

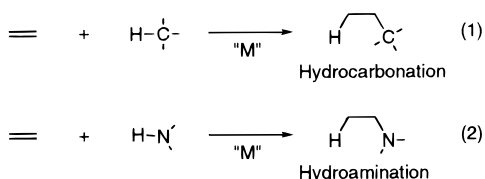
Palladium-Catalyzed Alkoxyallylation of Activated Olefins

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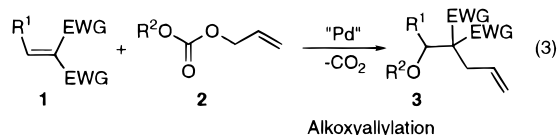
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Transition-metal catalysts have changed dramatically the addition mode of pronucleophiles to carbon–carbon multiple bonds. Hydrocarbonation of carbon pronucleophiles to alkenes,¹ allenes,² alkynes,³ enynes,⁴ 1,3-dienes,⁵ and methylenecyclopropanes⁶ has been developed (eq 1). Hydroamination of nitrogen pronucleophiles to allenes gives the corresponding hydroamination products (eq 2).⁷ We report the first palladium-catalyzed alkoxyallylation



of activated olefins **1** (eq 3). It is well-known in classical organic chemistry that alkoxy nucleophiles (RO[−]) add to **1** in a 1,4 manner to produce the corresponding β-alkoxyenolates. If the



alkylation of the enolates is needed, alkyl halides or related alkylating agents (RX) should be added to the resulting 1,4-

Table 1. Alkoxycarbonation of Olefins **1** with **2** Catalyzed by Pd(PPh₃)₄^a

entry	olefin 1	allylcarbonate 2	product 3	isolated yield (%)
1			3a	92
2		2a	3b	81
3		2a	3c	92
4		2a	3d	85
5		2a	3e	90
6		2a	3f	99
7		2a		56
8 ^b		2a	3g	70
9	1a		3h	95
10	1a		3i + 5^c 78 : 22	92
11	1a		3i + 5^c 77 : 23	66

^a Typical procedure: To a solution of **1a** (77 mg, 0.5 mmol) and Pd(PPh₃)₄ (29 mg, 0.025 mmol) in THF (5 mL) was added **2a** (78 mg, 0.6 mmol) at room temperature under Ar, and the mixture was stirred for 3 h. The solvent was removed in vacuo and the residue was purified by silica gel column chromatography (hexane/ethyl acetate = 10/1) to give **3a** (110 mg, 0.46 mmol, 92% yield). ^b Catalytic amounts of Et₃N (5 mol%) were added to the reaction mixture. ^c **3i** (α-adduct at the crotyl unit); PhCH(OEt)C(CN)₂CH₂CH=CHCH₃. **5** (γ-adduct at the crotyl unit); PhCH(OEt)C(CN)₂CH(CH₃)CH=CH₂.

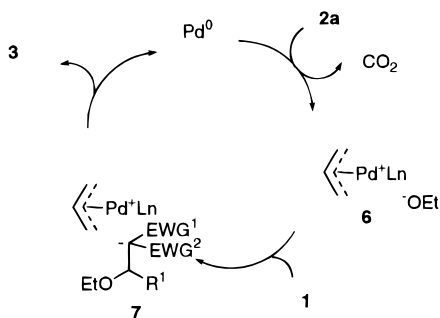
adducts. The present transition-metal-catalyzed variant enables us to perform related transformations all in one shot under neutral conditions.⁸

Ethylidenemalononitriles **1** underwent the facile alkoxyallylation with allylic carbonate **2** in the presence of catalytic amounts of Pd(PPh₃)₄ (5 mol %) to give the corresponding alkoxyallylation products **3** in high yields (eq 3). The results are summarized in Table 1. The reaction of **1a** with allyl ethyl carbonate **2a** proceeded very smoothly at room temperature, giving allyl-1-ethoxybenzylmalononitrile (**3a**) in 92% yield (entry 1). Other aromatic olefins, which have an electron-donating group such as methyl (**1b**) or methoxy (**1c**) and an electron-withdrawing group such as ester (**1d**) at the para position, gave the corresponding alkoxyallylation products **3b–d**, respectively, in high yields (entries 2–4). 2-Naphthylidenemalononitrile (**1e**) also gave the β-ethoxy-α-allyl adduct **3e** in 90% yield (entry 5). Not only aryl-substituted olefins but also alkyl-substituted olefins underwent the alkoxyallylation reaction. The reaction of *tert*-butyl-substituted alkene **1f** and **2a** proceeded very smoothly to give **3f** in 99% yield (entry 6). However, the reaction of *n*-pentyl-substituted olefin **1g**, which has protons at the γ-position, gave 4,4-dicyano-1,5-decadiene (**4**) in 56% yield (entry 7). The

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Scheme 1

Table 2. In Situ Alkoxy-Exchange Reaction^a

entry	R ³ OH (equiv)	yield (%) ^b	ratio (3a/9)
1	BuOH (1)	75	49:51
2	BuOH (10)	78	10:90
3	allylOH (1)	67	25:75
4	allylOH (10)	84	1:>99
5	BnOH (1)	78	1:>99
6	<i>i</i> PrOH (10)	67	>99:1

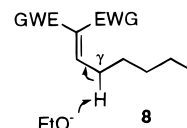
^a A mixture of **1a** (1 mmol), **2a** (1 mmol), and R³OH (1–10 mmol) was dissolved in THF (5 mL). Pd(PPh₃)₄ (0.05 mmol) was then added at room temperature, and the mixture was stirred for appropriate period.

^b Isolated yields based on **1a**.

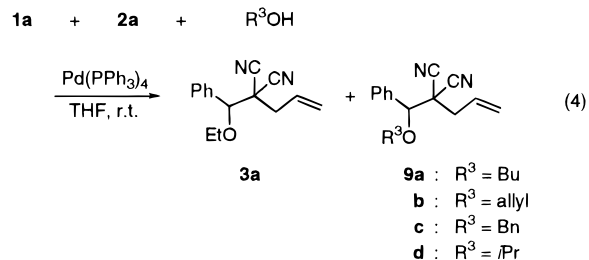
activated olefin **1h** derived from ethyl cyanoacetate underwent the alkoxyallylation by addition of catalytic amounts of triethylamine (entry 8). In the absence of triethylamine, **3g** was obtained in lower yield. Other activated olefins such as diethyl benzylidenemalonate, acrylonitrile, and ethyl propiolate did not undergo the alkoxyallylation.⁹ Next, we examined various allylic carbonates. Methallyl ethyl carbonate **2b** reacted with **1a** to give the corresponding ethoxymethallylation product **3h** in 95% yield (entry 9). The reaction of **1a** with crotyl ethyl carbonate **2c** proceeded very smoothly to give a 78:22 mixture of **3i** (α -adduct) and **5** (γ -adduct) in 92% yield (entry 10). The reaction of **1a** with α -methallyl ethyl carbonate **2d** gave a 77:23 mixture of **3i** and **5** in 66% yield (entry 11). Accordingly, the C–C bond formation of the substituted allyl groups takes place predominantly at the less-hindered carbon site.

A plausible mechanism for the alkoxyallylation reaction is shown in Scheme 1. Oxidative addition of allyl ethyl carbonate **2a** to palladium(0) would give the cationic π -allylpalladium complex **6**¹⁰ and then the resulting ethoxy anion would react with olefins **1** to give the π -allylpalladium complexes **7** having β -ethoxylated enolates. Reductive elimination from **7** would give the products **3** and palladium(0). In the case of substituted allyl derivatives **2b** and **2c**, the reductive coupling would take place predominantly at the less-hindered site. If there is a γ -hydrogen atom in **1** (see entry 7, **1g**), EtO[−] would abstract the proton instead of addition to the β -position and the resulting enolate would undergo coupling with allyl group to give **4** (see **8**).

It occurred to us that, by addition of other alcohols (R³OH), the alkoxy group R³O might be introduced at the β -position of **1**

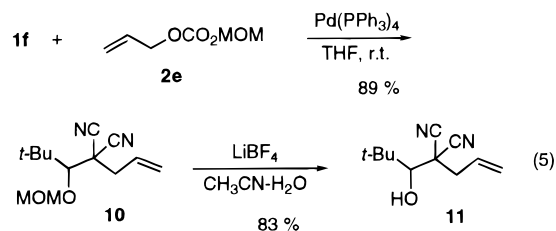


instead of EtO group (eq 4). If this is the case, such an intermolecular delivery of R³O group matches more strongly with the concept of “alkoxyallylation”. The reaction of **1a** (1 equiv),



2a (1 equiv), and butanol (1 equiv) in the presence of catalytic amounts of Pd(PPh₃)₄ (5 mol %) gave a 49:51 mixture of **3a** and **9a** in 75% yield (Table 2, entry 1). However, the use of 10 equiv of butanol gave a 10:90 mixture of **3a** and **9a** (entry 2). Very interestingly, the reaction of **1a**, **2a**, and 1 equiv of allyl alcohol gave higher ratio of the exchanged alkoxy product, **3a**:**9b** = 25:75 (entry 3), and the use of 10 equiv of allyl alcohol gave **9b** exclusively in 84% yield (entry 4). Furthermore, in the case of benzyl alcohol, only benzyloxy allylated product **9c** was obtained in 78% yield even by the use of 1 equiv of benzyl alcohol (entry 5). These interesting selectivities can be explained by using the MNDO calculation.¹¹ It showed that the electron charge on the oxygen atom of ethoxy anion is −0.7500 and that of butoxy anion is −0.7413. However, those of allyloxy and benzyloxy anions are −0.7411 and −0.7229, respectively. These results indicate that an equilibrium between ethoxy anion and the other alkoxy anions lies to that of higher electron charge and such an anion may attack olefins, predominantly. Although the electron charges of ethoxy anion and isopropoxy anion (−0.7497) are very similar, **3a** was obtained in 67% yield exclusively even in the presence of 10 equiv of *i*-PrOH since isopropoxy anion is more bulky in comparison with ethoxy anion (entry 6).

If we can extend the alkoxyallylation to hydroxyallylation, synthetic applicability of the present palladium-catalyzed methodology may broaden. The reaction of **1f** with allyl methoxymethyl carbonate **2e** proceeded very smoothly in the presence of Pd(PPh₃)₄ catalyst to give **10** in 89% yield, and the resulting ether **10** could be converted easily to the corresponding alcohol **11** in 83% yield (eq 5).



In conclusion, activated olefins **1** can be converted into β -alkoxy- α -allylated adducts **3** in one shot under essentially neutral conditions through intermolecular delivery of RO group. This kind of transformation is not easily available via conventional organic reaction; transition-metal-catalyzed reaction enables us to perform such a new type of transformation.

Supporting Information Available: Experimental data for compounds **3–11** (4 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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(11) MOPAC version 7 was used for MNDO calculation.