

Palladium-Catalyzed Allylation of Imines with Allyl Alcohols

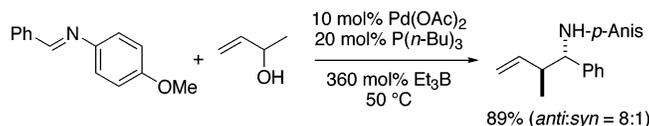
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ABSTRACT



A catalytic system, Pd(OAc)₂ (10 mol %)-P(*n*-Bu)₃ (20 mol %)-Et₃B (360 mol %), promotes allylic alcohols to undergo the allylation of anisidine-imines of aromatic and aliphatic aldehydes and furnishes homoallylamines in good to moderate yields. The reaction shows unique stereoselectivity, giving *anti*-isomers selectively.

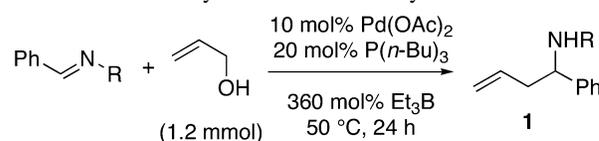
Allylations both at the carbonyl carbon and at the α -carbon to the carbonyl of aldehydes are among the most useful methods to elaborate molecules. As compared with aldehydes, aldimines are less reactive, and their nucleophilic allylation has been less explored, though this is very useful for the preparation of homoallylamines of an ubiquitous structural motif of natural products.¹

Recently, we have demonstrated that a Pd-Et₃B catalytic system nicely activates allylic alcohols to promote both nucleophilic allylation at the carbonyl carbon² and electrophilic allylation at the α -carbon of aldehydes.³ Unfortunately, however, the catalytic system failed in selective nucleophilic allylation of primary and secondary aliphatic aldehydes, providing mixtures of C1 (nucleophilic) and C2 (electrophilic) allylation products in comparable amounts.^{2b}

Here, we would like to disclose that the same Pd-Et₃B catalytic system is successfully extended to the nucleophilic allylation of aldimines of aromatic aldehydes and even aldimines of aliphatic aldehydes bearing enolizable protons.

In Scheme 1 are shown typical reaction conditions; the reaction was conducted as follows: in situ formation of a

Scheme 1. Pd-Catalyzed Allylation of a Variety of Benzaldehyde-Imines with Allyl Alcohol



amine	% Isolated Yield of 1
<i>p</i> -MeOC ₆ H ₄ NH ₂	72
<i>o</i> -MeOC ₆ H ₄ NH ₂	83
<i>p</i> -MeC ₆ H ₄ NH ₂	96
PhNH ₂	93
<i>p</i> -ClC ₆ H ₄ NH ₂	76
<i>o</i> -HOC ₆ H ₄ NH ₂	<i>a</i>
PhCH ₂ NH ₂	37
<i>c</i> -C ₆ H ₁₁ NH ₂	37

^a A complex mixture of products.

benzaldehyde-imine (30 min at reflux in 1 mL of THF), distillation of an azeotropic mixture of THF-H₂O two times,⁴

[†] Graduate School of Science and Technology, Nagasaki University.

(1) For recent reviews on allylation of aldehydes and imines, see: (a) Puentes, C. O.; Kouznetsov, V. J. *Heterocycl. Chem.* **2002**, *39*, 595. (b) Denmark, S. E.; Almstead, N. G. In *Modern Carbonyl Chemistry*; Otera, J., Ed.; Wiley-VHC: Weinheim, 2000; Chapter 10. (c) Chemler, S. R.; Roush, R. W. In *Modern Carbonyl Chemistry*; Otera, J., Ed.; Wiley-VHC: Weinheim, 2000; Chapter 11. (d) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069.

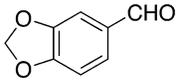
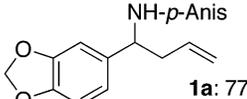
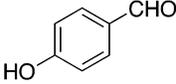
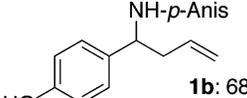
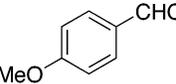
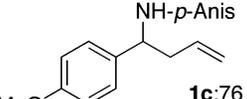
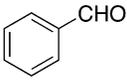
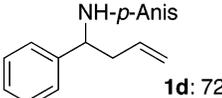
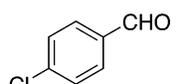
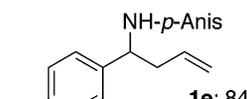
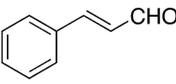
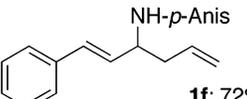
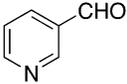
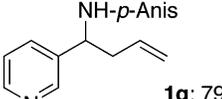
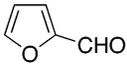
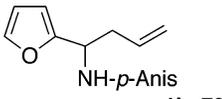
(2) (a) Kimura, M.; Kiyama, I.; Tomizawa, T.; Horino, Y.; Tanaka, S.; Tamaru, Y. *Tetrahedron Lett.* **1999**, *40*, 6795. (b) Kimura, M.; Tomizawa, T.; Horino, Y.; Tanaka, S.; Tamaru, Y. *Tetrahedron Lett.* **2000**, *41*, 3627.

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and exposure of the imine residue to a mixture of Pd(OAc)₂ (10 mol %), P(*n*-Bu)₃ (20 mol %), Et₃B (360 mol %), and allyl alcohol (120 mol %) at 50 °C for 24 h under N₂. The table shown in Scheme 1 indicates that yields of homoallylamine **1** sharply depend on the kinds of amines, and aromatic amines are the reagents of choice. The best yield was recorded with *p*-toluidine; however, we utilized *p*-anisidine because of its synthetic utility. *p*-Anisidine could be readily removed to give rise to a primary homoallylamine.

Table 1 summarizes the allylation of *p*-anisidine–imines of aromatic aldehydes. The reaction is compatible with

Table 1. Allylation of Aromatic Aldehydes–*p*-Anisidine Imine with Allyl Alcohol^a

Run	Aldehyde	Time (h)	% Yield of 1 ^b
1		22	 1a : 77
2		24	 1b : 68
3		24	 1c : 76
4		24	 1d : 72
5		24	 1e : 84
6		40 ^c	 1f : 72%
7		20	 1g : 79
8		24	 1h : 73

^a Reaction conditions: an aldehyde (1.0 mmol) and *p*-anisidine (1.05 mmol) in THF (1 mL) at reflux for 0.5 h; distillation of THF (azeotropic removal of water) under N₂; then Pd(OAc)₂ (0.1 mmol), P(*n*-Bu)₃ (0.2 mmol), allyl alcohol (1.2 mmol), and Et₃B (3.6 mmol, 1 M *n*-hexane) and THF (1 mL) at 50 °C. ^b Yields refer to the isolated, spectroscopically homogeneous materials. ^c At room temperature.

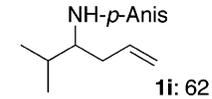
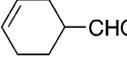
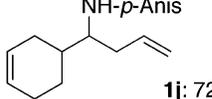
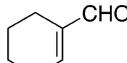
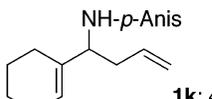
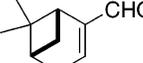
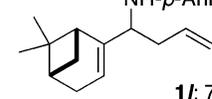
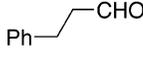
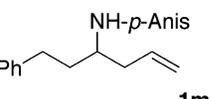
electron-donating (runs 1–3) and electron-withdrawing substituents (run 5). Heteroaromatic aldehydes also behave similarly and provide homoallylamines in reasonable yields (runs 7 and 8).

The yields of **1d** decreased to 31%, 29%, and 0% when PPh₃ (20 mol %), P(*c*-Hex)₃ (20 mol %), and DPPP (10 mol %) were used, respectively, in place of P(*n*-Bu)₃ (20 mol %). Reduction of the amount of Et₃B (360 mol %) to 240 mol % caused an apparent drop in the yield of **1d** (56%); however, loading half amounts of Pd(OAc)₂–P(*n*-Bu)₃, i.e., 5–10 mol %, caused only a slight fall in the yield of **1d** (65%). Interestingly, yields are temperature dependent; reactions take place and are completed at room temperature within 24 h; however, at this temperature the yields drop significantly (e.g., **1d** in 28% yield).

It may be worth noting that even in the presence of an acidic OH group (run 2) and a basic amino group (run 7) it is not necessary to use any extra amount of Et₃B; i.e., the optimized amount of Et₃B for ordinary aldehydes is sufficient enough for the allylation of such substrates.

In Table 2 is summarized the allylation of *p*-anisidine–imines of aliphatic aldehydes. Except for primary aldehydes

Table 2. Allylation of Aliphatic Aldehydes–*p*-Anisidine Imine with Allyl Alcohol^a

Run	Aldehyde	Time (h)	% Yield of 1 ^b
1		24	 1i : 62
2		26	^c
3		24	 1j : 72
4		24	 1k : 41
5		24	 1l : 71
6		18	 1m : 31

^a See footnote *a* in Table 1. ^b See footnote *b* in Table 1. ^c Complex mixture of products.

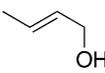
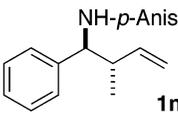
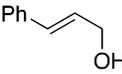
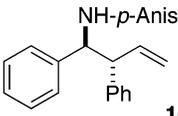
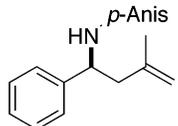
(run 6), ordinary secondary aldehydes recorded acceptable yields. Runs 2 and 4, as compared with runs 1 and 3, respectively, clearly suggest that the yields go down as the acidities of α-protons increase. This is supported by the reaction of cinnamaldehyde (run 6, Table 1), which does not possess enolizable protons. The good yield encountered with myrtenal (run 5) may be attributed to steric protection of

(4) Without removing water, reactions become dirty (many tailing spots on TLC) and no allylation products are detected.

allylic protons by bridged carbons from an approach of a base.

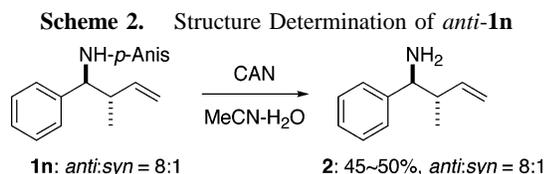
As is expected,¹ all allylic alcohols examined showed the same regioselectivity providing the most branched homoallylamines (runs 1–4, Table 3); however, the stereoselec-

Table 3. Allylation of Benzaldehyde-*p*-Anisidine Imine with Substituted Allylic Alcohols^a

Run	Allyl Alcohol	Temp (°C) / Time (h)	% Yield of 1 ^b (<i>anti:syn</i>) ^c
1		50/24	 1n : 82 (5:1)
2		50/24	1n : 89 (8:1)
3		rt/18	 1o : 64 (1:1)
4		50/18	1m : 68 (2:1)
5		50/8	 1p : 71%

^a See footnote a in Table 1. ^b See footnote b in Table 1. ^c Ratios were determined on the basis of ¹H NMR (400 MHz).

tivity was quite unexpected and turned out to be subject to the kind of substituents and the substitution patterns. Generally, α -substituted allylic alcohols showed higher stereoselectivity, giving *anti*-**1** preferentially over *syn*-**1** (runs 1 vs 2 and runs 3 vs 4). Furthermore, in contrast to many precedents^{1,5,6} indicating that phenyl group generally displays better stereoselectivity than methyl group does, in the present case, methyl group showed higher selectivity than phenyl group (runs 2 vs 4).⁷ The structure of *anti*-**1n** was verified by the comparison of the ¹H NMR spectral data with those of an authentic sample after conversion to an amine **2** (Scheme 2).⁸ Furthermore, the structure of *anti*-**1n** was

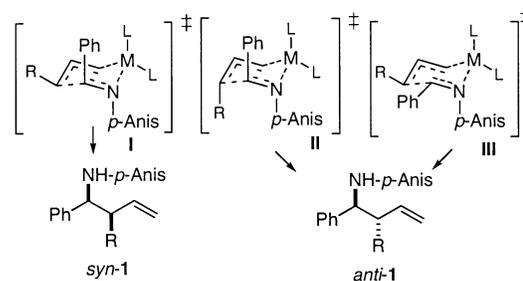


determined unequivocally by X-ray crystallographic analysis of the tosylamide derivative.⁹

Under the reaction conditions, allylboranes are expected to react with an imine as soon as it is formed,¹⁰ hence, the

results observed in runs 1, 2, and 4 (Table 3) suggest that (*Z*)-allylboranes are formed selectively via transmetalation between Et₃B and π -allylpalladium species (*syn*- or *anti*-isomer, which might equilibrate to each other) and react with *trans*-imine through a transition state **II** (ML₂ = BEt₂).¹¹ To the best of our knowledge, however, this is the first example demonstrating *anti*-selectivity for the allylation of imines starting with *trans*-crotyl-type (and α -methylallyl-) substrates; all precedents starting with *trans*-crotyl substrates suppose a transition state like **I** to rationalize their *syn*-selective allylations.^{5,12} These transition states **I** and **II** share a common structural feature, placing both substituents of *trans*-aldimine at quasi-diaxial position of cyclic six-membered chairlike conformation (Scheme 3). The confor-

Scheme 3. The Most Probable Transition State Leading to *anti*-**1**



mation is preferred over the corresponding quasi-diequatorial conformation because the latter experiences severe gauche repulsion between *p*-anisyl and the ligands on metal (in this case, two Et groups on B).¹³ A transition state **III** that is characterized by *cis*-imine is another candidate, which seems to be most stable because of no 1,3-diaxial repulsions. At the moment, it is premature to assign which of the transition states **II** or **III** is responsible; the former supposing (*Z*-

(6) For example, in the presence of Pd(PPh₃)₄ (5 mol %) and Et₂Zn (240 mol %) in THF (3 mL)-*n*-hexane (1.2 mL) at room temperature, α - and γ -methylallyl alcohols (1 mmol) react with benzaldehyde (1.2 mmol) to provide mixtures of *anti*- and *syn*-2-methyl-1-phenyl-3-buten-1-ols in the same ratio (2.4:1). The same reactions with α - and γ -phenylallyl alcohols provide *anti*- and *syn*-1,2-diphenyl-3-buten-1-ols in the same, but in higher ratios of 10:1: Tamaru, Y. *J. Organomet. Chem.* **1999**, 576, 215.

(7) Under present conditions, 1,3-disubstituted allylic alcohols, such as 1,3-dimethylallyl alcohols and 2-cyclohexenol, failed to give expected homoallylamines.

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(9) Crystallographic data (excluding structure factors) for the structure of **2** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-256123. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44)1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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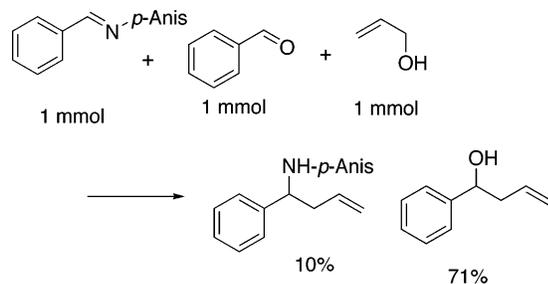
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allylboranes and the latter a less stable *cis*-aldimine as intermediates.

Finally, it should be noted that the success of the present allylation is not due to increased reactivity of allylboranes toward imines.¹⁴ In fact, competition reaction of allyl alcohol with imine and benzaldehyde (1 mmol each) revealed that the latter was ca. 7 times more reactive than the former (Scheme 4). Rather, the success may owe its origin to

Scheme 4. Competition Reaction of Benzaldehyde–Imine and Benzaldehyde under Catalytic Conditions



minimization of side reactions that aldehydes suffer from, especially to reduced capability of imines undergoing enolization.

In conclusion, we have demonstrated that a Pd–Et₃B catalytic system is capable of promoting allylation of anisidine-aldimines of aromatic and aliphatic aldehydes using allylic alcohols as allylating agents. The advantage of using

allylic alcohols¹⁵ rather than other allylating agents, e.g., allylic metals (Zn,¹⁶ In,^{5,12b,c} Pd)¹⁷ and metalloids (B,¹⁰ Si,¹⁸ Sn,^{11,19} Ge),²⁰ may be apparent from their ready availability and stability as well as nontoxic side products (H₂O and organoboric acids).

Acknowledgment. We acknowledge partial support of this work from the Ministry of Education, Science, Sports, and Culture, Japanese Government.

Supporting Information Available: Experimental procedures and characterization data for **1a–p** and Chem3D presentation of X-ray structure of **2** (CIF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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