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Pd(0)-Catalyzed Amphiphilic Allylation of Aldehydes with Vinyl Epoxide

Masanari Kimura,[†] Ryutaro Mukai,[†] Takato Tamaki,[†] Yoshikazu Horino,[‡] and Yoshinao Tamaru*
*Department of Applied Chemistry, Faculty of Engineering, Nagasaki University, 1-14 Bunkyo-machi,
Nagasaki 852-8521, Japan*

Received December 5, 2006 E-mail: tamaru@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, Pd(0)-catalyzed α-allylation of active methylene compounds that proceeds via a π-allylpalladium species (the Tsuji−Trost reaction) has been studied extensively.[1] On the other hand, among many nucleophilic alkylation methods, allylation of the carbonyl carbon with allyl alcohols via the same π-allylpalladium species is unique, since the reaction is not only electronically opposite from the Tsuji−Trost reaction (umpolung) but is also capable of utilizing allyl alcohols as an allyl anion equivalent.[2]

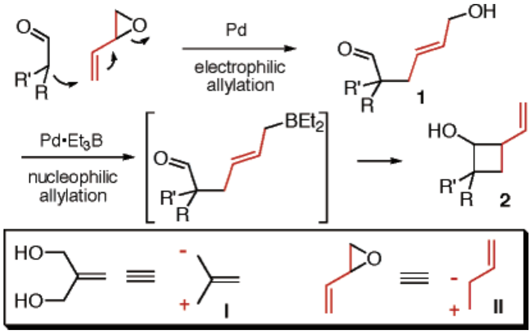
Recently, we demonstrated that under Pd(0)−Et$_3$B catalysis 2-hydroxymethyl-2-propen-1-ol served as a zwitterionic trimethylenemethane equivalent **I** (Scheme 1).[3] Here we would like to disclose that vinyl epoxide is also capable of undergoing amphiphilic allylation of aldehydes where, under Pd(0) catalysis, the allylic ether moiety serves as an allyl cation and reacts with aldehydes at the α-position, giving 6-hydroxy-4-hexenals (**1**) in good yields.[4] The allyl alcohol moiety of **1** in turn serves as an allyl anion under the catalysis of Pd(0)−Et$_3$B and furnishes 2-vinylcyclobutanols **2** in good-to-modest yields.[5] Thus, vinyl epoxide works as a synthetic equivalent of a zwitterionic 3-butenyl 2-anion−l-cation **II** (Scheme 1). The second step is worth noting; there are many precedents on the palladium-catalyzed ring-opening reaction of cyclobutanol;[6] however, no report has appeared, to the best of our knowledge, on the reverse cyclobutanol synthesis.[7] Aldehydes with an α-proton of relatively high acidity can provide **2** in one flask without isolation of **1**.

It is well documented that the allylic ether C−O bond of vinyl epoxide is subject to the Pd-catalyzed substitution with active methylene compounds;[8] however, a literature survey revealed that no report appeared on the allylic substitution with aldehydes. This is probably because aldehyde enolates are supposed to cause many side reactions. To our pleasant surprise, however, under neutral conditions aldehydes smoothly reacted with vinyl epoxide at room temperature in the presence of Pd(PPh$_3$)$_4$ (5 mol %) and provided **1a**−**h** in good yields (Scheme 2).[9]

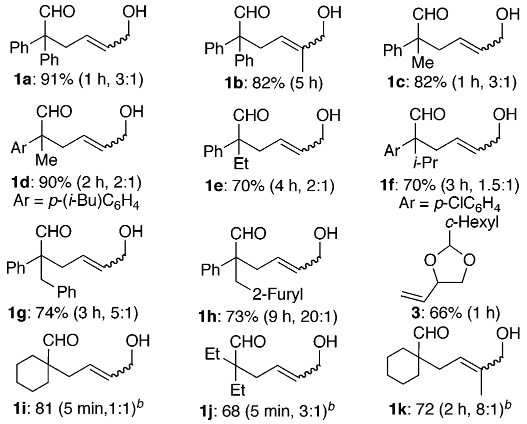
Aldehydes with a relatively less acidic α-proton failed to provide **1** and instead furnished an acetal **3** selectively (Scheme 2).[10] In such cases, their trimethylsilyl enol ethers[11] worked to provide **1** in acceptable yields (**1i**−**k**, footnote b in Scheme 2).

Nucleophilic allylation via umpolung of the allyl alcohol moiety of **1a** under Pd(0)−Et$_3$B catalysis largely depends on the kind of phosphine ligands, and n-Bu$_3$P is the ligand of choice (runs 1 and 2, Table 1). With bidentate ligands, no umpolung took place; instead, 1,3-transposition of hydroxy group occurred, providing a lactol **4** selectively. Interestingly, the *trans*-**2a**/*cis*-**2a** ratio changed dramatically from cis selective to trans selective during heating at 50 °C, suggesting isomerization under the conditions. Other monodentate phosphine ligands showed high cis selectivity; unfortunately, however, they recorded poorer yields.

Scheme 1

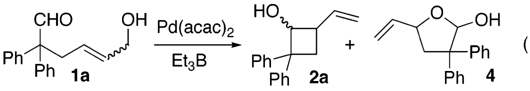


Scheme 2. Pd(0)-Catalyzed α-Allylation of Aldehydes with Vinyl Epoxides[a]



[a] An aldehyde (1 mmol) or its trimethylsilyl enol ether (for **1i**−**k**), a vinyl epoxide (1.2 mmol), Pd(PPh$_3$)$_4$ (5 mol %) in DMSO (2.5 mL) at rt; % isolated. In parentheses are shown figures in order of reaction time and *E* to *Z* ratio. [b] Silyl enol ether of aldehyde is used.

Table 1. Pd(0)-Catalyzed Cyclization of **1a** Forming **2a**[a]



run	ligand	time (h)	% isolated yield [*trans*:*cis*]	
			2a	**4**
1	n-Bu$_3$P	8	82 [6:1]	0
2	n-Bu$_3$P	1	52 [1:10]	0
3	Ph$_3$P	7	25 [1:>30]	0
4	(EtO)$_3$P	15	50 [1:>30]	0
5	DPPE	4	0	48
6	DPPF	4	0	71

[a] Conditions: **1a** (1 mmol), Pd(acac)$_2$ (10 mol %), a phosphine ligand (20 mol % for a monodentate ligand, 10 mol % for a bidentate ligand), Et$_3$B (300 mol %, 1 M in hexane) in THF (5 mL) under N$_2$ at 50 °C. DPPE and DPPF stand for bis(diphenylphosphino)ethane, and bis(diphenylphosphino)ferrocene, respectively.

Under the conditions thus optimized, the umpolung−cyclization of other 6-hydroxy-4-hexenals **1** was examined. Table 2 indicates that the reaction is general for a variety of **1**, providing *trans*-**2**

[†] Graduate School of Science and Technology, Nagasaki University.
[‡] Department of Applied Chemistry, Graduate School of Science and Engineering, University of Toyama, 3190 Gohuku, Toyama 930-8555.

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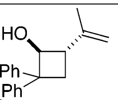
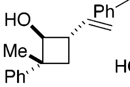
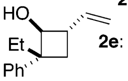
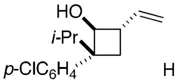
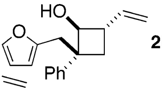
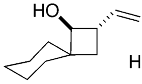
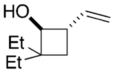
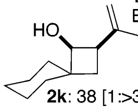
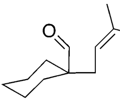
Table 2. Palladium-Catalyzed Cyclization of **1** Forming **2**^{a}

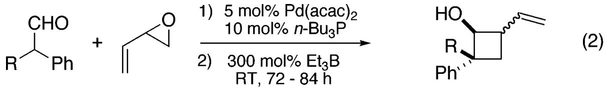
run	**1**	time (h)	% isolated yield of **2** [*trans*:*cis*]
1	**1b**	9	 **2b**: 50 [>30:1]^{b,d}
2	**1b**	24	**2b**: 35 [>30:1]^{b,d}
3	**1c**	6	 **2c**: 60 [>30:1]^{b}
4	**1e**	7	 **2e**: 71 [14:5:4:1]^{c}
5	**1f**	7	 **2f**: 80 [5:2:1:1]^{c}
6	**1h**	12	 **2h**: 61 [9:1]^{b}
7	**1i**	6	 **2i**: 51 [2:1]^{b}
8	**1j**	2	 **2j**: 55 [8:1]^{b}
9	**1k**	8	 **2k**: 38 [1:>30]^{b}  **5**: 20

[a] Conditions: **1** (1 mmol), Pd(acac)$_2$ (10 mol %), *n*-Bu$_3$P (20 mol %), Et$_3$B (300 mol %, 1 M in hexane) in THF (5 mL) at 50 °C under N$_2$. [b] Trans to cis ratio regarding hydroxy and vinyl substituents. [c] 1,2-*trans*, 1,4-*trans*: 1,2-*cis*, 1,4-*trans*:1,2-*trans*,1,4-*cis*:1,2-*cis*, 1,4-*cis*. [d] In addition to **2b**, α,α-diphenylacetaldehyde was obtained in 5% (run 1) and 52% yield (run 2).

selectively, being trans with respect to OH and the vinyl group. Although the reason is not clear at the moment, the reaction of **1k** is one exception, which provides *cis*-**2k** exclusively. Interestingly, the product *cis*-**2k** readily underwent the retro-ene reaction to cleanly provide **5** with $t_{1/2} = {\sim}30$ h at room temperature (CDCl$_3$). For aldehydes bearing different substituents (**L**: large, **S**: small) on the α-carbon, hydroxy and **L** groups are placed trans to each other in high preference: e.g. >30:1 for **L** = Ph, **S** = Me (run 3), 18 (=14 + 4):6 (=5 + 1) for **L** = Ph, **S** = Et (run 4).

Based on the isomerization from *cis*-**2** to *trans*-**2** (e.g. runs 1 and 2, Table 1, with the exception of run 9, Table 2) and high preference of OH to be aligned with small substituents (**S**), the most likely reaction mechanism is proposed in Scheme 3. Allylborane[12] would form 8-membered-ring intermediates **III** and **IV**, which have anti conformation with respect to **L** and C=O and hence are responsible for the formation of *cis*-**2**·BEt$_2$ and *trans*-**2**·BEt$_2$, respectively, both OBEt$_2$ and **S** being cis.[13] Formation of α,α-diphenylacetaldehyde in as much as 52% yield during long heating at 50 °C (footnote d in runs 1 and 2, Table 2) suggests that fragmentation through an intermediate **V** might be accompanied as a serious side reaction that renders the yields of **2** within a range of good to modest.

One-pot sequential amphiphilic allylation with vinyl epoxide can be achieved (eq 2);

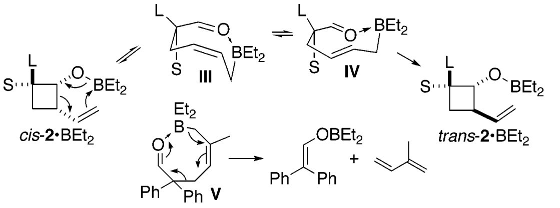


(2)

2a: R = Ph, 55% [*trans*:*cis* = 1:10]
2c: R = Me, 50% [*trans*:*cis* = 2:1]

a solution of α-phenylpropionaldehyde, vinyl epoxide (1.2 equiv), Pd(acac)$_2$ (0.1 equiv), and *n*-Bu$_3$P (0.2 equiv) in THF was stirred at room temperature for 3 h under N$_2$. Then, Et$_3$B (3 equiv, 1 M in THF) was added into the mixture, and the solution was stirred for 84 h at room temperature. Usual workup and purification provided a mixture of *trans*-**2c** and *cis*-**2c** (2:1) in 50% combined isolated yield.[14]

Scheme 3. Cyclization/Fragmentation of Allylborane Intermediates



[a] L and S Stand for large and small substituents, respectively.

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Supporting Information Available: Experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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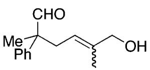
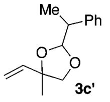
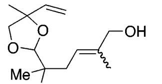
(9) DMSO is recommended as the solvent. For example, the reaction of α-phenylpropionaldehyde and isoprene oxide provides **1c′** (70%) selectively in DMSO for 5 h at rt. Other common solvents provide mixtures of products: **1c′** (30%), **3c′** (31%), **6** (17%) in acetonitrile for 3 h; **1c′** (20%), **3c′** (21%), **6** (17%) in THF for 22 h; **1c′** (12%), **3c′** (42%), **6** (20%) in CH$_2$Cl$_2$ for 20 h.



1c'



3c'



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(12) Allylborane may be generated by oxidative addition of Pd(0) upon the allylic C−O bond of **1**, followed by transmetallation of the π-allylpalladium thus formed with Et$_3$B.

(13) Although the equilibrium between **III** and *cis*-**2**·BEt$_2$ may be speculative, it would be feasible due to the ring strain and *cis* orientation of the substituents. Note the ready retro-ene reaction of **2k** to **5** at rt.

(14) In DMSO (2.5 mL), under otherwise identical conditions, the first allylation proceeded smoothly (2 h, rt), but the second allylation was very slow and required heating at 50°C for 84 h, yielding *trans*-**2c** (31%) as a single isomer.

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