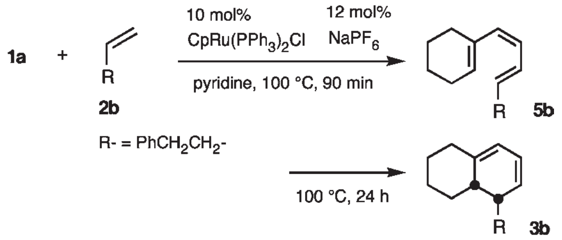
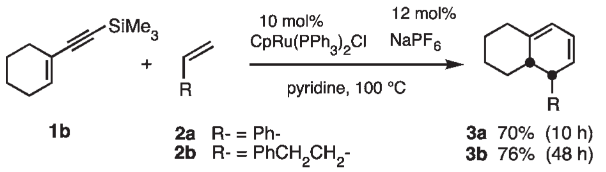
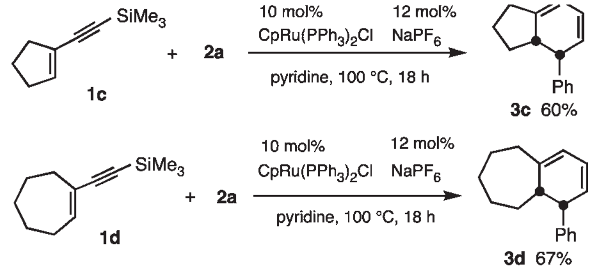


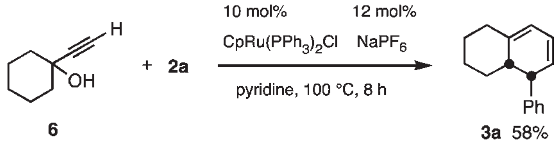
The yields of **3a** and **3b** are moderate at around 50%. One of the major side reactions to be suppressed in order to improve yield is the self-dimerization of the ene-yne **1a** at the terminal triple bond, which is also catalyzed by ruthenium.[4,7] We have found that, in contrast to phenylethyne, the corresponding silyl-protected form 1-phenyl-2-(trimethylsilyl)ethyne fails to undergo self-dimerization under the present reaction conditions.[8] On the other hand, it has been reported that 1-phenyl-2-(trimethylsilyl)ethyne reacts with a ruthenium(II) complex to afford a ruthenium vinylidene complex through 1,2-migration of the silyl group in a manner analogous to a terminal alkyne.[9] In order to favor the desired coupling reaction over the self-dimerization, we next tried the reaction of silyl-protected ene-yne **1b** with olefins **2a** and **2b**. As expected, the yields of the cyclohexadiene derivatives **3a** and **3b** were improved to 70% and 76%, respectively.[10] It is likely that protiodesilylation takes place during conversion of **1b** to the corresponding ruthenium vinylidene complex, probably due to the presence of water in the reaction medium.



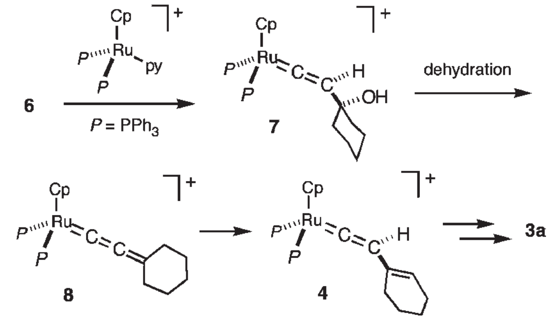
Other examples of stereoselective formation of six-membered ring conjugated dienes from ene-ynes and styrene **2a** are shown below.



It has been reported that a ruthenium vinylvinylidene complex analogous to **4** can be prepared from a terminal propargyl alcohol via dehydration.[11] In fact, the starting ene-yne **1** in the catalytic process could be replaced by a propargyl alcohol like **6**, which is easily prepared by nucleophilic addition of an acetylide anion to cyclohexanone. Heating a pyridine solution of **6** and **2a** (10 equiv) at 100 °C for 8 h in the presence of [CpRu(PPh$_3$)$_2$Cl] (10 mol%) and NaPF$_6$ (12 mol%) also afforded **3a** in 58% yield.



Initially, ruthenium hydroxyvinylidene complex **7** is formed from **6**. Dehydration follows to give ruthenium allenylidene complex **8**,[12] which tautomerizes to ruthenium vinylvinylidene complex **4**. Then, coupling with styrene **2a** and subsequent electrocyclic ring-closing reaction occur in a similar manner to the cases with the ene-ynes **1a** and **1b**. This method provides an alternative preparative access to the starting substance.



In summary, a new domino reaction is developed in which six-membered cyclic conjugated diene is formed in a regio- and stereoselective manner from an ene-yne and an alkene, both of which lack electron-withdrawing or -releasing substituents.

Dedicated to Professor Teruaki Mukaiyama with admiration for his outstanding contributions and uncompromising enthusiasm toward organic synthesis.

References and Notes

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10 Typical experimental procedure: A mixture of [CpRu(PPh$_3$)$_2$Cl] (20.4 mg, 28 μmol), NaPF$_6$ (5.7 mg, 34 μmol), silyl-protected ene-yne **1b** (50.0 mg, 280 μmol), and 4-phenyl-1-butene **2b** (421 μL, 2.8 mmol) in pyridine (1.5 mL) was heated at 100 °C for 48 h. The cooled reaction mixture was filtered through a pad of florisil and the filtrate was purified by preparative thin layer chromatography on silica gel (hexane) to afford diene **3b** (50.6 mg, 76%) as a colorless oil.

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