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Nucleophilic allylation of *N*,*O*-acetals with allylic alcohols promoted by Pd/Et_3B and Pd/Et_2Zn systems

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ABSTRACT

Pd/Et_3B and Pd/Et_2Zn systems promote the nucleophilic allylations of 2-aminotetrahydrofuran and 2-aminotetrahydropyran with allylic alcohols to provide ω-hydroxyhomoallylamines in high yields. The transformation is applicable to the allylation of non-protective carbohydrates, such as ribose and deoxyribose.

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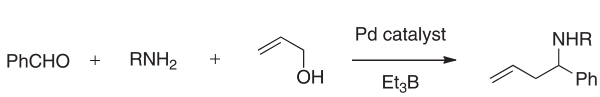
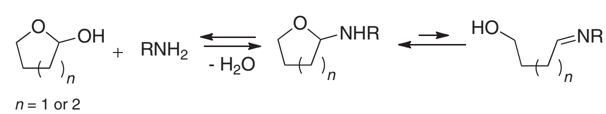
Pd-catalyzed allylations are among the most efficient strategies for C–C bond formation in organic synthesis.[1] In particular, nucleophilic allylations of aldimines have well been utilized extensively for fundamental skeleton elongations of carbon chains of nitrogen-containing physiologically active molecules. Although aldimines are widely synthetically useful for valuable functionalizations, it is highly problematic that they tend to be less reactive than aldehydes.[2] Recently, we have demonstrated that a combination of a Pd catalyst and Et_3B nicely promotes aldimines prepared from aromatic aldehydes and primary aliphatic amines bearing enolizable protons to provide homoallylamines in excellent yields (Scheme 1).[3] In this case, it is necessary to activate the aldimines using either amines or aldehydes with electron withdrawing groups.

N,*O*-Acetals are currently used as potent constituents of iminosugars for the development of glycosidase inhibitors in a wide range of diseases, such as viral infections, inherited lysosomal disorder, and diabetes.[4] Although 2-hydroxytetrahydrofuran and 2-hydroxytetrahydropyran with primary amines readily lead to 2-aminotetrahydrofurans and 2-aminotetrahydropyrans, respectively (Scheme 2), the low concentration of the ω-hydroxyimine tautomers in equilibrium with the *N*,*O*-acetals often renders the attack by nucleophiles more difficult.[5] Herein, we report that the Pd/Et_3B and Pd/Et_2Zn systems have been successfully extended to the nucleophilic allylation of *N*,*O*-acetals prepared from 2-hydroxytetrahydrofuran and 2-hydroxytetrahydropyran with primary amines in the presence of allylic alcohols, providing ω-hydroxy homoallylamines in good to excellent yields in a one-pot synthesis. The reactivity and regioselectivity associated with the unique nucleophilic allylation of *N*,*O*-acetals from a wide variety of carbohydrates and primary amines are also reported.



Scheme 1. Allylation of aldimine with allyl alcohol promoted by Pd/Et_3B.



Scheme 2. Equilibrium between cyclic hemiaminal and ω-hydroxyamine.

Table 1 summarizes the allylation of *N*,*O*-acetals prepared from a wide variety of primary amines with 2-hydroxytetrahydropyran. The reaction was conducted as follows: in situ formation of *N*,*O*-acetals from various amines and 2-hydroxytetrahydropyran (30-min reflux in 1 mL of THF solvent), azeotropic distillation of THF/H_2O two times, and exposure of a mixture of $Pd(OAc)_2$ catalyst, *n*-Bu_3P, Et_3B, and allyl alcohol dissolved in THF to the *N*,*O*-acetal residue. The reaction mixture was stirred at 50 °C under nitrogen atmosphere. *p*-Methoxy, *p*-methyl, and *p*-chloro substituted anilines were useful for the allylation reaction, providing the corresponding allylated δ-hydroxyhomoallylamines **1a**–**1d** in good

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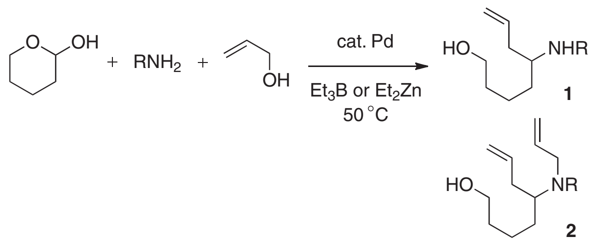
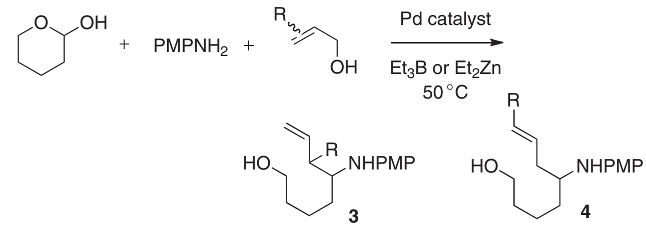
Table 1
Palladium-catalyzed allylation of aldimines prepared from 2-hydroxytetrahydropyran and amines[a]

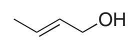
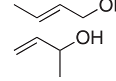
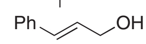
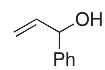
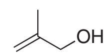


Entry	RNH_2 R	Time (h)	Yield (%)	
		Et_3B/Et_2Zn	Et_3B	Et_2Zn
1	p-$OMeC_6H_4$	24/5	**1a**:74	**1a**:53, **2a**:10
2	p-MeC_6H_4	24/24	**1b**:72	**1b**:45, **2b**:12
3	Ph	24/24	**1c**:69	**1c**:45, **2c**:12
4	p-ClC_6H_4	24/24	**1d**:66	**1d**:53, **2d**:10
5	c-C_6H_{11}	24/5	**1e**[b]	**1e**:76, **2e**:8
6	Bn	24/5	**1f**[b]	**1f**:53, **2f**:10
7	n-C_6H_{13}	24/5	**1g**:50	**1g**:49, **2g**:7

[a] An aldimine, prepared in situ from 2-hydroxytetrahydropyran (1 mmol) and amine (1.05 mmol), allyl alcohol (1.2 mmol), $Pd(OAc)_2$ (10 mol %), n-Bu_3P (20 mol %), and Et_3B (3.6 mmol) or Et_2Zn (4.8 mmol) at 50 °C for the periods of time indicated.
[b] Intractable mixture of products.

Table 2
Pd-catalyzed allylation of aldimines prepared from 2-hydroxytetrahydropyran and $PMPNH_2$ (PMP = p-$MeOC_6H_4$) with substituted allylic alcohols[a]



Entry	Allylic alcohol	Time (h)	Yield% (*syn*:*anti*)	
		Et_3B/Et_2Zn	Et_3B	Et_2Zn
1		24/5	**3a**:55 (1.3:1)	**3a**:48 (3:1)
2		24/5	**3a**:68 (3.2:1)	**3a**:42 (3:1)
3		24/5	**3b**:68 (6.5:1)	**3b**:16 (*syn*) **4b**:37 (*E*)
4		24/6	**3b**:70 (*syn*)	**3b**:21 (*syn*) **4b**:48 (*E*)
5		24/5	**3c**:65	**3c**:17

[a] An aldimine, prepared in situ from 2-hydroxytetrahydropyran (1 mmol) and $PMPNH_2$ (1.05 mmol), allyl alcohol (1.2 mmol), $Pd(OAc)_2$ (10 mol %), n-Bu_3P (20 mol %), and Et_3B (3.6 mmol) or Et_2Zn (4.8 mmol) at 50 °C for the periods of time indicated.

yields (Table 1, entries 1–4). Although the reaction of cyclohexylamine and benzylamine resulted in formation of intractable mixtures of allylation products in the presence of Et_3B, the desired products **1e** and **1f** were produced in reasonable yields that were promoted by Et_2Zn along with the N-allylated homoallylamines **2** (Table 1, entries 5 and 6). The combination of Pd(0) and Et_2Zn tends to accelerate not only nucleophilic allylation at the imine carbon atom but also the electrophilic allylation on the nitrogen atom of δ-hydroxyhomoallylamine to form N-allylated homoallylamines **2**.[3a] n-Hexylamine showed marginal success in the formation of **1g**, irrespective of the promoters, Et_3B or Et_2Zn (Table 1, entry 7).

It has been reported that nucleophilic allylation of carbonyls and imines with α- and γ-substituted allylmetal species in the presence of a Pd catalyst tends to take place with high regioselectivity, providing more substituted allylated products via six-membered ring transition states.[6] However, in the present study, the selectivities are unexpected. Some results using substituted allylic alcohols are summarized in Table 2. *trans*-2-Buten-1-ol and 1-methyl-2-propen-1-ol show marginal success in the formation of a mixture of *syn* and *anti* methyl substituted homoallylamine **3a** (Table 2, entries 1 and 2). Phenyl substituted allyl alcohols displayed better stereoselectivity than those with a methyl group. Cinnamyl alcohol provided the desired *syn*- and *anti*-**3b** in a 6.5:1 ratio by treatment with Et_3B (Table 2, entry 3). Under similar conditions, α-phenylallyl alcohol provided *syn*-**3b** as the sole product (Table 2, entry 4). In contrast to the results of Et_3B, Et_2Zn shows alternative regioselectivity giving rise to the linear product (*E*)-**4b** predominantly along with the branched isomer **3b** as a minor isomer (entries 3 and 4).

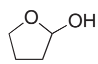
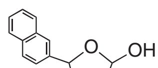
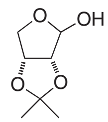
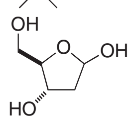
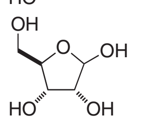
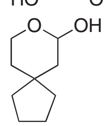
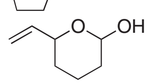
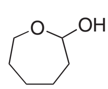
Next, we examined the Pd-catalyzed allylation of *N*,*O*-acetals prepared from various lactols with p-anisidine. The results using Et_3B and Et_2Zn are summarized in Table 3. 2-Hydroxytetrahydrofuran provided **1h** in modest yield by means of Et_3B, whereas Et_2Zn induced nucleophilic allylation and further electrophilic allylation on the nitrogen atom to give the N-allylated homoallylamine **2h** selectively (Table 3, entry 1).[3a,7] 5-(2-Naphthyl)-2-hydroxytetrahydrofuran afforded **1i** as a mixture of *syn* and *anti* isomers in a 1:1 ratio irrespective of employment of Et_3B or Et_2Zn (Table 3, entry 2). 3,4-*O*-Isopropylidene-2-hydroxytetrahydrofuran underwent similar nucleophilic allylation providing a mixture of *syn* and *anti* isomers **1j** in a 1:5 ratio (Table 3, entry 3).

Et_3B was insufficient for similar allylation of carbohydrates, such as, deoxyribose and ribose, whereas an excess amount of Et_2Zn successfully promoted the reaction, giving rise to the desired allylation products **1k** and **1l**, respectively (Table 3, entries 4 and 5).[8] A spirocyclic acetal was also an adequate substrate and the corresponding allylated product **1m** was obtained in a reasonable yield (Table 3, entry 6).

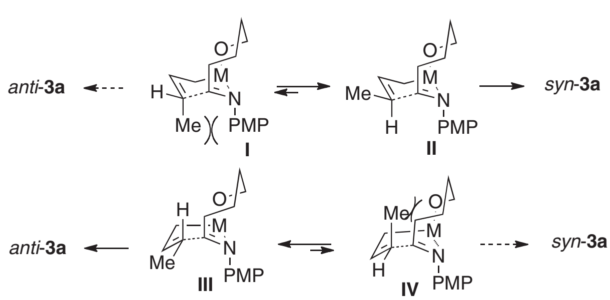
6-Vinyl-2-hydroxytetrahydropyran displayed similar reactivity by treatment with Et_3B to provide homoallylamine **1n** in a 4:1 ratio (Table 3, entry 7). A seven-membered cyclic hemiacetal underwent similar allylation with Et_3B to provide hydroxyhomoallylamine **1o**, while Et_2Zn gave the allylated products **1o** and **2o** in modest yield (Table 3, entry 8).

Although it is premature to rationalize the regio- and stereoselectivities for the present reaction, some plausible reaction mechanisms are shown in Schemes 3 and 4. Based on the results of Table 2, an allyl metal species generated from methyl substituted allylic alcohols might react with the hydroxyimine via transition state **II** to avoid steric repulsion between the methyl group and the substituent on the nitrogen atom (transition state **I**), resulting in selective formation of the *syn*-**3a** isomer as depicted in Scheme 3. As for the formation of *anti*-**3a**, the alternative structural feature associated with the six-membered boat-like transition state **III** would be probable. Regarding the selectivity of α-phenyl allyl alcohol and cinnamyl alcohol, Et_3B provided the branched isomer *syn*-**3b** exclusively, whereas Et_2Zn promoted the selective formation of thermodynamically more stable isomer (*E*)-**4b** along with *syn*-**3b** shown in Scheme 4. It is intriguing that Et_2Zn would render a quasi-equatorial conformation of the phenyl group to minimize the steric repulsion against the ligand on Zn (M = Zn), which is entirely in contrast to the result of the steric repulsion between the ethyl group of Et_3B (M = BEt) and the phenyl substituent in Scheme 4.

Table 3
Pd-catalyzed allylation of aldimines prepared from lactols and $PMPNH_2$ (PMP = *p*-$MeOC_6H_4$) [a]

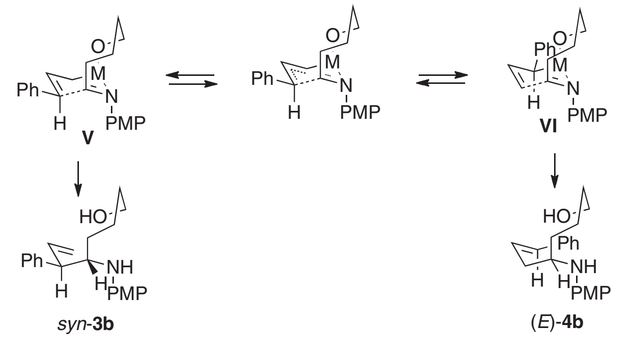
Entry	Lactol	Time (h)	Yield% (*syn*:*anti*)	
		Et_3B/Et_2Zn	Et_3B	Et_2Zn
1		48/24	**1h**:38	**1h**:15 **2h**:61
2		24/24	**1i**:66 (1:1)	**1i**:48 (1:1)
3		24/24	**1j**:83 (1:5)	**1j**:75 (1:5)
4		24/24	**1k**[b]	**1k**:58 (1.6:1)
5		24/24	**1l**[b]	**1l**:54 (1.3:1)
6		27/24	**1m**:75	**1m**:69
7		27/24	**1n**:63 (4:1)	**1n**:25 (4:1) **2n**:36
8		30/24	**1o**:57	**1o**:12 **2o**:13

[a] An aldimine, prepared in situ from lactol (1 mmol) and $PMPNH_2$ (1.05 mmol), allyl alcohol (1.2 mmol), $Pd(OAc)_2$ (10 mol %), *n*-Bu_3P (20 mol %), and Et_3B (3.6 mmol) or Et_2Zn (4.8 mmol) at 50 °C for the periods of time indicated.
[b] Intractable mixture of products.



Scheme 3. Reaction mechanism for the formation of a mixture of *syn*- and *anti*-**3a** from methyl substituted allyl alcohols.

In conclusion, the combination of Pd catalyst with Et_3B or Et_2Zn promotes 2-aminotetrahydrofuran or 2-aminotetrahydropyran, prepared from tetrahydrofuran or tetrahydropyran with a primary amine in situ, to undergo nucleophilic allylation with allylic alcohols to provide γ- and δ-hydroxyhomoallylamines in high yields. The reaction is compatible with non-protected carbohydrates, such as deoxyribose and ribose, to afford polyhydroxyhomoallylamines in reasonable yields. These reaction protocols might be of great interest to organometallic chemistry as well as to the transformation of biologically active molecules such as carbohydrates and aminocarbohydrates.



Scheme 4. A plausible reaction mechanism for the formation of a mixture of *syn*-**3b** and (*E*)-**4b** from phenyl substituted allyl alcohols.

Acknowledgments

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References and notes

1. (a) Kimura, M.; Tamaru, Y. *Mini-Rev. Org. Chem.* **2009**, *6*, 392–397; (b) Tamaru, Y.; Kimura, M. *Pure Appl. Chem.* **2008**, *80*, 979–991; (c) Cleghorn, L. A. T.; Grigg, R.; Savic, V.; Simic, M. *Tetrahedron* **2008**, *64*, 8731–8737; (d) Kimura, M.; Mukai, R.; Tamaki, T.; Horino, Y.; Tamaru, Y. *J. Am. Chem. Soc.* **2007**, *129*, 4122–4123; (e) Muzart, J. *Eur. J. Org. Chem.* **2007**, 3077–3089; (f) Kazmaier, U.; Deska, J.; Watzke, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 4855–4858; (g) Kimura, M.; Futamata, M.; Mukai, R.; Tamaru, Y. *J. Am. Chem. Soc.* **2005**, *127*, 4592–4593; (h) Tamaru, Y. *Eur. J. Org. Chem.* **2005**, 2647–2656; (i) Mukai, R.; Horino, Y.; Tanaka, S.; Tamaru, Y.; Kimura, M. *J. Am. Chem. Soc.* **2004**, *126*, 11138–11139; (j) Kimura, M.; Horino, Y.; Mukai, R.; Tanaka, S.; Tamaru, Y. *J. Am. Chem. Soc.* **2001**, *123*, 10401–10402; (k) Tamaru, Y. *J. Organomet. Chem.* **1999**, *576*, 215–231; (l) Ferraris, D.; Dudding, T.; Young, B.; Drury, W. J.; Letcka, T. *J. Org. Chem.* **1999**, *64*, 2168–2169; (m) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207–2293.
2. (a) Grote, R. E.; Jarvo, E. R. *Org. Lett.* **2009**, *11*, 485–488; (b) Shaghafi, M. B.; Kohn, B. L.; Jarvo, E. R. *Org. Lett.* **2008**, *10*, 4743–4746; (c) Barczak, N. T.; Grote, R. E.; Jarvo, E. R. *Organometallics* **2007**, *26*, 4863–4865; (d) Selander, N.; Kipke, A.; Sebelius, S.; Szabó, K. J. *J. Am. Chem. Soc.* **2007**, *129*, 13723–13731; (e) Sieber, J. D.; Morken, J. P. *J. Am. Chem. Soc.* **2006**, *128*, 74–75; (f) Woodward, A. R.; Burks, H. E.; Chan, L. M.; Morken, J. P. *Org. Lett.* **2005**, *7*, 5505–5507; (g) Sebelius, S.; Szabó, K. J. *Eur. J. Org. Chem.* **2005**, 2539–2547; (h) Shibata, I.; Nose, K.; Sakamoto, K.; Yasuda, M.; Baba, A. *J. Org. Chem.* **2004**, *69*, 2185–2187; (i) Yanada, R.; Kaieda, A.; Takemoto, Y. *J. Org. Chem.* **2001**, *66*, 7516–7518; (j) Cooper, I. R.; Grigg, R.; MacLachlan, W. S.; Thornton-Pett, M.; Sridharan, V. *Chem. Commun.* **2002**, 1372–1373; (k) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069–1094; (l) Kobayashi, S.; Nagayama, S. *J. Am. Chem. Soc.* **1997**, *119*, 10049–10053; (m) Nakamura, H.; Iwama, H.; Yamamoto, Y. *J. Am. Chem. Soc.* **1996**, *118*, 6641–6647.
3. (a) Kimura, M.; Tamaki, T.; Nakata, M.; Tohyama, K.; Tamaru, Y. *Angew. Chem., Int. Ed.* **2008**, *47*, 5803–5805; (b) Shimizu, M.; Kimura, M.; Watanabe, T.; Tamaru, Y. *Org. Lett.* **2005**, *7*, 637–640.
4. (a) Liautard, V.; Desvergnes, V.; Martin, O. R. *Org. Lett.* **2006**, *8*, 1299–1302; (b) Dondoni, A.; Perrone, D. *Tetrahedron* **2003**, *59*, 4261–4273.
5. (a) Kimura, M.; Tatsuyama, Y.; Kojima, K.; Tamaru, Y. *Org. Lett.* **2007**, *9*, 1871–1873; (b) Kojima, K.; Kimura, M.; Ueda, S.; Tamaru, Y. *Tetrahedron* **2006**, *62*, 7512–7520; (c) Kimura, M.; Kojima, K.; Tatsuyama, Y.; Tamaru, Y. *J. Am. Chem. Soc.* **2006**, *128*, 6332–6333; (d) Kimura, M.; Miyachi, A.; Kojima, K.; Tanaka, S.; Tamaru, Y. *J. Am. Chem. Soc.* **2004**, *126*, 14360–14361.
6. (a) Flahaut, A.; Toutah, K.; Mangeney, P.; Roland, S. *Eur. J. Inorg. Chem.* **2009**, 5422–5432; (b) Shimizu, M.; Kimura, M.; Tamaru, Y. *Chem. Eur. J.* **2005**, *11*, 6629–6642; (c) Kimura, M.; Shimizu, M.; Shibata, K.; Tazoe, M.; Tamaru, Y. *Angew. Chem., Int. Ed.* **2003**, *42*, 3392–3395; (d) Shimizu, M.; Kimura, M.; Tanaka, S.; Tamaru, Y. *Tetrahedron Lett.* **1998**, *39*, 609–612; (e) Tamaru, Y.; Tanaka, A.; Yasui, K.; Goto, S.; Tanaka, S. *Angew. Chem., Int. Ed.* **1995**, *34*, 787–789.
7. Pd/Et_2Zn system promotes allyl alcohols to undergo nucleophilic allylation of a wide range of carbonyl compounds and aldimines. The modest yields by Pd/Et_3B system might be due to the formation of by-products encompassing the electrophilic α-allylation of enolizable aldimines or intractable mixture of boronic acid esters.
8. (a) Kobayashi, S.; Wakabayashi, T.; Oyamada, H. *Chem. Lett.* **1997**, 831–832; (b) Li, X.-R.; Loh, T.-P. *Tetrahedron: Asymmetry* **1996**, *7*, 1535–1538; (c) Prenner, R. H.; Binder, W. H.; Schmid, W. *Liebigs Ann. Chem.* **1994**, 73–78; (d) Hachiya, I.; Kobayashi, S. *J. Org. Chem.* **1993**, *58*, 6958–6960; (e) Schmid, W.; Whitesides, G. M. *J. Am. Chem. Soc.* **1991**, *113*, 6645–6674.