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Pd-Catalyzed Allylic Alkylation of Phenylvinylcarbinols with Some Nucleophiles

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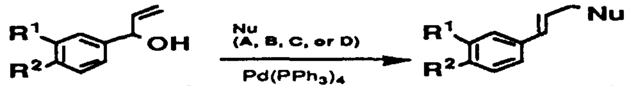
Abstract: Allylic alkylation of phenylvinylcarbinols with various nucleophiles proceeded smoothly under mild reaction conditions in the presence of $Pd(PPh_3)_4$ providing an efficient methodology for the synthesis of estrogens and their analogs.

Since the first work by Tsuji *et al* [1], many studies[2] have been published on the Pd-catalyzed allylic alkylation of allylic esters[3] and ethers[4], vinyl epoxides[3b,5], and mono- and dienes[4a,6]. However, only a handful of examples of alkylation of allylic alcohols were reported to proceed under extreme reaction conditions[7], and a hydroxyl group is described not to function as an effective leaving group in the Pd-catalyzed reactions[5,8,9]. Despite of the general belief, we found that allylic alcohols activated by a phenyl group (**1a**) or methoxyphenyl groups (**1b, c**) underwent allylic alkylation with various nucleophiles, such as 2-methyl-1,3-cyclopentanedione (**A**), 2,4-pentanedione (**B**), methyl acetoacetate (**C**), and diethyl malonate (**D**), in the presence of Pd(PPh3)4 under mild reaction conditions.



1 a: $R^1 = R^2 = H$
b: $R^1 = H$, $R^2 = OMe$
c: $R^1 = R^2 = OMe$

2 a, b, c, d, e, or f

In order to identify the best catalyst, the reaction of **1c** and **A** was first carried out using various possible catalyst. The results are listed in Table 1. The table clearly indicates that $Pd(PPh_3)_4$ is the best and only catalyst possibly applicable to the alkylation of **1**.

Table 1. Results of the reactions between **1c** and (**A**) with various catalysts.

Entry	Catalyst		Solvent	Bath temp. (°C)	Time (min)	Yield (%)
1	$Ni(acac)_2$	(1 mol %)	dioxane (1 ml)	120-130	90	44.4
2	$Ni(acac)_2$	(1 mol %)	dioxane (1 ml)	110-120	120	recovery
3	$Ni(acac)_2$	(1 mol %)	none	120-130	90	49.3
4	MS-4A	(large excess)	none	120-130	90	recovery
5	$MgSO_4$	(large excess)	xylene (1 ml)	130-140	30	47.9
6	KF	(10 mol %)	xylene (1 ml)	130-140	120	50.7
7	$Pd(PPh_3)_4$	(1 mol %)	THF (1 ml)	110-120	30	98.6

Table 2. Results of Pd-catalyzed reactions between phenylvinylcarbinols and nucleophiles.

Carbinol	R^1	R^2	Nucleophile [a)]	Product [b)]	Yield (%) [c)]
1a	H	H	**A**	**2a**	61.4
1b	H	OMe	**A**	**2b**	95.4
1c	OMe	OMe	**A**	**2c**	98.6
			B	**2d**	99.4
			C	**2e**	99.3
			D	**2f**	81.6

a) See text. b) All products were characterized by ^{1}H-NMR, IR, and FD-MS. c) Isolated yield.

In a typical reaction, a mixture of 3,4-dimethoxyphenylvinylcarbinol **1c** (0.5 mmol), **A**(0.6 mmol), and $Pd(PPh_3)_4$ (1 mol %) was stirred in refluxing dry THF(1 ml) under argon atmosphere. After the reaction mixture became clear, the product **2c** was isolated by preparative TLC developed with AcOEt-hexane (1:1). The yield was 98.6 %.

Using the catalyst, reaction was examined between carbinols **1a-c** and several nucleophiles **A-D**. The results are summarized in Table 2.

The reaction of **3a** or **3b** leads to a useful and convenient method also for the preparation of key intermediates, **4a** or **4b** for the synthesis of estrogenic compounds[10].

3a R=H
3b R=OMe

4a (87.6 %)
4b (86.3 %)

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