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Palladium-Catalyzed Etherification of Allyl Alcohols Using Phenols in the Presence of Titanium(IV) Isopropoxide

Tetsuya Satoh, Masahiro Ikeda, Masahiro Miura,* and Masakatsu Nomura

Department of Applied Chemistry, Faculty of Engineering, Osaka University, Suita, Osaka 565, Japan

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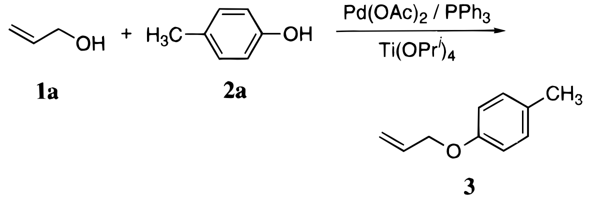
Palladium-catalyzed reaction of allylic compounds with carbon, nitrogen, and oxygen nucleophiles is of genuine synthetic utility.[1] The reaction is usually carried out using allyl esters or carbonates as substrates. In contrast, and in spite of their ready availability, the reaction with allyl alcohols has been relatively less explored.[2] We have reported that palladium-catalyzed nucleophilic substitution of allyl alcohols using zinc enolates can proceed efficiently in the presence of titanium(IV) alkoxides and LiCl;[3] the alkoxides appear to enhance the reactivity of allyl alcohols toward palladium(0) species. We considered that, when phenols are employed as nucleophiles for the reaction, a convenient method to prepare allyl aryl ethers could be realized; the ethers are useful compounds in organic synthesis, particularly as the substrates of the Claisen rearrangement.[4] Consequently, as part of our study of palladium-catalyzed synthetic reactions using phenols as substrates,[5,6] we have examined the reaction of allyl alcohols with phenols in the presence of a palladium catalyst and titanium(IV) isopropoxide.

When a mixture of allyl alcohol (**1a**, 4 mmol) and *p*-cresol (**2a**, 1 mmol) was heated in the presence of Pd(OAc)$_2$ (0.025 mmol) and PPh$_3$ (0.1 mmol) in C_6H_6 (5 mL) under nitrogen at 50 °C for 20 h, 1-(4-methylphenoxy)-2-propene (**3**) was produced in a yield of 34% (entry 1 in Table 1).[6] The reaction should be accompanied by formation of water. Addition of molecular sieves (MS4A) for its removal, however, showed no positive effect (entry 2). On the contrary to this normal desiccant, addition of Ti(OPr^i)$_4$ (0.25 mmol) was found to remarkably enhance both the reaction rate and yield of **3**. Thus, the yield reached 93% within 1 h (entry 3). The reaction of allyl alcohols with zinc enolates, mentioned above, required addition of a chloride source such as LiCl together with Ti(OR)$_4$ to proceed efficiently.[3] However, this was not necessary for the present reaction. It was confirmed that the reaction did not occur in the absence of the palladium species (entry 4). Note that compound **3** could also be produced in good yield in the reaction at room temperature or using a smaller amount of the palladium catalyst (1 mol %) (entries 5, 7, and 8). In the latter case, either addition of MS4A or increase in the amount of PPh$_3$ added was needed to prevent catalyst deactivation which is probably due to water formed during the reaction.

Table 1. Reaction of Allyl Alcohol (1a) with *p*-Cresol (2a)[a]



entry	Pd(OAc)$_2$:PPh$_3$:Ti(OPr^i)$_4$ (in mmol)	time (h)	yield of **3** (%)[b]
1	0.025:0.1:0	20	34
2[c]	0.025:0.1:0	7	26
3	0.025:0.1:0.25	1	93
4	0:0.2:0.25	1	0
5[d]	0.025:0.1:0.25	20	91
6	0.01:0.04:0.25	1	61
7[c]	0.01:0.04:0.25	1	93
8	0.01:0.1:0.25	1	90

[a] Reaction conditions: **1a** (4 mmol), **2a** (1 mmol), in C_6H_6 (5 mL) at 50 °C. [b] Determined by GLC analysis. [c] Reaction was carried out using MS4A (200 mg). [d] Reaction at rt.

Treatment of **1a** using phenols substituted by both electron-withdrawing and electron-donating groups (**2c**−**e**) also gave ethers **5**−**7** in good yields (Table 2). In the case of **2c**, the use of Ti(OPr^i)$_4$ was essential for the reaction to proceed catalytically. A phenol bearing a bulky substituent, Bu^t, at 2-position could also be reacted, whereas a more sterically crowded phenol, 2,6-di-*tert*-butylphenol, did not undergo the reaction.

When 3,5-dimethoxyphenol (**2g**) whose aryl moiety seems to be relatively electron rich[7] was employed, C-allylated products **9** and **10** were obtained,[4f,8] no O-allylated products being detected (Scheme 1). Depending on the ratio of **1a**/**2g** used, monoallylated product **9** or diallylated product **10** was selectively produced. Since 1-(3,5-dimethoxyphenoxy)-2-propene (**11**) was found to be transformed to **9** under the present conditions, the C-allylated products may also be formed, at least in part, by isomerization of the ether **11**.

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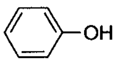
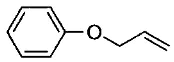
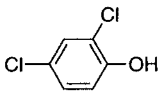
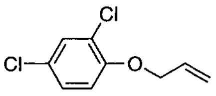
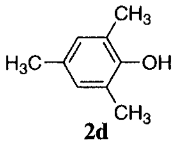
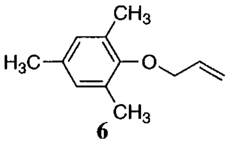
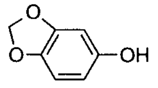
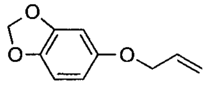
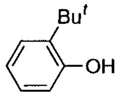
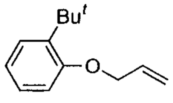
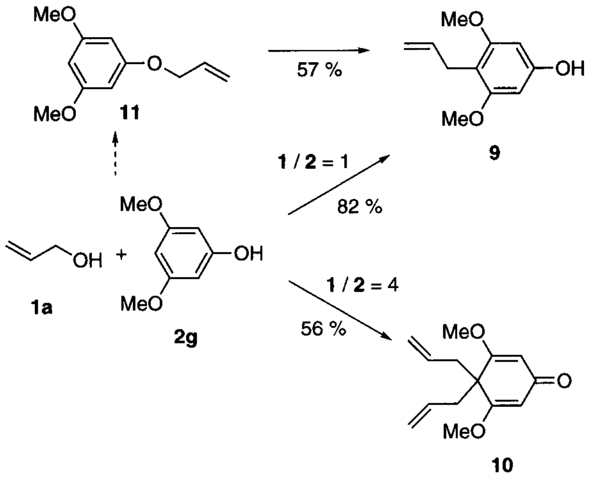
Table 2. Reaction of Allyl Alcohol (1a) with Phenols 2b–f[a]

2	product	yield (%)[b]
 **2b**	 **4**	87
 **2c**	 **5**	78 (69) 2[c]
 **2d**	 **6**	78 (64)
 **2e**	 **7**	73 (67)
 **2f**	 **8**	81 (78)

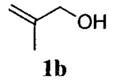
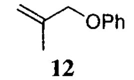
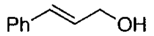
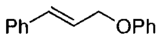
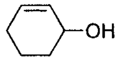
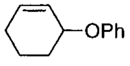
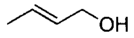
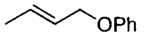
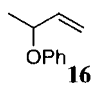
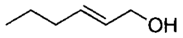
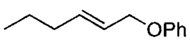
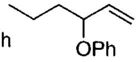
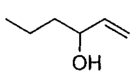
[a] Reaction conditions: **1a** (4 mmol), **2** (1 mmol), $Pd(OAc)_2$ (0.01 mmol), PPh_3 (0.04 mmol), $Ti(OPr^i)_4$ (0.25 mmol), and MS4A (200 mg) in C_6H_6 (5 mL) at 50 °C for 4-20 h. [b] GLC yield based on amount of **2** used. Value in parentheses indicates yield after purification. [c] Without $Ti(OPr^i)_4$.

Scheme 1



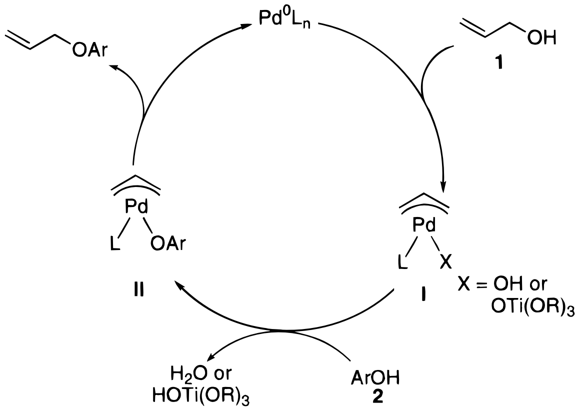
Results for etherification of a number of allyl alcohols **1b**–**g** with phenol (**2b**) using $Pd(OAc)_2$, PPh_3, $Ti(OPr^i)_4$, and MS4A are summarized in Table 3. All of allyl alcohols examined underwent etherification smoothly to give the corresponding phenyl ethers in 71–89% yields, while mixtures of regioisomeric ethers were formed in the cases using **1e**–**g**. The fact that **1f** and **1g** gave the same products may suggest that the reaction process involves a common π-allylpalladium intermediate.

Table 3. Reaction of Allyl Alcohols 1b-g with Phenol (2b)[a]

1	product(s)		yield (%)[b]
 **1b**	 **12**		89
 **1c**	 **13**		75
 **1d**	 **14**		72
 **1e**	 **15**	 **16**	76 (81/19)
 **1f**	 **17**	 **18**	81 (67/33)
 **1g**	**17**	**18**	71 (68/32)

[a] Reaction conditions: **1** (1 mmol), **2b** (2 mmol), $Pd(OAc)_2$ (0.01 mmol), PPh_3 (0.04 mmol), $Ti(OPr^i)_4$ (0.25 mmol), and MS4A (200 mg) in C_6H_6 (5 mL) at 50 °C for 4-20 h. [b] GLC yield based on amount of **1** used.

Scheme 2



A possible mechanism for the formation of allyl aryl ethers from **1** and **2** is illustrated in Scheme 2, in which the substituent on allyl alcohol is omitted. Alcohol **1** or an allyl titanate, formed by alcohol exchange reaction between **1** and isopropoxide in $Ti(OPr^i)_4$,[3] reacts with Pd^0 species generated *in situ*[9] to afford a π-allylpalladium intermediate (**I**). Subsequently, the reaction of **I** with phenol **2** followed by reductive elimination gives allyl aryl ether. Under the present reaction conditions using $Ti(OPr^i)_4$, treatment of cinnamyl alcohol (**1c**) without phenols gave dicinnamyl ether quantitatively within 1

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(9) One of the other possible functions of $Ti(OPr^i)_4$ may be acceleration of the reduction of $Pd(OAc)_2$ to Pd^0 species as was observed in our previous work: Satoh, T.; Itoh, K.; Miura, M.; Nomura, M. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 2121.

h, while part of this was transformed to cinnamyl isopropyl ether by elongation of the reaction time. Dicinnamyl ether may be formed by the reaction of **I** with another cinnamyl titanate molecule.[10] In the presence of phenols, which may be relatively more reactive toward the palladium center, **I** should be predominantly transformed to **II** to afford aryl ether. It would also be possible that **II** is formed by ligand exchange between **I** and $Ti(OAr)_n(OR)_{4-n}$ species generated in the reaction medium

Experimental Section

^1H and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz, respectively. MS data were obtained by EI. GLC analysis was carried out using a silicon OV-17 column (i.d. 2.6 mm × 1.5 m) or with a CBP-1 capillary column (i.d. 0.5 mm × 25 m).

1-(3,5-Dimethoxyphenoxy)-2-propene (**11**) was prepared by the reaction of allyl chloride with **2g** using K_2CO_3 as base in DMF at 40 °C. Other starting materials were commercially available. Solvents were purified by standard methods before use.

Etherification of Allyl Alcohols Using Phenols. A mixture of **1** (1−4 mmol), **2** (1−2 mmol), $Pd(OAc)_2$ (2.2 mg, 0.01 mmol), PPh_3 (10 mg, 0.04 mmol), $Ti(OPr^i)_4$ (0.075 mL, 0.25 mmol), MS4A (200 mg), and benzene (5 mL) was stirred under nitrogen at 50 °C for 4−20 h. After cooling, the reaction mixture was poured into dilute hydrochloric acid, extracted with ether, and dried over sodium sulfate. Product was isolated by column chromatography on silica gel using hexane−ethyl acetate (99:1) as eluent.

Products **3**,[4a] **4**,[4f] **5**,[11] **6**,[12] **7**,[13] **8**,[14] **12**,[15] **13**,[4f] **14**,[4f] **15**,[15] **16**,[15] **17**,[4f] and **18**[4f] are known.

4-Allyl-3,5-dimethoxyphenol (9): mp 85−87 °C; ^1H NMR (DMSO-d_6) δ 3.16 (d, 2H, $J = 5.9$ Hz), 3.33 (s, 6H), 4.81 (t, 1H, $J = 1.5$ Hz), 4.84 (dt, 1H, $J = 4.4$, 1.5 Hz), 5.73−5.83 (m, 1H), 6.05 (s, 2H), 7.29 (s, 1H); MS m/z 194 (M^+). Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.26. Found: C, 67.83; H, 7.21.

4,4-Diallyl-3,5-dimethoxy-2,5-cyclohexadien-1-one (10): mp 71−72 °C; ^1H NMR ($CDCl_3$) δ 2.57 (d, 4H, $J = 7.3$ Hz), 3.70 (s, 6H), 4.92 (dt, 2H, $J = 5.9$, 1.0 Hz), 4.96 (dd, 2H, $J = 13.2$, 2.0 Hz), 5.33−5.49 (m, 2H), 5.54 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 40.99, 51.19, 55.79, 103.27, 117.75, 132.20, 172.92, 188.37; MS m/z 234 (M^+). Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.59; H, 7.76.

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