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Palladium-catalyzed cycloreduction of 5-allen-1-ynes

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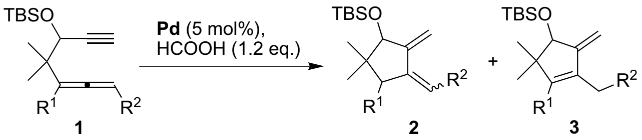
Abstract—The palladium-catalyzed cycloreduction of 5-allen-1-ynes gave the corresponding 1,2-bisalkylidenecyclopentanes in excellent chemoselectivity and chemical yields. Incorporating an electron-withdrawing group at the acetylenic position showed to be better substrates for the present cycloreduction.

Transition metal-catalyzed carbon–carbon bond-forming reactions based on allenes are of current interest in organic synthesis.[1] Since functionalized carbocycles are very common structural subunits in many biologically active natural compounds,[2] their preparation becomes of paramount interest in organic synthesis.[3] Recently, we reported that 6-allen-1-ynes exhibited different modes of cyclizations depending on metallic catalysts. $Pd(PPh_3)_4$ catalyzed 6-allen-1-ynes to the six-membered carbocycles, whereas $RhCl(PPh_3)_3$ catalyzed the allenynes to give the five membered rings chemoselectively.[4] Since the Pd-catalyzed cyclization of allenynes resulted in formation of very valuable 1,2-bisalkylidenecycloalkanes, we are interested in further exploring the scope and limitations of this cycloreduction toward 5-allen-1-ynes.

Here we wish to report a successful Pd-catalyzed cycloreduction methodology leading to a series of 1,2-bisalkylidenecyclopentanes in good to excellent yields.

At first, we examined allenyne **1a** (Eq. 1) was subjected for Pd-catalytic conditions in different reaction mediums, and the results thus obtained were summarized in Table 1. When a mixture of the allenyne **1a** in DMF (1.2 mL) was treated with $Pd(PPh_3)_4$ (5 mol %) and HCOOH (1.2 equiv) and stirred at 50 °C for 3 h, the reaction was completed to give the cycloreduced product **2a** in 76% yield after silica gel column chromatography (entry 1).



(1)

The same reaction in 1,4-dioxane resulted in formation of 1:1 mixture of **2a** and its isomerized product **3a** (entry 2). When we re-examined the same reaction with 5 mol % of palladium acetate and 10 mol % of triphenylphosphine in DMF gave only **2a**, whereas in 1,4-dioxane gave a mixture of **2a**:**3a** in 2:1 ratio (entries 3 and 4).[5] The optimal conditions (shown in entry 1) were tested with the analogs **1b** and **1c**, which have a methyl substituent on either 1 or 3-allenic carbon atom. Both **1b** and **1c** were cycloreduced to give the corresponding products **2b** and **2c** exclusively in excellent yields. These may arise from the steric effect that the initial hydropalladation occur at the sterically less hindered double bond in the allenes. When we tested allenyne **1d** contained phenyl group at the terminal acetylenic position, unfortunately, we could not get the expected product **2d** even exposed to 100 °C for longer reaction time and the starting material was retrieved (Eq. 2). Complete recovery of the starting material suggested that carbopalladation at the triple bond to the alkenylpalladium intermediate ***I*** could not occur under these conditions.

Keywords: Allenyne; Palladium; Cycloreduction; Electron-withdrawing group.

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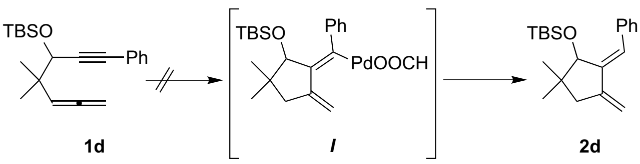
Table 1. Palladium-catalyzed cycloreduction of 5-allen-1-ynes (**1**)

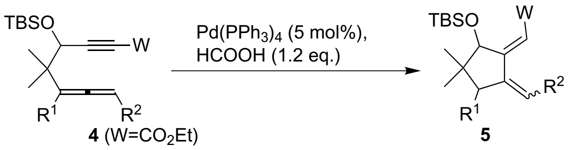
	Allenynes (**1**)		Pd catalyst	Solvent	Temperature (°C)/ time (h)	(%) Yield (products ratio[a])
1	**1a**	$R^1 = H$ $R^2 = H$	$Pd(PPh_3)_4$	DMF	50/3	76 (**2a** only)
2	**1a**		$Pd(PPh_3)_4$	1,4-Dioxane	50/1	81 (**2a**:**3a** = 1:1)
3	**1a**		$Pd(OAc)_2$ $2PPh_3$	DMF	50/1.5	75 (**2a** only)
4	**1a**		$Pd(OAc)_2$ $2PPh_3$	1,4-Dioxane	50/1	69 (**2a**:**3a** = 2:1)
5	**1b**	$R^1 = Me$ $R^2 = H$	$Pd(PPh_3)_4$	DMF	50/6	92 (**2b** only)
6	**1c**	$R^1 = H$ $R^2 = Me$	$Pd(PPh_3)_4$	DMF	50/2	91 (**2c** only, *E*/*Z* = 1/1)

[a] Determined by the ^1H NMR integration of the isolated products.



cond: $Pd(PPh_3)_4$ (5 mol%), HCOOH (1.2 eq.), DMF, 100 °C

(2)

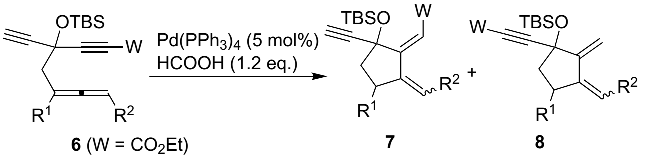


(3)

In sharp contrast, when an electron-withdrawing group was introduced to the triple bond (**4a**–**c**), the present reaction occurred smoothly, implying that the polarized triple bond might be more reactive toward HPdOOCH species (Eq. 3). In order to find out the optimal condition for these reactions, we have performed the reactions in different solvents, such as 1,4-dioxane, DMF, chloroform, toluene, and ethanol (see Table 2).[6]

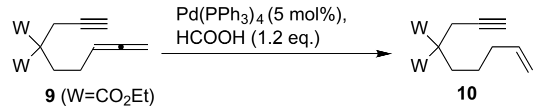
This cycloreduction of **4a** in 1,4-dioxane occurred even at room temperature very slowly (entry 1) and completed at 60 °C in 1 h to give the cycloreduced product **5a** without formation of other byproducts (entry 2). The optimal conditions (entry 3) were applied to **4b** and **4c**, which have a methyl substituent on either 1 or 3-allenic carbon atom. As we expected, both **4b** and **4c** were smoothly cycloreduced to the corresponding products **5b** and **5c** in quantitative yields, respectively (entries 7 and 8).

From the above observations, it is worthwhile to know the behavior of the substrate, if we put both groups on the same substrate, for example, one is the terminal free acetylene group and the other is the conjugated alkynecarboxylate group. Hence we prepared three more substrates **6a**–**c**. All the three substrates **6a**–**c** underwent cycloreduction successfully under the above conditions and gave only the expected products **7a**–**c** in good yields as shown in Eq. 4 and Table 3.



(4)

It is worthwhile to note that only the electron-withdrawing group-incorporated triple bond was participated in cycloreduction process to give the corresponding products **7** with a trace of **8**. This might imply a mechanistic clue that the present reaction involve a highly ionic process, so that the reactions occurred well in polar solvent such as 1,4-dioxane or DMF.



(5)

Mechanistically, the key for these reactions seemed to depend upon the electronic nature on the triple bond. The 1,2-diene group in the substrate **9** has shown to have higher reactivity toward hydropalladation to give the reduced product **10** than the triple bond (Eq. 5).[7] Based on this, HPdOOCH, a formal species formed from the oxidative addition of HCOOH to Pd(0), would

Table 2. Pd-catalyzed cycloreductions of an electron-withdrawing group introduced on allenynes **4**

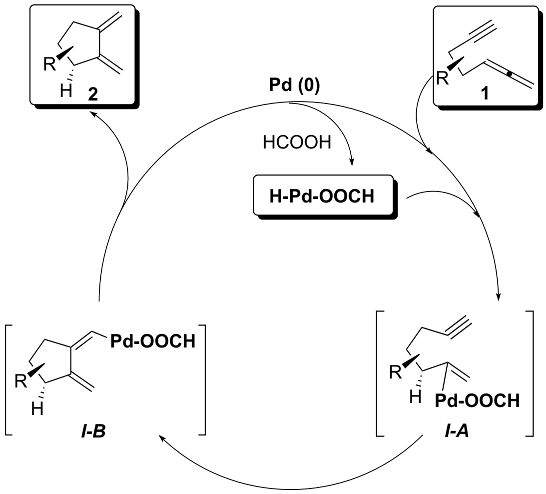
Entry	Allenynes W, R^1, R^2		Pd catalyst	Solvent	Temperature (°C)/time (h)	Products (% Yield)
1	**4a**	CO_2Et, H, H	$Pd(PPh_3)_4$	1,4-Dioxane	Rt/70	**5a** (75)
2				1,4-Dioxane	60/1	**5a** (96)
3				DMF	50/1	**5a** (97)
4				$CHCl_3$	50/3	**5a** (65)
5				Toluene	50/3	**5a** (64)
6				EtOH	50/1	**5a** (92)
7	**4b**	CO_2Et, Me, H	$Pd(PPh_3)_4$	DMF	50/1	**5b** (93)[a]
8	**4c**	CO_2Et, H, Me	$Pd(PPh_3)_4$	DMF	50/3	**5c** (91)[a]

[a] The reactions in 1,4-dioxane gave the almost same results as these (about 2:1 mixture of *E*/*Z* isomers were obtained).

Table 3. Cycloreduction of allenediynes **6**

Entry	Substrates (R^1, R^2)		Solvent	Temperature (°C)/time (h)	Products[a] (% Yield)
1	**6a**	(H, H)	DMF	50/0.5	**7a** (82)
2	**6a**	(H, H)	1,4-Dioxane	50/1.5	**7a** (78)
3	**6b**	(Me, H)	DMF	50/0.5	**7b** (65)
4	**6c**	(H, Me)	DMF	50/0.5	**7c** (76; *E* only)

[a] A trace of the products **8** were formed by analyzing ^{1}H NMR spectra of the crude products.



Scheme 1. A proposed mechanism.

add to the allenyl group via hydropalladation to form the vinylpalladium species ***I–A***. The species ***I–A*** may then undergo carbopalladation with the pendant acetylene functionality to form the alkenylpalladium intermediate ***I–B***. Reductive cleavage of the species ***I–B*** by the pendant formate ligand led to form the products like **2**, **5**, and **7**[8] (Scheme 1).

In summary, all three types of allenynes **1a**–**c**, **4a**–**c**, and **6a**–**c** exhibited the same mode of cycloreduction reactions in the presence of a catalytic amount of $Pd(PPh_3)_4$ and a stoichiometric amount of HCOOH in DMF or 1,4-dioxane. The present cycloreductions afforded valuable synthetic intermediates, 1,2-bisalkylidenecyclopentanes.[9] It is also worth noting that 5-allen-1-ynes conjugated with an electron-withdrawing group at the alkyne group showed better substrates than the other 5-allen-1-ynes.

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5. All new products were fully characterized by using ^{1}H, ^{13}C NMR, FT-IR, and high-resolution mass spectra. The relative stereochemistry for **2b**, **5b**, and **7b** were tried to confirm by 2D NOESY experiments. The exact relative stereochemistries for those derivatives will be confirmed by X-ray studies and will be reported in a full paper when ready.
6. A typical procedure for cycloreduction of an electron-withdrawing group-substituted 5-allen-1-yne **4a**: In a 5 mL test tube the allenyne **4a** (33.0 mg, 0.102 mmol), $Pd(PPh_3)_4$ (6.0 mg, 0.0051 mmol), and dry DMF (1.2 mL) were

added. The resulting mixture was treated with HCOOH (5.0 μL, 0.122 mmol) under Ar atmosphere. The mixture was stirred for 10 min at room temperature and for 1 h at 50 °C. The reaction mixture was concentrated and separated by silica gel chromatography (eluent: ethyl acetate/*n*-hexane (1/20)) to give the cycloreduced product **5a** (32.1 mg, 97%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.09 (s, 1H), 5.59 (dd, $J = 3.2$, 1.6 Hz, 1H), 5.08 (br s, 1H), 4.99 (s, 1H), 4.11–4.26 (m, 2H), 2.54 (d, $J = 15.6$ Hz, 1H), 2.00 (dd, $J = 15.6$, 1.2 Hz, 1H), 1.30 (t, $J = 7.2$ Hz, 3H), 1.08 (s, 3H), 0.83 (s, 9H), 0.75 (s, 3H), 0.13 (s, 3H), −0.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.17, 160.65, 147.49, 111.33, 109.57, 78.05, 60.02, 42.88, 41.17, 26.04, 25.22, 22.46, 18.53, 14.51, −4.46, −4.88.

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