

Water Enables Direct Use of Allyl Alcohol for Tsuji–Trost Reaction without Activators

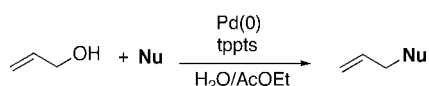
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ABSTRACT



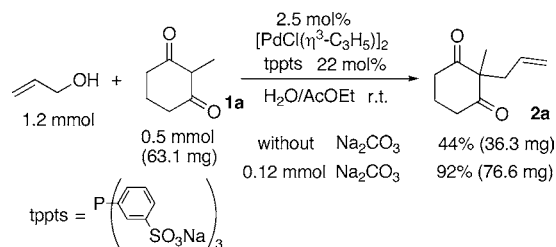
An aqueous biphasic reaction system enables the direct use of allyl alcohol in the Tsuji–Trost reaction without the help of any activating reagents for allyl alcohol. The reaction conditions are neutral to basic, allowing the use of amines as the nucleophile. Theoretical calculations have elucidated the importance of hydration of the hydroxy group for the smooth generation of π -allylpalladium species.

The Tsuji–Trost reaction using a π -allylpalladium intermediate has served as a pivotal reaction in a number of syntheses of natural and unnatural compounds. The reaction often employs Pd(0) complexes and activated allyl alcohol derivatives, in particular, allylic halides, acetates, and carbonates. Much attention has been paid to the direct use of allyl alcohols for the allyl source. However, the precedent protocols require stoichiometric or catalytic activators for allyl alcohols such as acids, Lewis acids, Et₃B, and CO₂, due to inherent low leaving aptitude of the hydroxy group.¹ However, acidic activators cannot be compatible with basic nucleophiles such as amines. Recently, particular ligands have been reported to enable such conversion without the aid of activators.² Here we wish to disclose another solution: the direct use of allyl alcohol for the Tsuji–Trost

reaction at room temperature is achieved in an aqueous system without any activator. Although there have been a number of reports on the Tsuji–Trost reaction with allylic acetates or carbonates in aqueous media,³ none of them accomplished the direct use of allyl alcohol without activators.⁴ The reaction conditions are neutral to basic, allowing the use of amines as the nucleophile.

We attempted the Tsuji–Trost reaction in water with allyl alcohol as an allyl source. We selected 2-methylcyclohexane-1,3-dione (**1a**) as a nucleophile and conducted the reaction with the catalyst combination of [PdCl(η^3 -C₃H₅)]₂ and tppts in water. In an ethyl acetate–water biphasic system, the allylated product **2a** was obtained in 44% yield as a sole product (Scheme 1). While the allylation reaction was

Scheme 1



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(1) (a) Lu, X.; Jiang, X.; Tao, X. *J. Organomet. Chem.* **1988**, 344, 109. (b) Satoh, I.; Ikeda, M.; Miura, M.; Nomura, M. *J. Org. Chem.* **1997**, 62, 4877. (c) Tamaru, Y.; Horino, Y.; Araki, M.; Tanaka, S.; Kimura, M. *Tetrahedron Lett.* **2000**, 41, 5705. (d) Stary, J.; Stara, I. G.; Kocovsky, P. *Tetrahedron* **1993**, 34, 179. (e) Lumin, S.; Falck, J. R.; Capdevila, J.; Karara, A. *Tetrahedron Lett.* **1992**, 33, 2091. (f) Sakamoto, M.; Shimizu, I.; Yamamoto, A. *Bull. Chem. Soc. Jpn.* **1996**, 69, 1065. (g) Patil, N. T.; Yamamoto, Y. *Tetrahedron Lett.* **2004**, 45, 3101.

(2) (a) Ozawa, F.; Okamoto, H.; Kawagishi, S.; Yamamoto, S.; Minami, T.; Yoshifuji, M. *J. Am. Chem. Soc.* **2002**, 124, 10968. (b) Kayaki, Y.; Koda, T.; Ikariya, T. *J. Org. Chem.* **2004**, 69, 2595.

Table 1. Tsuji–Trost Reaction with Allyl Alcohol in Aqueous Biphasic System^a

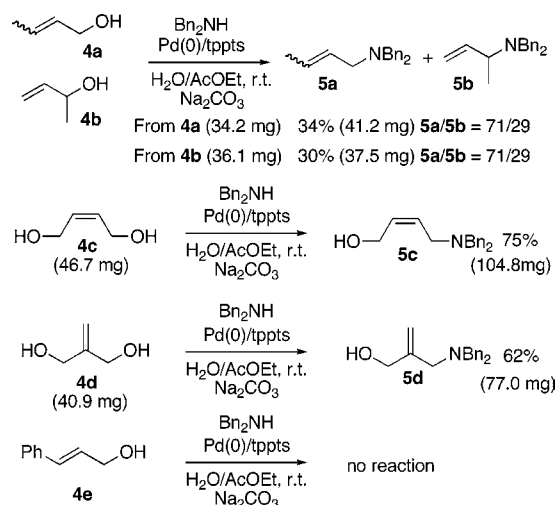
$\text{CH}_2=\text{CH}-\text{CH}_2-\text{OH} + \text{NuH} \xrightarrow[\text{AcOEt/H}_2\text{O}/(\text{Na}_2\text{CO}_3)]{\text{Pd(0)/tppts 5 mol\%}} \text{CH}_2=\text{CH}-\text{CH}_2-\text{Nu}$					
entry	nucleophile	time (h)	Na_2CO_3 (mmol)	product	yield (%)
1	1b 75.1 mg	14	none	2b 45.3 mg	43
2	1b 48.1 mg	14	1.2	3b 72.8 mg	84
3	1c 63.2 mg	13	1.2	2c 61.9 mg	75
4	1d 70.1 mg	18	0.12	3d 79.5 mg	72
5	1d 70.1 mg	18	1.2	3d 84.7 mg	77
6	1e 73.1 mg	18	0.12	3e 81.5 mg	72
7	1e 73.1 mg	18	1.2	3e 112.2 mg	99
8	Bn_2NH 93.1 mg	1f 21	none	2f 105.1 mg	94
9	BnNH_2 48.9 mg	1g 21	0.12	3g 56.1 mg	66
10	1g 51.1 mg	21	1.2	3g 66.7 mg	75
11 ^b	PhNH_2 1h 110.6 mg	18	none	2h 110.6 mg	83

^a Reaction conditions: $[\text{PdCl}(\eta^3\text{-C}_3\text{H}_5)]_2$ (4.6 mg, 0.0125 mmol), tppts (62.5 mg, 0.11 mmol), water (5 mL), AcOEt (5 mL), allyl alcohol (0.08 mL, 1.2 mmol), and nucleophile (0.05 mL, 0.5 mmol). ^b Aniline (2.2 mmol) and allyl alcohol (1.0 mmol) were employed.

sluggish in water alone, no reaction proceeded in ethyl acetate under otherwise identical reaction conditions. Addition of a catalytic amount of sodium carbonate improved the yield of **2a** to 92%.

Table 1 summarizes the results of allylation of various nucleophiles with allyl alcohol. Acetylacetone (**1b**) underwent monoallylation in the absence of Na_2CO_3 , while the addition of the base provided diallylated product in good

Scheme 2



yield (entries 1 and 2). Ethyl acetoacetate (**1c**) afforded monoallylated product as a sole product (entry 3). Cyclic diketones **1d** and **1e** afforded the desired products in good yields in the presence of catalytic Na_2CO_3 (entries 4–7). The reaction system also accomplishes conversion of amines to the corresponding allyl- or diallylamines (entries 7–11). Aniline (**1f**) underwent selective monoallylation in the absence of Na_2CO_3 . No trace of diallylaniline was detected, while the addition of Na_2CO_3 provided it.

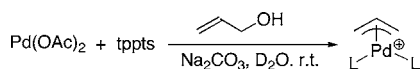
Crotyl alcohol (**4a**) and its regioisomer **4b**, 1-buten-3-ol, yielded a mixture of isomeric amines **5a** and **5b** in the same ratio, suggesting that the reaction proceeds via the π -allyl intermediate (Scheme 2). The reaction of diols **4c** and **4d** with dibenzylamine selectively afforded monoaminated products **5c** and **5d** in 75% and 62%, respectively. None of diaminated products were detected in the crude reaction mixture. Because cinnamyl alcohol (**4e**) was completely recovered under the reaction conditions, a very hydrophobic substrate seems not reactive in this system. The selective monoamination of diols **4c** and **4d** may be explained as follows. While diols **4c** and **4d** are hydrophilic enough to have reactivity, increased hydrophobicity of the products **5c** and **5d** after the initial amination retards the second amination.

We confirmed that allylpalladium species can be readily formed from allyl alcohol in water at room temperature. Treatment of allyl alcohol with a stoichiometric amount of a water-soluble palladium complex, prepared from $\text{Pd}(\text{OAc})_2$ and a trisodium salt of tris(*m*-sulfonatophenyl)phosphine (tppts), provided a π -allylpalladium species on the basis of

(3) (a) Safi, M.; Sinou, D. *Tetrahedron Lett.* **1991**, 32, 2025. (b) Genêt, J. P.; Blart, E.; Savignac, M. *Synlett* **1992**, 715. (c) Blart, E.; Genêt, J. P.; Safi, M.; Savignac, M.; Sinou, D. *Tetrahedron* **1994**, 50, 505. (d) Kobayashi, S.; Lam, W. W.-L.; Manabe, K. *Tetrahedron Lett.* **2000**, 41, 6115. (e) Danjo, H.; Tanaka, D.; Hayashi, T.; Uozumi, Y. *Tetrahedron* **1999**, 55, 14341. (f) Uozumi, Y.; Shibatomi, K. *J. Am. Chem. Soc.* **2001**, 123, 2919. (g) Bergbreiter, D. E.; Liu, Y.-S. *Tetrahedron Lett.* **1997**, 38, 7843.

(4) Recently, Kobayashi has reported allylation in aqueous media with a carboxylic acid as an activator. Manabe, K.; Kobayashi, S. *Org. Lett.* **2003**, 5, 3241.

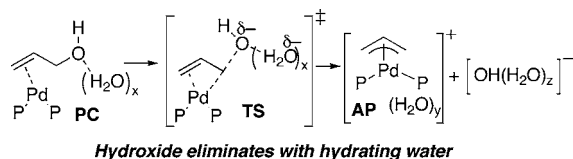
Scheme 3



^1H NMR and ^{31}P NMR analyses in D_2O (Scheme 3). The NMR spectra of the reaction mixture were almost identical with the solution of $[\text{PdCl}(\eta^3\text{-allyl})]_2$ in D_2O .⁵

Initially, we speculated that carbon dioxide from sodium carbonate might act as the activator, since Yamamoto et al. have already reported a formation of π -allylpalladium from allyl alcohol under a pressure of CO_2 (30 atm) via a half-carbonate ester.^{1f} However, the fact that the reaction also proceeds in the absence of sodium carbonate clearly rules out this possibility. Involvement of allyl acetate via transesterification with AcOEt is not probable because the reaction occurred in an Et_2O –water biphasic system.⁶ At this time, we propose the reaction mechanism in which water activates allyl alcohol via hydration of the hydroxy group and stabilizes the resulting hydroxide ion by strong solvation with water, as outlined in Scheme 4. In organic solvents, elimina-

Scheme 4



tion of naked hydroxide is a very unfavorable process. In water, however, the hydroxide ion can leave with hydrating water molecules and the negative charge can be delocalized in the water cluster.

To elucidate the effect of water, we have conducted theoretical calculations.⁷ The geometry of palladium complexes **PC** and the transition state **TS** was optimized with the B3LYP functional. The 6-31G* basis set was employed except for Pd, with which LANL2DZ+ECP were used (denoted as BS1). During optimization, solvent effects were taken into account by means of the Onsager method.⁸ At the optimized geometries, energies were calculated with the PCM method at the B3LYP/BS1 level.⁹

The calculated activation energy with the PCM method was very high ($E_a = 60.7$ kcal/mol).¹⁰ We then included hydrating waters coordinating to the hydroxy group. Addition of hydrating waters changed the structure of transition state depending on the number of waters during reoptimization. Introduction of hydrating waters significantly lowered the activation energy, and increasing the number of waters resulted in decrease of the activation energy ($E_a = 36.0$ for

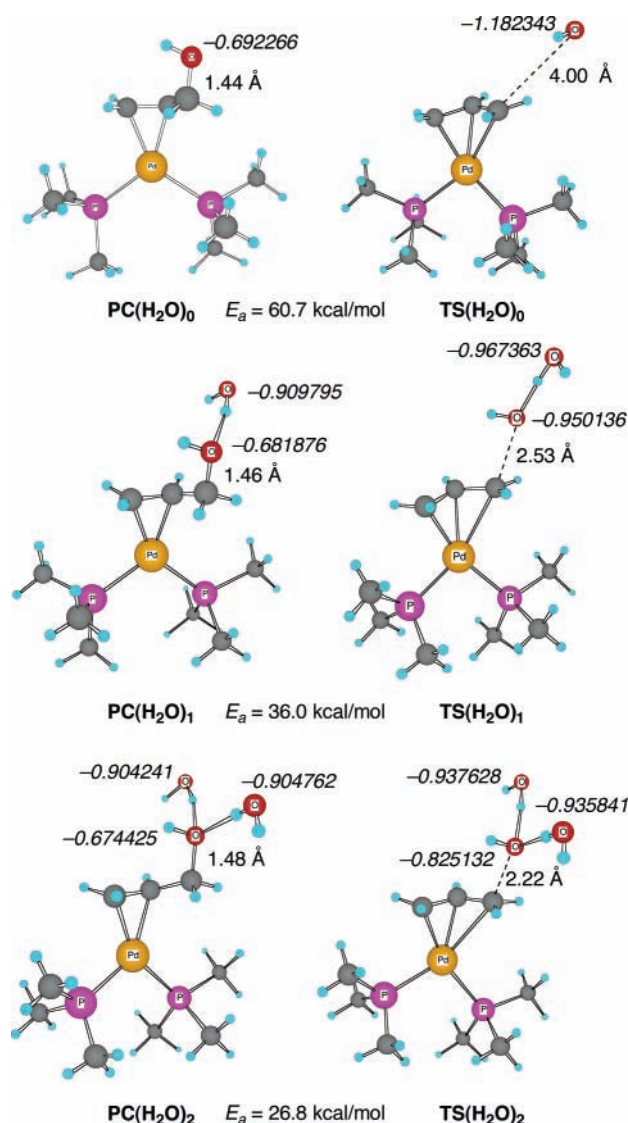


Figure 1. Calculated structures, Mulliken charges (italics), and activation energies.

one water hydration, whereas $E_a = 26.8$ kcal/mol for two water hydration). Electron population analyses (Mulliken charge) indicate that negative charge delocalizes in the solvating waters in **TS**, and an increased degree of hydration results in decreasing each charge on oxygen atoms (Figure 1). In the real system, a greater number of water molecules

(5) See the Supporting Information.

(6) The reaction of acetylacetone (**1b**) with allyl alcohol in an Et_2O –water biphasic system provided **3b** in 53% yield under otherwise identical conditions as entry 2 in Table 1.

(7) For theoretical calculations involving π -allylpalladium, see: (a) Delbecq, F.; Lapouge, C. *Organometallics* **2000**, *19*, 2716. (b) Branchadell, V.; Moreno-Manas, M.; Pleixats, R. *Organometallics* **2002**, *21*, 2407. (c) Solin, N.; Szabó, K. J. *Organometallics* **2001**, *20*, 5464. (d) Szabó, K. J. *Chem. Eur. J.* **1997**, *3*, 592. (e) Szabó, K. J. *Chem. Eur. J.* **2000**, *6*, 4413. (f) Solin, N.; Narayan, S.; Szabó, K. J. *J. Org. Chem.* **2001**, *66*, 1686. (g) Szabó, K. J.; Hupe, E.; Larsson, A. L. E. *Organometallics* **1997**, *16*, 3779. (h) Szabó, K. J. *Organometallics* **1996**, *15*, 1128. (i) Szabó, K. J. *J. Am. Chem. Soc.* **1996**, *118*, 7818. (j) Sakaki, S.; Takeuchi, K.; Sugimoto, M.; Kurosawa, H. *Organometallics* **1997**, *16*, 2995. (k) Sakaki, S.; Satoh, H.; Shono, H.; Ujino, Y. *Organometallics* **1996**, *15*, 1713. (l) Biswas, B.; Sugimoto, M.; Sakaki, S. *Organometallics* **1999**, *18*, 4015. (m) Branchadell, V.; Moreno-Manas, M.; Pajuelo, F.; Pleixats, R. *Organometallics* **1999**, *18*, 4934. (n) Hagelin, H.; Åkermark, B.; Norrby, P.-O. *Chem. Eur. J.* **1999**, *5*, 902; (m) Dedieu, A. *Chem. Rev.* **2000**, *100*, 543.

should be involved in solvation, lowering the activation energy more effectively.

In conclusion, we have found that aqueous reaction media enable the direct use of allyl alcohol as the allyl source for the Tsuji–Trost reaction without the help of any activating reagents. Theoretical calculations have elucidated the importance of hydration of the hydroxy group in allyl alcohol for the smooth generation of the π -allylpalladium intermedi-

(8) Optimization with the PCM method failed to converge.

(9) Cossi, M.; Scalmani, G.; Rega, N.; Barone, V. *J. Chem. Phys.* **2002**, *117*, 43.

(10) π -Allylpalladium (**AP**) is stabilized in water by 18.4 kcal/mol from its optimized structure in a vacuum (B3LYP/BS1), whereas the Pd(0)–olefin complex (**PC**) is destabilized by 14.3 kcal/mol. This can be one of the driving forces.

ate. Further research to expand the scope and improve the efficiency is currently underway in our laboratory.

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Supporting Information Available: General procedures, ^1H and ^{31}P NMR spectra of allylpalladium intermediates in D_2O , and the Cartesian coordinates. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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