Palladium-Catalyzed Cyclization of Cyclopropyl-Substituted 1,6-Enynes to 5.7-Bicyclic Trienes or Monocyclic Trienes Depending upon the Leaving Group

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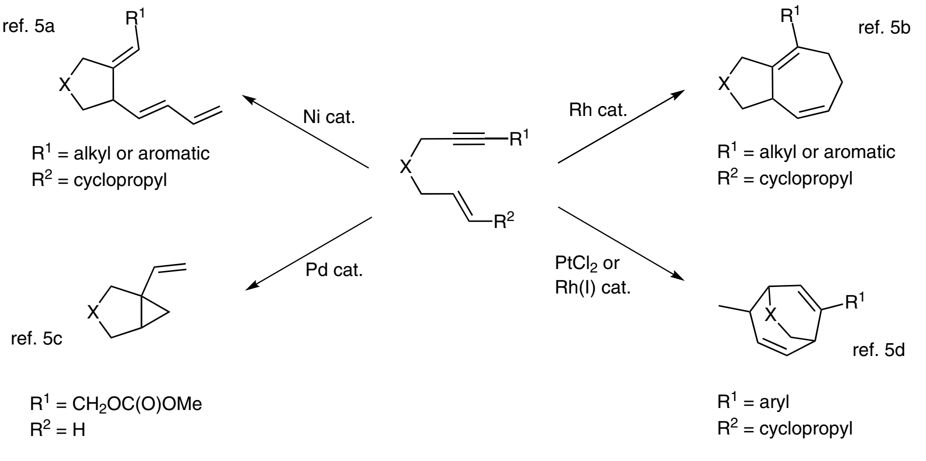
Abstract: Palladium-catalyzed cyclization of cyclopropyl-substituted 1,6-enynes proceeded in two ways depending on the presence or absence of a leaving group. In the presence of the leaving group, 5.7-bicyclic trienes were obtained as the sole products; in the absence of the leaving group, monocyclic trienes were isolated.

Key words: palladium, enynes, vinyl cyclopropanes, seven-membered rings, bicyclic compounds

Three-membered carbocycles are extremely important and versatile building blocks for organic chemistry.[1] The bonds between the carbon atoms are considerably weaker than a typical carbon–carbon bond, yielding a reactivity similar to or greater than that of alkenes. Their unique structural and electronic properties give rise to an array of very notable, characteristic transformations. For example, cyclopropyl groups engage in many rearrangement reactions including the vinylcyclopropane rearrangement and the divinylcyclopropane–cycloheptadiene rearrangement.[2] Cyclopropyl groups also participate in cycloaddition reactions such as formal [5+2] cycloadditions.[3] Vinyl cyclopropanes (VCPs) are considered to be particularly suitable C_5 building blocks in the formal [5+2] cycloaddition. Thus, a variety of transition-metal-catalyzed cyclizations have been developed over the past decades.[4]

In particular, Wender and co-workers[6] demonstrated that VCP is a very versatile strained cyclic synthon in the rhodium-catalyzed [5+2] cyclizations of cyclopropylen-ynes. However, the reaction products in the transition-metal-catalyzed reaction of cyclopropylen-ynes seem to be rather dependent upon the catalyst and the substituent on the alkyne (Scheme 1). For example, Louie et al.[5] found a size effect, due to the substituent on the alkyne, on the heterocyclic product formed in the $Ni(cod)_2$–SIPr-catalyzed reaction, although employment of $Ni(cod)_2$–I*t*Bu as a catalytic system solved the selectivity problem.

Pimm and co-workers reported[5] the formation of alk-1-enyl-(3-aza)bicyclo[3.1.0]hexanes in the palladium-catalyzed cyclization of olefinic propargylic carbonates. Recently, we reported[5] that the consecutive reactions of platinum- and rhodium-catalyzed cycloisomerization of enynes bearing a cyclopropyl and aryl group in the alkene and alkyne termini, respectively, afforded azabicyclo-[3.2.2]nona-2,8-dienes in high yields. While we were studying the design and development of new metal-catalyzed cycloaddition reactions as part of an on-going project,[7] we recently discovered Pd-catalyzed reactions of cyclopropylenynes that selectively afforded 4-methylene-hexahydroazulenes or 1-[(*E*)-buta-1,3-dienyl]-2-methylene-cyclopentanes depending upon the substituent on the alkyne moiety. We herein report our results.



Scheme 1 Metal-catalyzed cycloisomerization[5]

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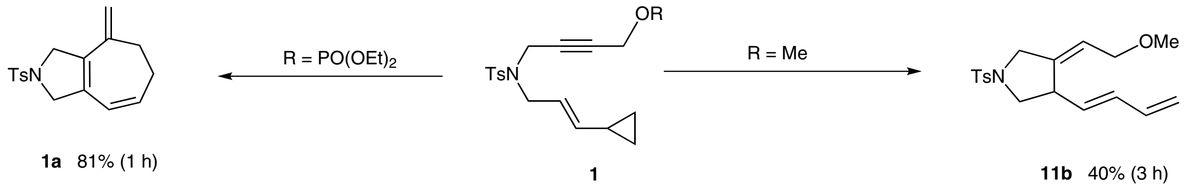


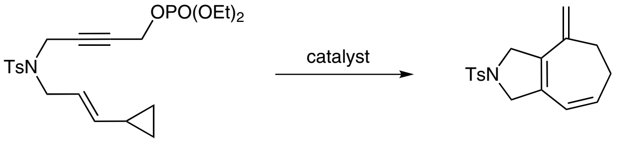
Scheme 2 Palladium-catalyzed cycloisomerization depending upon the leaving group

Initial treatment of olefinic propargylic diethyl phosphate **1** with a catalytic amount of $[Pd_2(dba)_3]$ in dioxane at 90 °C for one day gave bicyclic triene **1a** in 17% yield with 67% recovery of the reactant (Scheme 2).

The structure of **1a** was confirmed by ^{1}H and ^{13}C NMR studies.[8] It has a 4-methylene-1,2,3,4,5,6-hexahydroazulene skeleton, which can be considered to be an important building block because it may participate in a variety of functionalizations and tandem carbon–carbon bond-forming processes. The formation of **1a** suggests that the phosphate acts as a leaving group. Encouraged by the observation of the formation of **1a**, we also screened other palladium compounds (Table 1, entries 1–8). Among them, the best yield (81%) was observed in the presence of 5 mol% $Pd(OAc)_2$/10 mol% Ph_3P in dioxane for one hour. The yield of the reaction was also highly sensitive to the reaction solvent (entries 9 and 10). We also screened nickel compounds such as $Ni(acac)_2/Ph_3P$ (1:2) and $Ni(OAc)_2/Ph_3P$ (1:2) as potential catalysts. However, no reaction was observed with the nickel systems. We were able to establish the following optimized reaction conditions: 5 mol% $Pd(OAc)_2$, 10 mol% Ph_3P, in dioxane, at 90 °C for 1 hour.[9,10]

We first examined whether phosphate was the best leaving group under the optimized reaction conditions (Table 2). Olefinic propargylic compounds (entries 2 and 3) having an acetoxy or carbonate as a leaving group afforded the expected product **1a** in rather low yields (40 and 49%, respectively) under our reaction conditions. In the case of the carbonate, when the reaction was carried out in the

Table 1 Reaction of **1** under Various Reaction Conditions



Entry	Catalyst	Solvent	Temp (°C)	Time (h)	Yield (%)[c]
1[a]	$Pd_2(dba)_3$	dioxane	90	24	17
2[a]	$Pd(PPh_3)_4$	dioxane	90	24	42
3[a]	$Pd(OAc)_2$	dioxane	90	24	13
4[a]	$Pd(OAc)_2$/dppp (1:1)	dioxane	90	24	28
5[a]	$Pd(OAc)_2$/dppf (1:1)	dioxane	25	24	41
6[a]	$Pd(OAc)_2$/dppe (1:1)	dioxane	70	2	71
7[a]	$Pd(OAc)_2/P(o\text{-toly})_3$ (1:2)	dioxane	80	24	23 (52)[d]
8[b]	$Pd(OAc)_2/Ph_3P$ (1:2)	dioxane	100	1	81
9[b]	$Pd(OAc)_2/Ph_3P$ (1:2)	DCE	90	22	33
10[b]	$Pd(OAc)_2/Ph_3P$ (1:2)	toluene	90	1	39
11[b,e]	$Pd(OAc)_2$/dppp(1:1), CO (1 atm)	THF–MeOH	70	21	63
12[b]	$Ni(acac)_2/Ph_3P$ (1:2)	dioxane	90	24	n.r.[f]
13[b]	$Ni(acac)_2/Ph_3P$ (1:2)	dioxane	90	24	n.r.[f]

[a] Reaction conditions: Pd catalyst (10 mol%), enyne (0.22 g, 0.5 mmol), solvent (5 mL).

[b] Reaction conditions: Pd catalyst (5 mol %), enyne (0.22 g, 0.5 mmol), solvent (5 mL).

[c] Isolated yield.

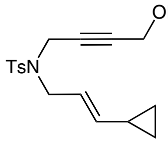
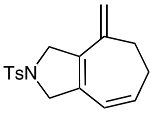
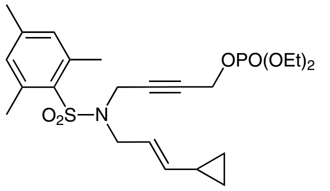
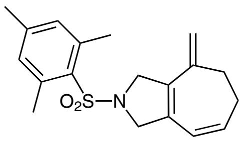
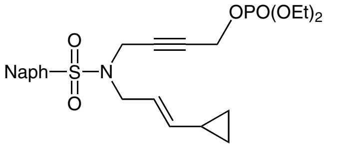
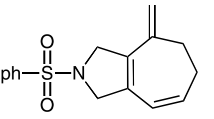
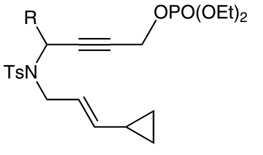
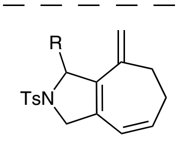
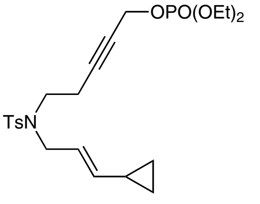
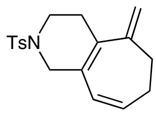
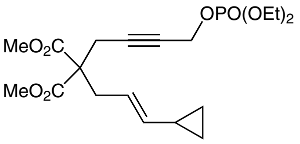
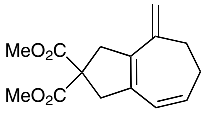
[d] Yields in parenthesis are for the recovered reactant.

[e] Reaction conditions: enyne (0.22 g, 0.5 mmol), $Pd(OAc)_2$ (5 mol%), THF (5 mL), MeOH (0.5 mL), CO (1 atm).

[f] n.r. = No reaction

presence of 5 mol% Pd(OAc)$_2$ and 5 mol% dppp under CO (1 atm), a higher yield (63%) was observed. The leaving group had a dramatic effect on the yield of the reaction and the best yield (81%) was observed with the phosphate group. Therefore, we examined the scope of substrates bearing a phosphate group under our reaction conditions. As the steric bulk of the N-tether groups increased (cf. entries 4 vs. 5), the yield decreased. The number of internal substituents (cf. entries 6 vs. 8) and the identity and position of the substituents (cf. entries 6 vs. 7) affected the

Table 2 Palladium-Catalyzed Cyclization of Cyclopropyl-Substituted 1,6-Enynes to 5.7-Bicyclic Trienes[a]

Entry	Substrate	Time (h)	Product yield (%)[b]
			
1	**1** R = PO(OEt)$_2$	1	**1a** 81
2	**2** R = COMe	1	**1a** 40
3[c]	**3** R = CO$_2$Me	1	**1a** 63
4	 **4**	4	 **4a** 65
5	 **5**	5	 **5a** 35
			
6	**6** R = Me	20	**6a** 93
7	**7** R = Et	4	**7a** 60
8	**8** R = gem-dimethyl	3	**8a** 43
9	 **9**	20	 **9a** 50
10	 **10**	4	 **10a** 47

[a] Reaction conditions: substrate (0.3 mmol), Pd(OAc)$_2$ (5 mol%), Ph$_3$P (10 mol%), dioxane (3 mL), 90 °C.

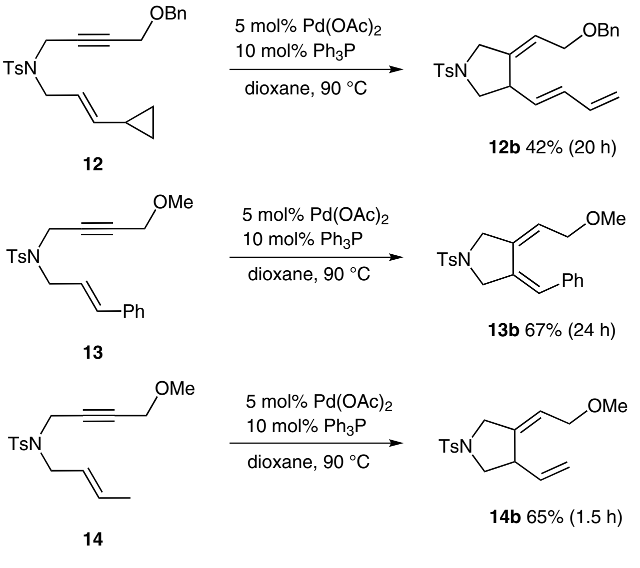
[b] Isolated yield.

[c] Under 1 atm CO.

yield of the reaction. A 1,7-enyne was also a good substrate (entry 9) and a carbon-tethered substrate (entry 10) also underwent the reaction.

We then investigated the reactions of substrates without having a leaving group to determine whether they gave a bicyclic triene as a product. When substrate **11** was treated in dioxane under the standard catalytic conditions, monocyclic triene 1-[(*E*)-buta-1,3-dienyl]-2-methylene-cyclopentane (**11b**), was isolated in 40% yield (Scheme 2).

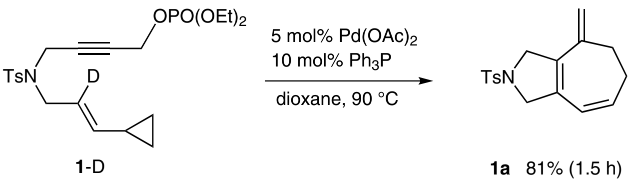
Zuo and Louie reported[5a] a similar reaction in the presence of Ni(cod)$_2$–NHC. To ascertain whether this rearrangement was typical, a range of substrates **12**–**14** were prepared and tested (Scheme 3).



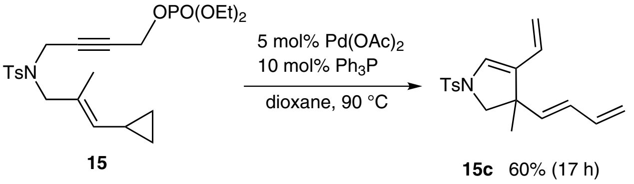
Scheme 3 Palladium-catalyzed cyclization of cyclopropyl-substituted 1,6-enynes to monocyclic trienes

With substrate **12**, containing the cyclopropyl group, monocyclic triene **12b** was isolated in 42% yield. With a phenyl (**13**) or methyl group (**14**) instead of a cyclopropyl group, monocyclic dienes **13b** and **14b** were isolated in 67 and 65% yields, respectively. Thus, the formation of cyclopentane derivatives was quite general for the palladium-catalyzed reaction of enyne substrates not bearing a leaving group. In the formation of a bicyclic triene from a substrate, both the leaving group and one of the hydrogen atoms were lost. To gain some information on the formation of bicyclic trienes, deuterated compound **1**-D was reacted under the standard reaction conditions (Scheme 4). When the product of the reaction was isolated, the deuterium was not found in the product. This observation suggested that the disappearing hydrogen atom was from the inner position of an alkene moiety.

Moreover, when a methyl group was introduced into the same position as that of the deuterium in **1**-D, a new cyclopentene derivative, **15c**, produced by the isomerization of an allene to a diene, instead of a bicyclic triene, was isolated in 60% yield (Scheme 5).



Scheme 4 Palladium-catalyzed cycloisomerization of **1**-D



Scheme 5 Palladium-catalyzed cycloisomerization of **15**

A similar reaction product was obtained in the palladium-catalyzed carbocyclization of aza-enallenes.[11] It seems that the presence of a methyl group blocks the formation of a seven-membered ring compound.

Based on the experimental observations, a plausible reaction mechanism for the formation of **a** has been proposed (Scheme 6). In the presence of a palladium catalyst, an equilibrium mixture of η^1-allenic and propargylic intermediate **I** forms,[12] which may be in equilibrium with η^3-propargyl intermediate **II**.[13] Both intermediates can be transformed into a (π-olefin)(σ-allenyl)palladium intermediate **III**. Carbon–carbon bond formation followed by ring-opening of the allyl group leads to intermediate **V**. The allyl group then attacks the central carbon of the allene group to form a seven-membered ring and regenerate the catalytic species to reenter the catalytic cycle. When the final step is blocked, **b** instead of **a** is formed.

In conclusion, we have demonstrated that palladium-catalyzed reaction of 1,6-enynes bearing a cyclopropyl moiety at the alkene affords bicyclic or monocyclic trienes as products depending on the presence or absence of a leaving group. The bicyclic or monocyclic trienes can form a class of important building blocks because they possess three double bonds that may be used for further derivatization.

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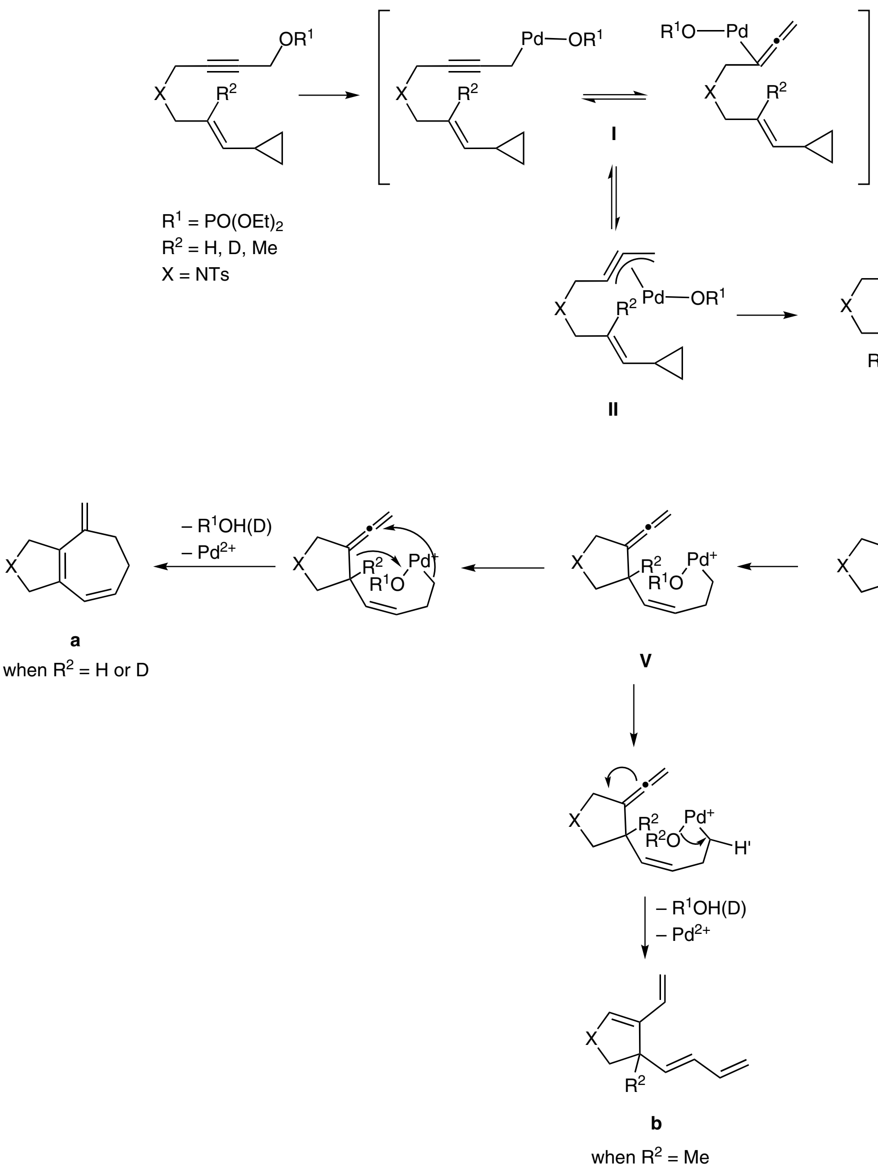

Scheme 6 A plausible mechanism

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(8) **Spectroscopic Data for 1a:** ^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.75 (d, *J* = 8.1 Hz, 2 H), 7.33 (d, *J* = 8.0 Hz, 2 H), 6.02 (dd, *J* = 5.4, 11.1 Hz, 1 H), 5.67 (d, *J* = 11.0 Hz, 1 H), 4.84 (s, 1 H), 4.73 (s, 1 H), 4.34 (d, *J* = 3.4 Hz, 2 H), 4.21 (d, *J* = 3.3 Hz, 2 H), 2.43 (s, 5 H), 2.31 (t, *J* = 7.3 Hz, 2 H). ^{13}C NMR (75 MHz, CDCl$_3$): δ = 143.6, 142.6, 136.8, 134.0, 132.1, 130.7, 129.9, 127.6, 121.9, 114.3, 58.8, 56.8, 34.0, 28.5, 21.6. HRMS (EI): *m*/*z* [M]$^+$ Calcd for $C_{17}H_{19}NO_2S$: 301.1137; found: 301.1142.

(9) **General Procedure:** To a flame-dried 10 mL Schlenk flask capped with a rubber septum, dioxane (2 mL), Pd(OAc)$_2$ (5 mol%), and Ph$_3$P (10 mol%) were added under a N$_2$ flow. Compound **1** (0.3 mmol) was added to the flask under N$_2$. The mixture was heated at 90 °C and the progress of the reaction was monitored by TLC. The mixture was cooled to room temperature, filtered, and the solvent was evaporated under reduced pressure. The product was purified by flash chromatography on a silica gel column (*n*-hexane–ethyl acetate, 10:1).

(10) In some transition-metal-catalyzed reactions, the presence of carbon monoxide was helpful to the reaction even though the reaction was not related to the carbonylation, see: (a) Füstner, A.; Davies, P. W.; Gress, T. *J. Am. Chem. Soc.* **2005**, *127*, 8244. (b) Chatani, N.; Morimoto, T.; Murai, S. *J. Am. Chem. Soc.* **1994**, *116*, 6049. (c) Bloome, K. S.; McMahen, R. L.; Alexanian, E. J. *J. Am. Chem. Soc.* **2011**, *133*, 20146. (d) Ozaki, T.; Nomoto, A.; Kamiya, I.; Kawakami, J.-i.; Ogawa, A. *Bull. Chem. Soc. Jpn.* **2011**, *84*, 155.

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