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Tandem nucleophilic allylation–alkoxyallylation of alkynylaldehydes via amphiphilic bis-π-allylpalladium complexes

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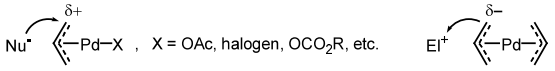
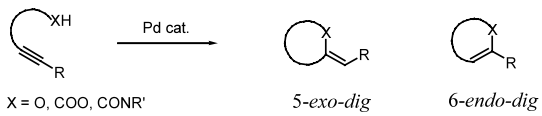
Abstract—The tandem nucleophilic allylation–alkoxyallylation reaction of the alkynylaldehydes **3** with allyl chloride and allyltributylstannane proceeded very smoothly in the presence of catalytic amounts of allylpalladium chloride dimer in THF at room temperature to give the corresponding 5-*exo*-*dig* products **4** as the major product in good to high yields along with 6-*endo*-*dig* products **5** as the minor product.

π-Allylpalladium complexes **1** are important key intermediates in the Tsuji–Trost reaction, and the π-allyl group exhibits an electrophilic reactivity toward carbanions and heteroatom nucleophiles.[1] We recently found that bis-π-allylpalladium complex **2** has a nucleophilic character and reacts with aldehydes and imines to give the corresponding homoallyl alcohols and amines.[2]

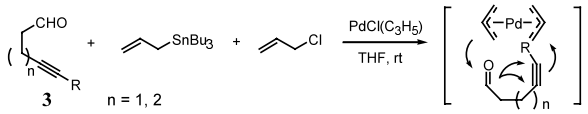


1 **2**

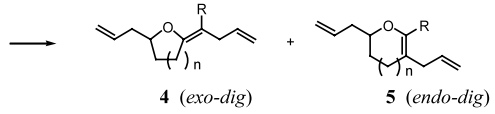
Moreover, the bis-π-allylpalladium complex acts as an amphiphilic allylating agent in the reaction with certain Michael acceptors to afford the corresponding bisallylation products.[3] Medium-sized carbocycles (10–12-membered rings) are synthesized selectively by using the amphiphilic bis-π-allylpalladium system in which two π-allyl units are bonded through a carbon tether.[4] We now report a new amphiphilic reaction using the bis-π-allylpalladium complex; the nucleophilic allylation of alkynylaldehydes **3** followed by the alkoxyallylation of the alkyne bond proceeds very smoothly in a tandem manner to produce the corresponding *exo*- and *endo*-cyclic ethers, **4** and/or **5** (Eq. (1)).



Scheme 1.



(1)



It is well known that the intramolecular additions of alcohols, carboxylic acids, amides, and nitriles to acetylenes proceed in the presence of palladium catalysts to produce various heterocycles (Scheme 1).[5–9]

The reaction reported in this paper is a combination of the nucleophilic allylation of bis-π-allylpalladium and the intramolecular addition reaction of the resulting alkoxy nucleophiles.

The reaction of the alkynylaldehydes **3** with allyltributylstannane and allyl chloride proceeded in the presence of catalytic amounts of the allylpalladium chloride dimer at room temperature in THF to give the corresponding bisallylated 5-*exo*-*dig* cyclic ethers **4** along with 6-*endo*-*dig* cyclic ethers **5** (Eq. (1), Table 1). Although various palladium catalysts, such as $PdCl_2(PPh_3)_2$, $Pd(PPh_3)_4$, $Pd_2(dba)_3{\cdot}CHCl_3$ and $Pd_2(dba)_3{\cdot}CHCl_3/4P(C_6F_5)_3$, were examined in the reaction of **3a**, the use of allylpalladium chloride dimer gave

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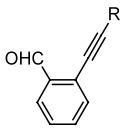
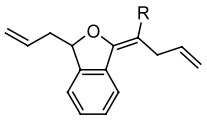
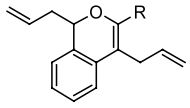
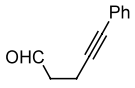
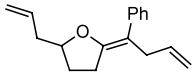
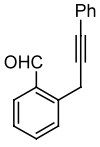
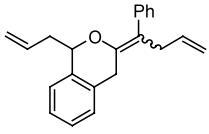
Table 1. The reaction of various alkynylaldehydes **3** with allyltributylstannane and allyl chloride in the presence of allylpalladium chloride dimer

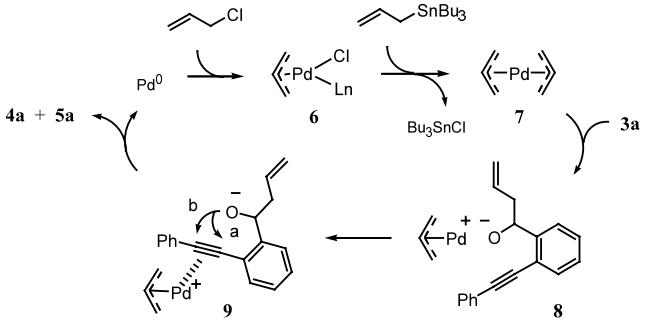
Entry	Substrate	Reaction time	Yields of products (%)[a]	
			5-*exo*-*dig* **4**	6-*endo*-*dig* **5**
				
			4a-e	**5a-e**
1	**3a** R = Ph	24 h	86	10
2	**3b** R = *p*-$CF_3C_6H_4$	20 h	98	—
3	**3c** R = TMS	48 h	94	6
4	**3d** R = *p*-$MeOC_6H_4$	48 h	51	37
5	**3e** R = *n*-Bu	72 h	25	59
6				
	3f	6 d	**4f**	
			50	
7				
	3g	6 d		**5g**
				90
				(1 / 1)

[a]Isolated yields based on the aldehyde.

the best result and the tandem nucleophilic allylation–alkoxyallylation products, **4a** and **5a**, were obtained in 86 and 10% yield, respectively (entry 1). The reaction of the alkynylaldehydes **3b–c**, which have an electron-withdrawing group such as CF_3 and TMS, gave the corresponding 5-*exo*-*dig* type products **4b–c** either exclusively or very predominantly, along with a small amount of the 6-*endo*-*dig* product **5c** (entries 2 and 3). In the case of the alkynylaldehydes **3d–e**, which have an electron-donating group such as MeO and Bu, the yield of the 6-*endo*-*dig* products **5d–e** increased and **5e** became a major product in the case of **3e** (entries 4 and 5). 5-Phenylpent-4-ynal **3f** also underwent the tandem nucleophilic allylation–alkoxyallylation to give the 5-*exo*-*dig* product **4f**, exclusively, in 50% yield (entry 6). The 6-*exo*-*dig* type product **5g** was obtained from **3g** in 90% yield as a 1:1 mixture of stereoisomers (entry 7).

A representative procedure for the tandem nucleophilic allylation–alkoxyallylation is as follows. To a mixture of **3a** (0.5 mmol, 103 mg) and the allylpalladium chloride dimer (0.05 mmol, 18.3 mg) in THF (3.0 mL) were added allyl chloride (1.5 mmol, 0.12 μL) and allyltributylstannane (0.6 mmol, 199 mg) under Ar, and the mixture was stirred at room temperature. The reaction progress was monitored by TLC. When **3a** was consumed, KF (300 mg) was added and the reaction mixture was stirred for 1 h. The mixture was filtered through a short silica gel column with ether and the filtrate was concentrated. Purification by HPLC (Mightysil, Si60 250-20 (5 μm)) with hexane gave the 5-*exo*-*dig* product **4a** (124 mg, 86%) and the 6-*endo*-*dig* product **5a** (14.0 mg, 10%).

A mechanistic rationale which accounts for the tandem nucleophilic allylation–alkoxyallylation of alkynylaldehydes is shown in Scheme 2. The oxidative addition of



Scheme 2.

Pd(0) to allyl chloride produces the π-allylpalladium chloride complex **6**. The transmetallation reaction between **6** and the allylic stannane gives the bis-π-allylpalladium complex **7**, which reacts with **3a** in a nucleophilic manner to give the π-allylpalladium intermediate **8**. The *anti*-attack of the alkoxy anion to the alkyne through path **a** or path **b** as shown in **9** would then afford the 5-*exo*-*dig* product **4a** or 6-*endo*-*dig* product **5a**, respectively.

The selectivity of 5-*exo* and 6-*endo* cyclization was dependent on the functional groups present on the acetylenes. As shown in Table 1, the alkynylaldehydes having an electron-withdrawing group (**3a**–**c**) gave the 5-*exo* products exclusively or very predominantly, while those having an electron-donating group at the R position (**3d**–**e**) afforded the 6-*endo* products in an increased yield or predominantly.

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