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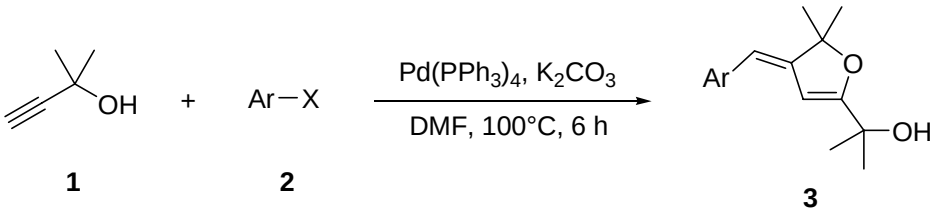
PALLADIUM-CATALYZED CYCLOCOTRIMERIZATION OF PROPARGYL ALCOHOLS WITH ARYL HALIDES

Shuichi Oi,* Hideki Orihara, Hiroshi Kawai, and Yoshio Inoue*

Department of Biomolecular Engineering, Graduate School of Engineering, Tohoku University, 6-6-11 Aramaki-Aoba, Aoba-ku, Sendai 980-8579, Japan
E-mail: oishu@aporg.che.tohoku.ac.jp

Abstract – Tertiary propargyl alcohols react with aryl halides in the presence of K_2CO_3 and a catalytic amount of palladium(0) complex affording 2:1 cyclocotrimerization products, 3-benzylidene-2,3-dihydrofuranes (**3**).

Palladium-catalyzed reaction of terminal acetylenes with aryl halides, referred to as the Sonogashira coupling reaction, has been recognized to be a good synthetic method for arylacetylenes.[1,2] The Sonogashira coupling reaction has been typically performed in the presence of copper salts and appropriate organic bases such as tertiary amines. There has been some reports that the reaction proceeds in the absence of copper salts when appropriate base or ligand is used.[3-10] We have found that the palladium-catalyzed reaction of tertiary propargyl alcohols with aryl halides in the presence of inorganic bases such as K_2CO_3 gives not the Sonogashira coupling products but 2:1 cyclocotrimerization products, 3-benzylidene-2,3-dihydrofuranes (**3**) (Scheme 1).

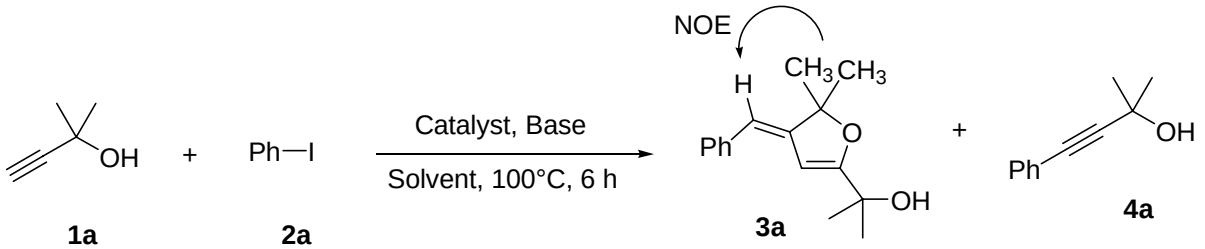


1 **2** **3**

Scheme 1

When 2-methyl-3-butyn-2-ol (**1a**, 10.0 mmol) and iodobenzene (**2a**, 5.0 mmol) were reacted in the presence of 0.1 mmol of $Pd(PPh_3)_4$ and 10 mmol of triethylamine in DMF at 100°C for 6 h, the Sonogashira coupling product (**4a**) was obtained predominantly together with a small amount of the cyclocotrimerization product (**3a**) (Table 1, Entry 1). On the contrary, the use of inorganic bases reversed

Table 1. Cyclocotrimerization of 2-methyl-3-butyn-2-ol (**1a**) with iodobenzene (**2a**).



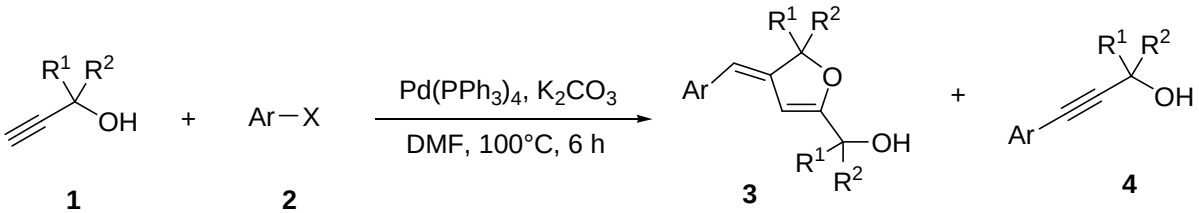
1a **2a** **3a** **4a**

Entry	Catalyst	Base	Solvent	Yield (%)	
				3a	**4a**
1	$Pd(PPh_3)_4$	Et_3N	DMF	9	48
2	$Pd(PPh_3)_4$	K_3PO_4	DMF	44	4
3	$Pd(PPh_3)_4$	K_2CO_3	DMF	43	0
4	$Pd(PPh_3)_4$	K_2CO_3	DMSO	31	10
5	$Pd(PPh_3)_4$	K_2CO_3	THF	11	0
6	$Pd(PPh_3)_4$	K_2CO_3	acetonitrile	24	8
7	$Pd(PPh_3)_4$	K_2CO_3	toluene	22	0
8	$Pd(dba)_2/2PPh_3$	K_2CO_3	DMF	32	0
9	$Pd(dba)_2/2P(Bu\text{-}n)_3$	K_2CO_3	DMF	21	0
10	$Pd(dba)_2/2P(OEt)_3$	K_2CO_3	DMF	0	0
11	$Pd(dba)_2$/dppe	K_2CO_3	DMF	32	0

the selectivity of the products. The reaction using K_3PO_4 as base gave 44% yield of **3a** and only 4% yield of **4a** (Entry 2). Moreover, the use of K_2CO_3 resulted in the exclusive formation of **3a** in 43% yield (Entry 3). The geometry of 3-benzylidene moiety of **3a** was determined to be *E* by NOE experiments. It is noted that the reaction gave only *E*-form selectively. The reaction was then examined in various solvents (Entries 3-7). Among the solvent examined, DMF showed the best result. The combination of $Pd(dba)_2$ with some phosphine ligands also exhibited the catalytic activity (Entries 8-11), however, the yields were lower than the reaction with $Pd(PPh_3)_4$.

Using the optimized reaction conditions (Table 1, Entry 3), reactions of propargyl alcohols with various aryl halides were examined (Table 2). A primary propargyl alcohol (**1b**) did not react with iodobenzene under the reaction conditions and a secondary propargyl alcohol (**1c**) gave only the Sonogashira product (**4b**) (Entries 1 and 2). Although a reason has not yet been clear, the cyclocotrimerization thus proved to be particular to the tertiary propargyl alcohols such as **1a** (Entry 3). The reaction of **1a** with bromobenzene gave the product in a better yield of 65% than that with iodobenzene, while the reaction with chlorobenzene did not give the product (Entries 4 and 5). Bromobenzenes substituted with either electron-donating or electron-withdrawing group (**2d-f**) reacted with **1a** affording the products in moderate yields (Entries 6-8). Bromonaphtharenes (**2g** and **2h**) also reacted well with **1a** affording the products in good yields (Entries 9 and 10).

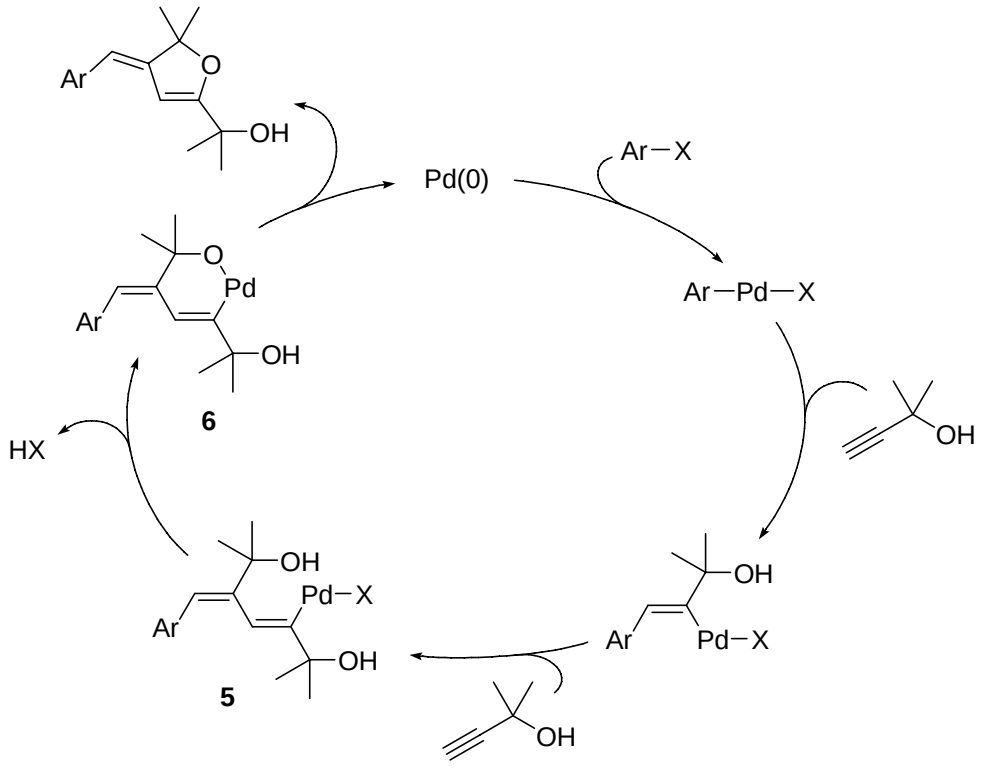
Table 2. Cyclocotrimerization of propargyl alcohols (**1**) with aryl halides (**2**).



1 **2** **3** **4**

Entry	R^1, R^2	Ar-X	Yield (%)	
			3	**4**
1	$R^1 = R^2 = H$ (**1b**)	Ph-I (**2a**)	0	0
2	$R^1 = H$, $R^2 = Me$ (**1c**)	**2a**	0	23 (**4b**)
3	$R^1 = R^2 = Me$ (**1a**)	**2a**	43 (**3a**)	0
4	**1a**	Ph-Br (**2b**)	65 (**3a**)	5
5	**1a**	Ph-Cl (**2c**)	0	0
6	**1a**	4-Me-C_6H_4-Br (**2d**)	45 (**3b**)	8
7	**1a**	4-MeO-C_6H_4-Br (**2e**)	22 (**3c**)	0
8	**1a**	4-F-C_6H_4-Br (**2f**)	50 (**3d**)	trace
9	**1a**	1-Naphthyl-Br (**2g**)	59 (**3e**)	5
10	**1a**	2-Naphthyl-Br (**2h**)	56 (**3f**)	6

Although there is little experimental evidence at present to determine the exact reaction pathway for the cyclocotrimerization, a possible reaction mechanism is shown in Scheme 2. A palladium(0) complex reacts with an aryl halide to give an arylpalladium(II) species. Sequential insertion of two propargyl



Scheme 2. Possible reaction mechanism

alcohols to the palladium-carbon bond affords the alkenylpalladium intermediate (**5**). Cyclization of **5** accompanied by elimination of HX then gives the palladacycle (**6**). The cyclocotrimerization product (**3**) is formed through reductive elimination from **6**, with the simultaneous regeneration of palladium(0) complex.

In conclusion, palladium-catalyzed cyclocotrimerization of tertiary propargyl alcohols with aryl halides is described. The use of inorganic bases such as K_2CO_3 is important to promote the cyclization. The reaction affords 3-benzylidene-2,3-dihydrofuranes in one step.

EXPERIMENTAL

General. Infrared (IR) spectra were recorded on JASCO FT/IR-350 Fourier transform infrared spectrophotometer. NMR spectra were recorded on Bruker AC-250, spectrometer. EIMS spectra were measured on Shimadzu GCMS-QP5050. All reactions were performed in Schlenk tubes under a N_2 atmosphere. Propargyl alcohols (**1a**-**c**), aryl halides (**2a**-**h**), $Pd(PPh_3)_4$, and anhydrous DMF was purchased and used as received. K_2CO_3 was dried at 250 °C under reduced pressure and stored under N_2. Flash chromatographies were performed using spherical silica gel (40-100 μm, Kanto Chemical). Elemental analyses were performed by the Microanalytical Laboratory of the Institute for Chemical Reaction Science, Tohoku University.

General procedure for the reaction of propargyl alcohols with aryl halides. A mixture of propargyl alcohol (10.0 mmol), aryl halide (5.0 mmol), K_2CO_3 (1.38 g, 10.0 mmol), and $Pd(PPh_3)_4$ (116 mg, 0.10 mmol) in 15 mL of dried and degassed DMF was stirred at 100 °C for 6 h. The reaction mixture was diluted with 30 mL of Et_2O, washed with water (30 mL x 3), and dried over $MgSO_4$. After the solvent was removed in *vacuo*, the residue was purified by silica gel flash chromatography (hexane-EtOAc, 10:1) to give the product. All reactions were performed using the same procedure.

3a. Colorless oil. ^{1}H-NMR ($CDCl_3$): δ (ppm) 7.29-7.32 (m, 5H), 6.03 (s, 1H), 5.68 (s, 1H), 2.11 (s, 1H), 1.47 (s, 6H), 1.45 (s, 6H). ^{13}C-NMR ($CDCl_3$): δ(ppm) 171.4, 150.8, 138.7, 128.4, 127.4, 110.9, 95.6, 89.8, 28.1, 27.9. IR (neat): 3400, 2960, 1600, 1500, 1380 cm^{-1}. MASS (EI): m/z 115, 143, 185, 211, 226, 244 (M^+). Anal. Calcd for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25. Found: C, 78.65; H, 8.01.

3b. Colorless oil. ^{1}H-NMR ($CDCl_3$): δ (ppm) 7.19 (d, *J* = 5.1 Hz, 2H), 7.09 (d, *J* = 5.1 Hz, 2H), 5.99 (s, 1H), 5.63 (s, 1H), 2.32 (s, 1H), 1.44 (s, 6H), 1.41 (s, 6H). ^{13}C-NMR ($CDCl_3$): δ(ppm) 170.8, 149.8, 135.8, 129.7, 129.2, 127.3, 110.8, 95.6, 89.7, 69.3, 28.0, 27.9, 21.1. IR (neat): 3400, 2980, 1600, 1510 cm^{-1}. MASS (EI): m/z 105, 157, 161, 185, 199, 225, 243, 258 (M^+). Anal. Calcd for $C_{17}H_{22}O_2$: C, 79.03; H, 8.58. Found: C, 78.92; H, 8.38.

3c. Colorless oil. ^{1}H-NMR ($CDCl_3$): δ (ppm) 7.35 (d, *J* = 8.8 Hz, 2H), 6.84 (d, *J* = 8.8 Hz, 2H), 6.19 (s, 1H), 5.67 (s, 1H), 3.36 (s, 3H), 1.96 (s, 1H), 1.39 (s, 6H), 1.37 (s, 6H). ^{13}C-NMR ($CDCl_3$): δ(ppm) 170.3,

156.7, 147.8, 127.6, 126.9, 126.5, 126.1, 109.4, 94.5, 88.2, 67.8, 53.3, 26.7. IR (neat): 3370, 2970, 1600, 1510, 1380, 1250, 1030 cm^{-1}. MASS (EI): m/z 121, 173, 187, 215, 241, 259, 274 (M^+). Anal. Calcd for $C_{17}H_{22}O_3$: C, 74.42; H, 8.08. Found: C, 74.32; H, 7.96.

3d. Colorless oil. ^{1}H-NMR ($CDCl_3$): δ (ppm) 7.32-7.24 (m, 2H), 7.07-6.95 (m, 2H), 5.96 (s, 1H), 5.63 (s, 1H), 1.68 (s, 1H), 1.46 (s, 6H), 1.44 (s, 6H). ^{13}C-NMR ($CDCl_3$): δ(ppm) 128.8, 128.7, 115.3, 115.0, 109.6, 95.1, 89.8, 69.3, 28.0, 27.9. IR (neat): 3410, 2980, 1600, 1510, 1230 cm^{-1}. MASS (EI): m/z 157, 161, 189, 203, 229, 247, 262 (M^+). Anal. Calcd for $C_{16}H_{19}O_2F$: C, 73.26; H, 7.30. Found: C, 73.12; H, 7.41.

3e. Colorless oil. ^{1}H-NMR ($CDCl_3$): δ (ppm) 8.03 (d, *J* = 5.2 Hz, 1H), 7.82 (d, *J* = 6.2 Hz, 1H), 7.70 (d, *J* = 8.3 Hz, 1H), 7.50-7.40 (m, 4H), 6.23 (s, 1H), 5.78 (s, 1H), 2.15 (s, 1H), 1.56 (s, 6H), 1.43 (s, 6H). ^{13}C-NMR ($CDCl_3$): δ(ppm) 170.8, 152.9, 136.0, 133.7, 131.7, 128.5, 126.5, 125.7, 125.6, 125.5, 124.4, 108.1, 95.7, 89.3, 69.3, 28.3, 27.9. IR (neat): 3400, 1620, 800 cm^{-1}. MASS (EI): m/z 141, 165, 193, 207, 235, 261, 279, 294 (M^+). Anal. Calcd for $C_{20}H_{22}O_2$: C, 81.60; H, 7.53. Found: C, 81.75; H, 7.56.

3f. Colorless oil. ^{1}H-NMR ($CDCl_3$): δ (ppm) 7.77-7.62 (m, 5H), 7.43-7.35 (m, 2H), 6.14 (s, 1H), 5.81 (s, 1H), 2.22 (s, 1H), 1.48 (s, 12H). ^{13}C-NMR ($CDCl_3$): δ(ppm) 170.8, 151.3, 136.3, 133.8, 131.7, 127.8, 127.64, 127.55, 126.3, 126.04, 125.57, 125.1, 111.0, 95.7, 90.0, 69.4, 28.1, 27.9. IR (neat): 3400, 1620, 750 cm^{-1}. MASS (EI): m/z 141, 165, 193, 207, 235, 261, 279, 294 (M^+). Anal. Calcd for $C_{20}H_{22}O_2$: C, 81.60; H, 7.53. Found: C, 81.38; H, 7.22.

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