Chemoselectivities in Palladium Catalyzed Eneyne Cyclizations

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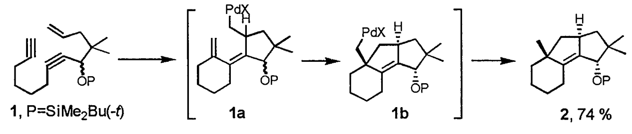
(Received April 4, 1997; CL-970248)

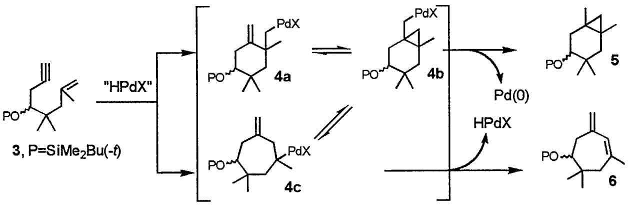
Palladium catalyzed 1,7-eneyne cyclizations proceeded endo- or exo-mode depending on solvent: polar solvent afforded the exo-mode predominantly, non-polar solvent did the endo mode product.

Palladium compounds have found widespread applications in modern organic synthesis,[1] especially for the one-step construction of polycyclic compounds.[2] From the mechanistic viewpoint in enediyne cyclizations, three different pathways have been proposed; a neopentyl type alkyl palladium intermediate was proven to be a possible intermediate.[3] Such an intermediate has chemoselectively afforded the corresponding three-, five-, or six-membered carbocycle under the different circumstances.[4] Recently we have reported that even some palladium catalyzed enediyne cyclizations which could form the alkylpalladium species **1a** possessing a β-hydrogen, yielded the corresponding five membered ring systems **2** *via* [2+2+1] process (Scheme 1).[5]



Scheme 1.

In continuing our interest, we have designed a structurally simple eneyne **3** in order to find any further synthetic utilities and to revision any important factors for altering the cyclization pathways (Scheme 2).



Scheme 2.

The palladium catalyst, HPdX, has been known to react with the terminal acetylene group of the eneyne substrate **3** to form the vinyl palladium species regiospecifically, which then undergoes cyclization shown in exo-mode *via* **4a** and / or in endo-mode *via* **4c**.[6] Eventually, palladium catalyzed cyclization of the eneyne **3** would form the corresponding **5** and / or **6**. In fact, cyclization under palladium catalysis in DMF successfully formed a mixture of the corresponding products **5** and **6**.[7] More studies using the substrate **3** were conducted in variations of palladium catalysts and solvents as shown in Table 1.

Table 1. Pd-Catalyzed cyclizations of eneyne **3**

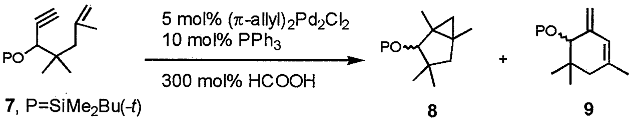
	Reagent Systems	Solvent	T(°C)/ Time (h)	Ratio[a] (**5** : **6**)	Yield (%)
1	5 % (π-AllylPdCl)$_2$	DMF	80/2	1:3	77
	20 mol% PPh$_3$		60/2	1:5	80
	300 mol% HCOOH	HMPA	60/3	1:2	75
		Toluene	70/6	1:0	95
		CH$_3$CN	70/16	1:0	78
2	5 mol% Pd(OAc)$_2$	DMF	65/2	0:1	80
	20 mol% PPh$_3$	Toluene	60/2	mixture	-
	300 mol% HCOOH	CH$_3$CN	60/3	mixture	-
3	5 mol% Pd(PPh$_3$)$_4$	DMF	60/2	0:1	79
	300 mol% HCOOH	Toluene	60/5	mixture	-
4	5 mol% PdCl$_2$(PPh$_3$)$_2$ 300 mol% HCOOH	DMF	60/18		no rxn
5	5 mol% PdCl$_2$	DMF	60/23		no rxn
	20 mol% PPh$_3$	Toluene	60/19	1:0	95
	300 mol% HCOOH				
6	5 mol% PdCl$_2$(CH$_2$PPh$_3$)$_2$	DMF	60/18		no rxn
	300 mol% HCOOH	Toluene	60/5		no rxn
7	5 mol% Pd$_2$(dba)$_3$ 20 mol% PPh$_3$ 300 mol% HCOOH	DMF	60/3	mixture	-

[a] Determined by ^{1}H NMR comparing integration of the crude products. The reactions formed unknown products were designated as "mixture".

In the first set of reactions was utilized allylpalladium chloride dimer as a catalyst. Dipolar solvent such as DMF and HMPA afforded two products, the cyclopropanation products **5** and the cycloheptenoid product **6** in 2 : 1 to 5 : 1 by measuring the integration of the crude reaction product. In sharp contrast, nonpolar solvent such as toluene or acetonitrile afforded the cycloheptenoid product **6** exclusively. Similar trends were also found in the use of the other palladium catalysts. While palladium acetate in DMF yielded the cyclopropanation products **5** exclusively, that in toluene or acetonitrile did a mixture of products along with the cycloheptanoid product **6**. Pd(PPh$_3$)$_4$ in DMF yielded the cyclopropanation products **5** predominantly (79%) and PdCl$_2$ in toluene formed the other product **6**. Palladium acetate in toluene or acetonitrile, Pd(PPh$_3$)$_4$ in toluene, Pd$_2$(dba)$_3$ in DMF yielded a complex mixture of cyclized products along with the product **5** and **6**. PdCl$_2$(PPh$_3$)$_2$ or PdCl$_2$ in DMF, and PdCl$_2$(dpe)$_2$ in DMF or toluene did not undergo cyclization. In most cases, the endo-mode product **5** was isolated as 1 : 1 diastereomeric mixtures; each isomer was separated by using flash chromatography. From these results, we could conclude that the present cyclization has been governed by the several factors such as mostly by solvent and by palladium catalyst. Furthermore, the cyclization modes highly depended upon the reaction solvent.

Mechanistically, the intermediate **4a** could further undergo cyclopropanation to give the corresponding neopentyl type intermediate **4b**. Our previous report indicated that the intermediate **4b** could be reductively cleaved to give the corresponding product **5**. The intermediate **4c** could be formed from the substrate **3** by endo-mode cyclization. In addition, the intermediate **4c** could be formed by equilibration with the intermediate **4a** and / or **4c**. Endo-mode cyclized intermediate **4c** eventually undergoes β-elimination to give the conjugated diene **6**. The optimal conditions were applied to the homologue of the eneyne substrate **3**. The eneyne **7** afforded only cyclohexene product **9** in the tested three solvent. Any cyclopropanation product **8** was not detected by analyzing ^{1}H NMR spectra of the crude products (Table 2). Presumably, the thermal stability of the six-membered intermediate like **4c** over that of the three membered intermediate like **4b** competes over the solvent effect shown in the reaction of eneyne **3**.

Table 2. Pd-Catalyzed cyclizations of eneyne 7



Solvent	T(°C)/Time (h)	**9** (%)
DMF	60/2	70
Toluene	70/6	26
CH_3CN	70/3	23

In conclusion, we have demonstrated the very important factors which could control the chemoselectivity in palladium catalyzed eneyne cyclizations. 1,6-Eneyne always gave the endo-mode cyclization unless it could form any other stable products. 1,7-Eneyne proceeded endo- or exo-mode depending on solvent. Polar solvent such as DMF or HMPA afforded the exo-mode product **5** predominantly after reductive cleavage of alkylpalladium intermediate **4b**, while non-polar solvent did the endo-mode product *via* **4c** followed by β-elimination.

The successful control in chemoselectivities and the excellent chemical yields combine to provide a synthetically useful methodology. Further studies with general eneyne substrates are in progress.

The work was financially supported by the Korea Science and Engineering Foundation (971-0302-016-2).

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7 Cyclized products **5**, **6**, and **9** have been fully characterized by ^{1}H NMR (300 MHz), ^{13}C NMR (75 MHz), IR, and HRMS.