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Rhodium catalyzed [2+2+2] cyclizations of 1,6-enynes

Chang Ho Oh,* Hye Rhyan Sung, Seung Hyun Jung and Young Mook Lim

Department of Chemistry, Hanyang University, Sungdong-Gu, Seoul 133-791, South Korea

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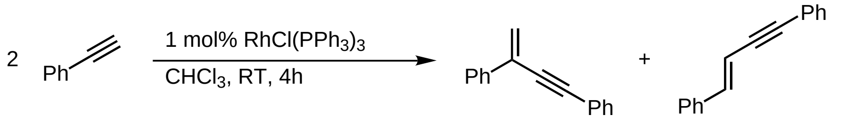
Abstract—Various terminal alkynes in the presence of 5 mol% of $RhCl(PPh_3)_3$ were homo-coupled to the conjugated enynes. 1,6-Enynes in the presence of 5 mol% $RhCl(PPh_3)_3$ and 10 mol% Ag(I) salts underwent [2+2+2]-cyclization among two triple bonds and one pendant double bond in good to excellent yields. © 2001 Elsevier Science Ltd. All rights reserved.

Effective construction of substituted cyclohexadienes has been a major challenge in synthetic organic chemistry due to the widespread appearance of biologically active natural products possessing six-membered rings. Most of the approaches to date involve various types of [4+2]- or [2+2+2]-cycloadditions. Transition metal-catalyzed alkyne triisomerization is a simple, powerful and very selective [2+2+2]-cyclization methodology for the synthesis of various benzene derivatives.[1] Palladium-catalyzed cyclizations of structurally well-designed enediynes and dienynes form cyclohexadienes and cyclohexenes, respectively, via [2+2+2] fashion.[2] We have long been interested in searching for an efficient and selective cyclization methodology using transition metal catalysts. In particular, palladium-catalyzed cycloreductions of enynes and enediynes have been explored in synthetically useful methodologies.[3] Rhodium compounds have been utilized to form metallacyclopentenes from vinylcyclopropanes that react with various π-systems to form [*m*+*n*] cycloadditions.[4] Also, rhodium compounds react with γ,δ-enal to form cyclopentanones.[5] Grigg and co-workers reported rhodium-catalyzed cyclizations of triynes to the benzene derivatives and, even in limited cases, cyclizations of diynes with alkenes to the cyclohexadiene derivatives via [2+2+2] process.[6] These reports prompted us to examine the possibility that rhodium-catalyzed [2+2+2] cyclizations of 1,6-enynes could provide an important class of carbocycles. Initially, we tested rhodium catalyzed C–C bond couplings between two terminal alkynes in a nonpolar solvent to form the conjugated enynes in a mixture of two isomeric products (Eq. (1)). It should be noted that the present reaction led to the isolation of the conjugated enyne without it undergoing further cyclization with another alkyne.[1]



(1)

We became aware that the initially formed conjugated enynes, in the presence of silver (I) salts, could undergo subsequent cyclizations with a pendant double bond to form the corresponding cyclohexadienes. Here, we wish to report our successful results on rhodium-catalyzed tandem dimerization–cyclizations of 1,6-enynes to the corresponding cyclohexadienes. We have chosen allyl propargyl ether (enyne **1a**) as the first substrate. When the enyne **1a** was treated with a catalytic amount of tris(triphenylphosphine)rhodium chloride (Wilkinson catalyst) in chloroform at room temperature, coupling between two alkynes occurred to form a 1:1 mixture of the conjugated enyne **2a** and the cyclohexadiene **3a**. When the same reaction was run at 50°C for 2 h, the cyclohexadiene **3a** was isolated in 55% yield along with the conjugated enyne **2a**. Use of silver triflate as a co-catalyst seemed to increase the reactivity of the rhodium catalyst toward enyne **1a** to form the cyclohexadiene **3a** in 84% yield (Scheme 1).

We have tested various co-catalysts such as silver tetrafluoroborate, borontrifluoride etherate, or zinc chloride and protic acids such as formic acid, acetic acid or

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Keywords: rhodium; cyclization; Wilkinson catalyst; cyclohexadiene.

* Corresponding author. Tel.: +82-2-2290-0932; fax: +82-2-2299-0762; e-mail: changho@hanyang.ac.kr

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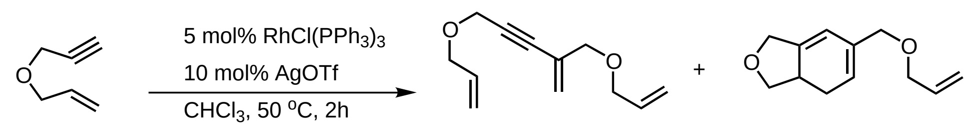


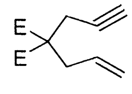
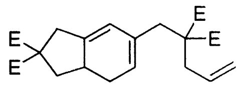
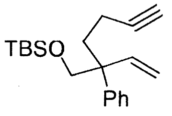
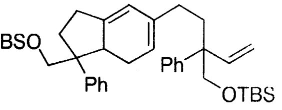
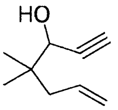
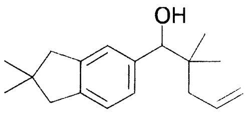
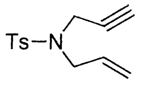
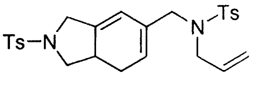
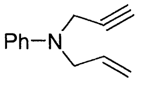
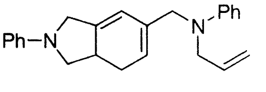
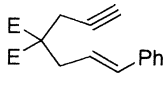
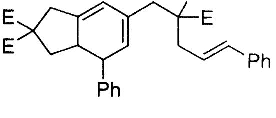
1a **2a** (<5%) **3a** (84%)

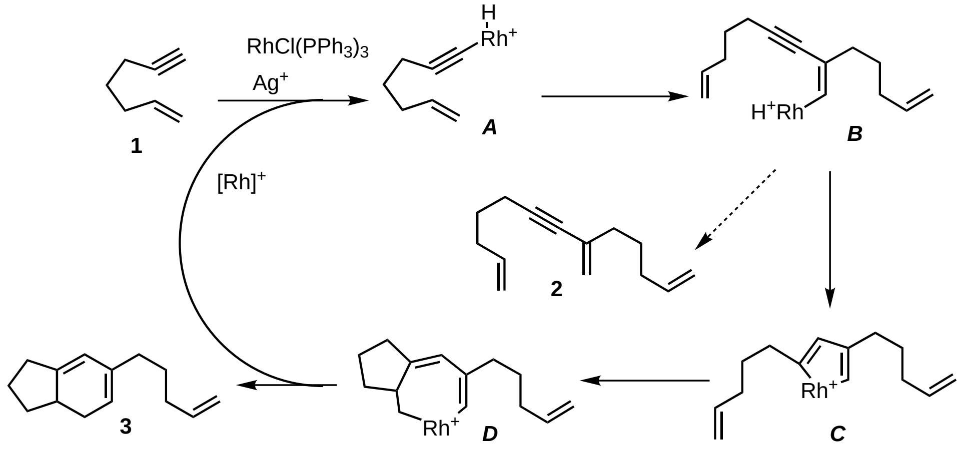
Scheme 1.

triflic acid. While use of silver tetrafluoroborate as a co-catalyst also led to smooth cyclization to give the cyclohexadiene **3a** in 79% yield, the other co-catalysts led to the reactions being sluggish and gave a mixture of unidentified products. In order to explore the scope of this cyclization method, we have tested a series of enynes **1c**–**1f** under the above conditions and summarized our results in Table 1.

All enynes (**1b**–**1f**) smoothly underwent C–C coupling and then subsequent cyclization to the desired products in excellent yields (60–89% yields).[7] Functional groups in the enyne substrates were tolerable toward ester, TBS ether, amine and sulfonamide. Hydroxy-containing enyne **1d**, however, was cyclized to the substituted benzene **4d**, presumably via dehydration of the cyclohexadiene **3d**. The steric factor around the double bond seemed to affect the final cyclization step. For example, the enyne **1g** with a 1,2-disubstituted double bond required longer reaction time for complete cyclization.[8] A mechanistic proposal can be inferred from the proposed mechanisms for hydroacylation, decarbonylation and other well-established transition-metal catalyzed processes (Scheme 2).[9] The cationic catalytic species $[Rh]^+$, presumably generated from $RhCl(PPh_3)_3$ plus AgOTf or $AgBF_4$, oxidatively adds to the *sp*C–H bond, forming alkynylhydridorhodium complex (**A**) that can add to a triple bond of another enyne to form intermediate **B**. The vinylhydridorhodium intermediate **B** could undergo either reductive elimination to form the enyne **2** or rhodacyclization to form the rhodacyclopentadiene intermediate **C**. The intermediate **C** might be further cyclized to the rhodacycloheptadiene **D** and then reductively cleaved to the cyclohexadiene **3** and the cationic rhodium species for the next catalytic cycle. Two pieces of evidence could support the proposed mechanism. First, when the present reaction of the enyne **1a** was carried out in $CDCl_3$, we could detect the formation of the conjugated enyne **2a** and the product **3a** by ^1H NMR monitoring. Upon heating, the cyclohexadiene **3a**

Table 1. Rhodium–catalyzed cyclizations of enynes with 5 mol% $RhCl(PPh_3)_3$ and 10 mol% Ag(+1) salt in $CHCl_3$

Substrates		Ag(+) salt	Temp (°C)	Time (h)	Products		Yield (%)
	**1b**	$AgBF_4$	50	2		**3b**	89
	**1c**	$AgBF_4$	50	1		**3c**	72
	**1d**	$AgBF_4$	50	2		**4d**	83
	**1e**	AgOTf	50	4		**3e**	71
	**1f**	$AgBF_4$	RT	12		**3f**	67
	**1g**	$AgBF_4$	70	27		**3g**	60



Scheme 2.

became a major product along with a trace of the initially formed **2a**. Second, when the conjugated enyne **2a** was isolated and further treated under the present conditions, no cyclization to the **3a** occurred. The presence of silver(I) salts might help further cyclization of the intermediate **B** or activate the rhodium catalyst to make it more cationic. Although the exact reaction mechanisms are still not clear, this method would provide structurally diverse cyclohexadienes from 1,6-enynes.

In summary, a 1:2 mixture of $RhCl(PPh_3)_3$ and silver(+1) salt catalyzed [2+2+2]-cyclizations of various 1,6-enynes to the corresponding cyclohexadienes in good to excellent yields. Further studies involving the use of other rhodium compounds and application of this methodology are under way and will be reported in a full paper.

Acknowledgements

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7. General procedure for [2+2+2] cyclization of enyne **1b**: In a 5 mL test tube were placed enyne **1b** (44.1 mg, 0.185 mmol), tris(triphenylphosphine)rhodium chloride (8.9 mg, 0.0096 mmol), silver tetrafluoroborate (3.9 mg, 0.020 mmol). Dry chloroform (1 mL) was added to the above solution by a syringe under an argon atmosphere. The reaction mixture was stirred for 2 h in a preheated 50°C oil bath. Then the reaction mixture was concentrated under reduced pressure and separated by flash chromatography (eluent: hexane/ethyl acetate (20/1)) to give the cyclized product **3b** (39.4 mg, 89%) as a colorless oil. New compounds **3a**, **3b**, **3c**, **4d**, **3e**, **3f** and **3g** were characterized by ^1H NMR, ^{13}C NMR, IR and high resolution mass spectra.
8. (a) As per one of the referee's comments, we have attempted rhodium-catalyzed cyclization in refluxing ethanol according to the Grigg's procedure (Ref. 6) for two enynes **1a** and **1b**. While the enyne **1a** under Grigg's conditions gave the cyclohexadiene in 60% yield, the enyne **1b** did not react at all to recover the starting enyne almost quantitatively.
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