

Communication

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Pd(0)-Catalyzed Amphiphilic Activation of Bis-allyl Alcohol and Ether

Ryutarō Mukai, Yoshikazu Horino, Shuji Tanaka, Yoshinao Tamaru,* and Masanari Kimura[‡]

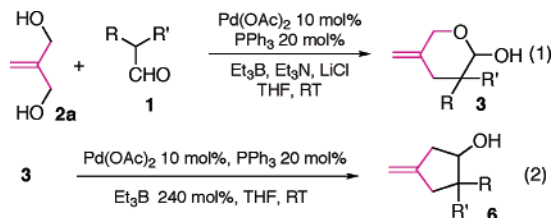
Department of Applied Chemistry, Faculty of Engineering, Nagasaki University, 1-14 Bunkyo-machi, Nagasaki 852-8521, Japan, and Graduate School of Science and Technology, Nagasaki University, 1-14 Bunkyo-machi, Nagasaki 852-8521, Japan

Received April 8, 2004; E-mail: tamaru@net.nagasaki-u.ac.jp

Alkylation of carbonyl compounds at the α -position and at the carbonyl carbon is among the most important methods to elaborate molecules. Especially, the most useful and studied is the Pd(0)-catalyzed α -allylation of active methylene compounds that proceeds via a π -allylpalladium(II) species (the Tsuji–Trost reaction).¹ Among many nucleophilic alkylation methods, allylation with allyl alcohols and ethers via a π -allylpalladium(II) species is unique, since the reaction is electronically opposite to the Tsuji–Trost reaction (umpolung).²

Here we would like to demonstrate a salient reactivity of symmetric bis-allyl alcohol, 2-hydroxymethyl-2-propen-1-ol (**2a**); one of the allyl alcohol moieties of **2a** undergoes electrophilic allylation at the α -position of aldehydes³ to give **3'**, and the other remaining allyl alcohol moiety, on the other hand, selectively reacts as an allylic nucleophile toward the aldehyde CO⁴ to furnish 3-methylenecyclopentanol **6** in good yields (Scheme 1). These two processes can be catalytically promoted by Pd(OAc)₂ in combination with triethylborane. That is, by the catalysis of Pd(OAc)₂·Et₃B, commercially available **2a** can be utilized as a synthetic equivalent of a zwitterionic trimethylenemethane species (Scheme 1).

When a mixture of α -phenylpropionaldehyde **1a** (1 mmol), **2a** (1.1 mmol), Pd(OAc)₂ (10 mol %), PPh₃ (20 mol %), and Et₃B (2.4 mmol) in dry THF (5 mL) containing Et₃N (1.2 mmol) and LiCl (1.0 mmol) was stirred at room temperature for 12 h, an α -allylation product **3a'** was isolated as its hemiacetal form **3a** in 93% isolated yield (eq 1 and run 1, Table 1). In the absence of



Et₃N and LiCl, under otherwise identical conditions (room temperature for 39 h), **3a** then undergoes intramolecular nucleophilic allylation and provides **6a** in 82% isolated yield (eq 2; run 1, Table 1). Thus, the additives Et₃N and LiCl nicely tune the electrophilic and nucleophilic allylation with allyl alcohols, i.e. these reagents promote electrophilic allylation while prohibiting nucleophilic allylation catalyzed by Pd(OAc)₂·Et₃B.^{3c}

The reaction is applicable to *sec*-aliphatic aldehydes **1b** and **1c** with less acidic α -protons (runs 2 and 3, Table 1). The cyclization of **3** to **6** shows remarkable stereoselectivity and **6a** and **6b** are obtained either as a single diastereomer or as a mixture of *trans*:*cis* = 2.2:1, respectively. In both cases, the hydroxy group is *cis* with respect to the smallest methyl group. The structure was determined on the basis of NOE experiments.

Scheme 1. Pd(0)-Catalyzed Amphiphilic Activation of Bis-allyl Alcohol **2a** toward Electrophilic and Nucleophilic Allylation of Aldehydes

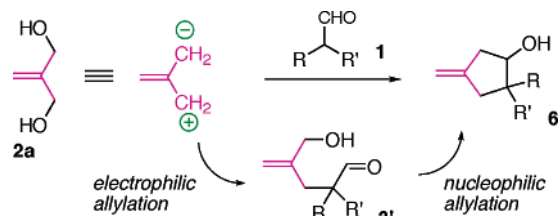
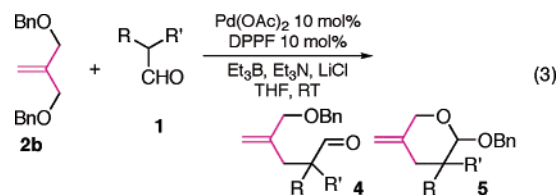


Table 1. Pd(0)·Et₃B Promoted Electrophilic (1 → 3) and Nucleophilic (3 → 6) Allylation of Aldehydes with Bis-allyl Alcohol **2a**^a

run	1	<i>t</i> ^b	3 : % yield	<i>t</i> ^b	6 : % yield
1		12	 3a : 93	39	 6a : 82
2		12	 3b : 70	12 ^c	 6b : 70 ^d
3		24	 3c : 70	24 ^c	 6c : 88

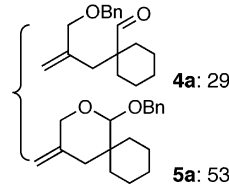
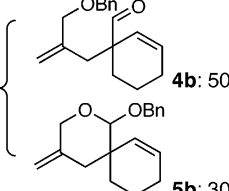
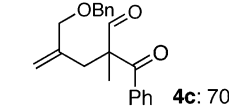
^a Reaction conditions (**1** → **3**): **1** (1 mmol) and **2a** (1.1 mmol), Pd(OAc)₂ (10 mol %), PPh₃ (20 mol %), Et₃B (2.4 mmol), Et₃N (1.2 mmol), and LiCl (1.0 mmol) in dry THF (5 mL) at room temperature under N₂; (**3** → **6**): the same as above except the absence of Et₃N and LiCl. ^b Reaction time (h) at room temperature, unless otherwise noted. ^c Reaction time (h) at 50 °C. ^d Diastereomeric mixture in a ratio of *trans*:*cis* = 2.2:1.

Bis-benzyl ether **2b** showed similar reactivity to **2a** for the reaction with **1c** and provided **4a**, a benzyl ether derivative of **3c**, in somewhat lower yield under the conditions shown in eq 1 (65%, 16 h at room temperature). Use of DPPF, in place of PPh₃, greatly improved the combined isolated yield of **4a** and **5b** (eq 3 and Table 2). Cyclohex-1-enecarbaldehyde (**1d**) selectively undergoes the



[‡] Graduate School of Science and Technology.

Table 2. Pd(0)·Et₃B-Promoted Electrophilic (1 → 4 + 5)^a and Nucleophilic (4 or 5 → 6) Allylation^b of Aldehydes with Bis-allyl Ether **2b**

1	t ^c	4 and 5: % yield	t ^d	6: % yield
1c	19	 4a : 29 5a : 53	7	6c : 86 ^e
			19	6c : 93 ^e
1d	40	 4b : 50 5b : 30	6	6d : 70 ^f
			6	6d : 73
1e	6 ^d	 4c : 70	6	6e : 40 ^g

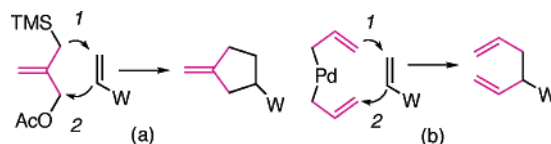
^a Reaction conditions: (**1c,d** → **4 + 5**): **1** (1 mmol) and **2b** (1.1 mmol), Pd(OAc)₂ (10 mol %), DPPF (10 mol %), Et₃B (2.4 mmol), Et₃N (1.2 mmol), and LiCl (1.0 mmol); (**1e** → **4c**): **1e** (2.2 mmol), **2b** (2 mmol), Pd(OAc)₂ (10 mol %), DPPF (10 mol %), Et₃B (0.6 mmol) in dry THF (5 mL) at room temperature under N₂. ^b Reaction conditions (**4** or **5** → **6**): **4** or **5** (1 mmol), Pd(OAc)₂ (10 mol %), PPh₃ (20 mol %), and Et₃B (4.8 mmol) in dry THF (5 mL) at 50 °C under N₂. ^c Reaction time (h) at room temperature. ^d Reaction time (h) at 50 °C. ^e Contamination with an olefinic isomer, 3-methyl-spiro[4.5]deca-3-en-1-ol (ca 10%). ^f Diastereomeric mixture of *syn:anti* = 2:1. ^g Diastereomeric mixture of 2.5:1.

allylation at the α-position via deprotonation of a γ-proton^{3c} and furnishes a mixture of **4b** and **5b** (Table 2). The acetals **5** may be derived from **4** via an intermediate, π-allylpalladium(II) benzyloxide: nucleophilic addition of benzyloxy anion upon the aldehyde C=O followed by cyclization of the thus-formed aldehyde oxyanion toward a π-allylpalladium(II) intermediate.⁵ The conversion of **4** and **5** to **6** was carried out separately at 50 °C under conditions similar to those applied to the conversion of **3** to **6**. The results are summarized in Table 2. β-Keto-aldehyde **1e** is so acidic that alkylation proceeds even in the absence of Et₃N.^{3a}

As are shown in eqs 4–6, for aldehydes that possess the α-proton with relatively high acidity and hence undergo readily α-allylation,^{3a} the electrophilic and nucleophilic allylations can be successfully performed with a single operation under the conditions applied to the nucleophilic allylation, i.e. in the absence of Et₃N and LiCl. Both **6a** and **6g** are obtained as a single diastereomer.

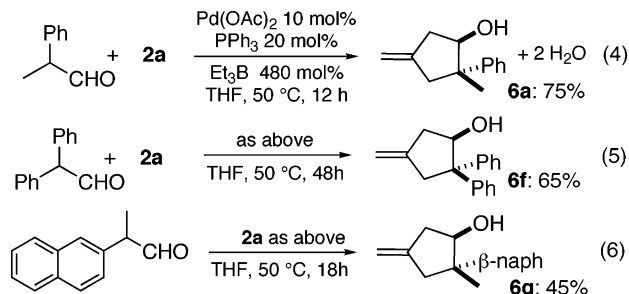
The present Pd(0)·Et₃B-based reaction is reminiscent of the Trost trimethylenemethane-palladium chemistry,⁶ Scheme 2a, and the Yamamoto bis-π-allylpalladium chemistry,⁷ Scheme 2b, especially the Trost one, because of the structural similarity of the products. However, the difference between the present reaction and the two precedents is apparent by taking the reaction sequence into consideration. While the reactions shown in Scheme 2 proceed in a sequence of nucleophilic–electrophilic alkylation, the present reactions proceed in the opposite order: electrophilic–nucleophilic.

Scheme 2. Pd(0)-Catalyzed Nucleophilic “1” and Electrophilic “2” Allylation^a



^a (a) Trimethylenemethane–palladium chemistry. (b) Bis-π-allylpalladium chemistry.

The ease of the experimental procedure and the amphiphilic activation as an allyl cation and as an allyl anion of a commercially available symmetrical diol **2a** may be the remarkable and useful features of the present reaction. That there is no need to take care of moisture is a further useful feature to be noted. Indeed, two moles of water are liberated as the side product (eqs 4–6).



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Supporting Information Available: Typical experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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