Pd·Et₃B-catalyzed alkylation of amines with allylic alcohols†

Masanari Kimura,* Makoto Futamata, Kazufumi Shibata and Yoshinao Tamaru*

Department of Applied Chemistry, Faculty of Engineering, Nagasaki University, 1-14 Bunkyo-machi, Nagasaki 852-8521, Japan. E-mail: masanari@net.nagasaki-u.ac.jp, tamaru@net.nagasaki-u.ac.jp; Fax: +81-95-847-9008; Tel: +81-95-847-9008

A combination of catalytic amounts of Pd (0.05 mmol) and Et₃B (0.3 mmol) promotes allylic alkylation of primary and secondary aromatic and aliphatic amines (1.0 mmol) by the direct use of allylic alcohols, providing tertiary amines in excellent yields under mild conditions (room temperature ~ 50 °C).

Palladium-catalyzed C–N bond formation is an efficient, indispensable method for the synthesis of nitrogen-containing natural and unnatural compounds of physiological interest.[1] Allylic alkylation of nitrogen-nucleophiles catalyzed by palladium has been widely explored so far;[2] however, although being the most straightforward and desirable from a practical, economical, and environmental point of view, the direct use of allylic alcohols as the allylating agents has been limited[3] primarily owing to the poor capability of the hydroxy group as a leaving group.

Recently, we have disclosed that allylic alcohols are converted directly to the corresponding π-allylpalladium intermediates in the presence of Et₃B and a catalytic amount of a Pd species. The thus-formed π-allylpalladium species are reactive enough to undergo α-alkylation of soft carbon-nucleophiles, such as malonates, Meldrum's acid,[4] *o*-hydroxyphenyl alkyl ketones,[5] and primary and secondary alkyl aldehydes [eqn. (1)].[6]

$$\text{OH} + R_1R_2NH \xrightarrow[\text{Et}_3\text{B}]{\text{Pd catalyst}} \text{NR}_1R_2 \quad \mathbf{1} \qquad (1)$$
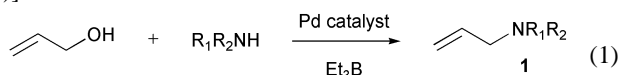
The palladium-catalyzed α-alkylation of alkyl aldehydes with allylic alcohols requires Et₃B (2.4 equivalents) and Et₃N (1.2 equivalents). Originally, we expected the primary role of Et₃B as a Lewis acid to activate allylic alcohols and that of Et₃N as a Lewis base to generate the enols of aldehydes activated by coordination with Et₃B. Recently, however, we have made an interesting observation that catalytic amounts of Et₃B and Et₃N (0.3 equivalents each) are sufficient enough to promote the α-alkylation of alkyl aldehydes.[7] Taking into consideration that Et₃B and Et₃N form a tight 1:1 Lewis acid–base complex;[8] our observation suggests that the presence of very tiny fractions of free Et₃B and Et₃N, in the Lewis acid–base equilibrium, is responsible for the reaction. This posed a question; what takes place when alkylation is carried out in the presence of a large excess of amine? Does Et₃B still maintain its capability of activating allylic alcohols under such conditions?

An ideal way to address this question may be to examine the alkylation of an amine itself since, under such conditions, the amine is necessarily present in a large excess as compared with Et₃B during the whole course of the reaction. Herein we disclose that a catalytic amount of Et₃B efficiently promotes the Pd-catalyzed alkylation of primary and secondary aromatic and aliphatic amines directly using allylic alcohols with a wide range of structural variety.

The alkylation of *N*-methylaniline (1.0 mmol) with allyl alcohol (1.2 mmol) was first examined in the presence of Pd(PPh₃)₄ (5 mol%) and an excess amount of Et₃B (2.4 mmol) in THF at room temperature under N₂ (eqn. (1) and run 1 in Table 1). The reaction proceeded smoothly and was completed after 30 h, giving rise to the expected alkylation product **1a** in 84% isolated yield. Significantly, as is shown in run 2, a catalytic amount of Et₃B turned out to effectively promote the reaction. Moreover, the reaction with a catalytic amount of Et₃B gave **1a** in a better yield within the same reaction time. Both the Pd catalyst and Et₃B, of course, were indispensable. In the absence of either of them, no alkylation took place and *N*-methylaniline was recovered (*e.g.*, run 3). Dibenzylamine was remarkably reactive, and the reaction was completed within 5 h at room temperature with 0.3 equivalents of Et₃B, providing **1b** in quantitative yield (run 4). On the other hand, dicyclohexylamine, although belonging to the same class of secondary alkyl amines but being quite different in the steric bulk, was marginally successful under the conditions applied to runs 1 and 2 (46% isolated yield, at 50 °C for 24 h). After screening of

Table 1 Pd·Et₃B promoted direct allylation of amines with allyl alcohol*[a]*

Run	Amine	Pd catalyst	Et₃B (mmol)	Reaction Conditions	Products	% Isolated Yield of **1**
1	PhMeNH	Pd(PPh₃)₄	2.4	r.t., 30 h		84
2	PhMeNH	Pd(PPh₃)₄	0.3	r.t., 30 h	NMePh **1a**	96
3	PhMeNH	Pd(PPh₃)₄	0	r.t., 30 h		0
4	Bn₂NH	Pd(PPh₃)₄	0.3	r.t., 5 h	NBn₂ **1b**	94
5	(*c*-C₆H₁₁)₂NH	Pd(OAc)₂/*n*-Bu₃P	0.3	50 °C, 24 h	N(*c*-C₁₆H₁₁)₂ **1c**	89
6	PhNH₂	Pd(OAc)₂/*n*-Bu₃P	0.3	50 °C, 24 h	NHPh **1d** 37; NPh₂ **1e**	51
7	BnNH₂	Pd(PPh₃)₄	2.4	50 °C, 24 h	NBn₂ **1f**	0
8	BnNH₂	Pd(OAc)₂/*n*-Bu₃P	0.3	50 °C, 20 h		90
9	*c*-C₆H₁₁NH₂	Pd(OAc)₂/*n*-Bu₃P	0.3	50 °C, 24 h	N(*c*-C₆H₁₁)₂ **1g**	87

[a] Reaction conditions: amine (1 mmol), allyl alcohol (1.2 mmol in runs 1–5; 3.0 mmol in runs 6–9), Pd catalyst (0.05 mmol), *n*-Bu₃P (0.2 mmol) and Et₃B (indicated amount) in dry THF (5 mL) under nitrogen.

several kinds of Pd complexes and ligands, the combination of Pd(OAc)$_2$ and n-Bu$_3$P turned out to be satisfactory in terms of the yield of **1c** and the reaction rate (run 5).

For the alkylation of primary amines, 3 equivalents of allyl alcohol were applied. The alkylation of aniline stopped halfway and provided a mono-alkylation product **1d** in a considerable amount (37%) together with a dialkylation product **1e** (51%, run 6). Alkyl amines were reactive enough and provided dialkylation products in excellent yields (runs 8 and 9). Surprisingly, in sharp contrast to the reaction of dibenzylamine, Pd(PPh$_3$)$_4$ was decisively ineffective for the alkylation of benzylamine (run 7); neither mono- nor dialkylation product was obtained at all.

The results for the alkylation of N-methylaniline with other allylic alcohols of a wide structural variety are summarized in Table 2, which reveal that the reaction is successful with primary, secondary, and tertiary allylic alcohols. Allylic alcohols bearing a methyl or a phenyl substituent either at the α- or the γ-position were converted exclusively into the corresponding γ-substituted allylamines with excellent stereoselectivity; thus, N-methylaniline was delivered at the least substituted allylic terminus. Crotyl alcohol and α-methallyl alcohol underwent alkylation with similar ease and provided N-2-butenyl-N-methylaniline (**1h**) in almost the same yields and with almost the same stereoselectivity (runs 1 and 2, Table 2). These results apparently indicate that each of the two pairs of reactions (runs 1 and 2; 3 and 4) proceeds via a common π-allylpalladium intermediate. It should be noted that β-methallyl alcohol provided **1j** in excellent yield (run 5); Pd-catalyzed alkylation of amines with β-substituted allylating agents are sometimes low yielding.[3b,c]

The reaction of cis-5-methoxycarbonylcyclohexen-3-ol (**2**) with N-methylaniline in the presence of Pd(PPh$_3$)$_4$ and Et$_3$B led to a stereoisomeric mixture of cis- and trans-**3** in a 2.6 : 1 ratio [eqn. (2)].[9] A rationale for this reaction is outlined in

$$\text{(2)}$$

2 (1.2 mmol)   PhMeNH (1 mmol)   Pd(PPh$_3$)$_4$ (5 mol%), Et$_3$B (2.4 mmol), 50 °C, 42 h   **3** (73%) [cis/trans = 2.6]

Scheme 1.[10] Triethylborane may coordinate to the hydroxy group of **2** to help it undergo oxidative addition to Pd(0). A trans-π-allylpalladium intermediate **I**, formed via inversion of configuration, may be subject to two pathways; one (path A) involves displacement of Pd(0) via an attack of an amine on the distal face of the cyclohexenyl ring with respect to Pd, which gives rise to cis-**3** with overall retention of configuration. The other (path B) involves an exchange of the ligand on Pd(II),

Scheme 1 Plausible reaction mechanism for allylic alkylation of N-methylaniline promoted by Pd·Et$_3$B.

Et$_3$B·OH, for an amine and the thus-formed amino(π-allyl)palladium(II) intermediate **II** would undergo reductive elimination to furnish trans-**3** with overall inversion of configuration. The stereochemical outcome of the present reaction is in accord with that reported for the Pd-catalyzed allylic amination of an acetic acid ester analog of **2** with diethylamine.[11]

In conclusion, we have demonstrated that a combination of Pd(0) and Et$_3$B, both in a catalytic amount, nicely promotes the di-alkylation of primary and the mono-alkylation of secondary aromatic and aliphatic amines by the direct use of allylic alcohols with a wide structural variety under mild conditions. The reaction proceeds with exclusive regioselectivity, giving rise to amines with the least branched allyl groups at the α-position and with high E-selectivity with respect to the allylic double bonds. The reaction, however, is not diastereoselective, and a cis-3-hydroxycyclohexenyl derivative furnishes a mixture of cis- and trans-3-aminocyclohexenes.

Notes and references

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7 Unpublished data: A mixture of Et$_3$B (0.3 mmol) and Et$_3$N (0.3 mmol) promotes the alkylation of 2-phenylpropanal (1.2 mmol) with cinnamyl alcohol (1.0 mmol) in the presence of Pd(OAc)$_2$ (0.05 mmol), PPh$_3$ (0.1 mmol), and LiCl (1.0 mmol) in THF at 50 °C for 22 h, yielding 2,5-diphenyl-2-methyl-4-pentenal in 83% isolated yield.

8 H. C. Brown, H. Bartholomay Jr. and M. D. Taylor, *J. Am. Chem. Soc.*, 1944, **66**, 435.

9 2-Cyclohexen-1-ol was exceptionally unreactive; N-methylaniline, in the presence of 0.3, 1.0, and 2.4 equivalents of Et$_3$B, provided a corresponding allylation product in 26, 45, and 96% yield, respectively, at 50 °C for 30 ~ 50 h. Accordingly, for the reaction of **2**, an excess amount of Et$_3$B was employed [eqn. (2)].

10 Isomerization of a trans-π-allylpalladium **I** into the corresponding cis-isomer via an intermolecular Pd(II) exchange mechanism might be responsible for the production of a mixture of cis- and trans-**3**.

11 B. M. Trost and E. Keinan, *J. Am. Chem. Soc.*, 1978, **100**, 7779.

Table 2 Pd·Et$_3$B promoted allylation of N-methylaniline with allylic alcohols[a]

Run	Allylic Alcohol	Et$_3$B (mmol)	Temp, Time	Product % Yield [Ratio]
1[b]	(crotyl alcohol)	0.3	r.t., 30 h	**1h** 93 [E:Z = 8:1]
2	(α-methallyl alcohol)	0.3	r.t., 30 h	**1h** 88 [E:Z = 8:1]
3	Ph (cinnamyl alcohol)	0.3	r.t., 24 h	**1i** 85 [only E]
4	Ph (1-phenyl-2-propenol)	0.3	r.t., 24 h	**1i** 82 [only E]
5	(β-methallyl alcohol)	0.6	50°C, 24 h	**1j** 88

[a] The reaction was undertaken in the presence of N-methylaniline (1 mmol), allylic alcohol (1.2 mmol), Pd(PPh$_3$)$_4$ (0.05 mmol), and Et$_3$B (indicated amount) in dry THF (5 mL) under nitrogen atmosphere. [b] A mixture of crotyl alcohol (E:Z = 9:1) was used.