DOI: 10.1002/adsc.200505135

Cross–Coupling Reactions of Allylic Alcohols in Water

Kei Manabe, Kenji Nakada, Naohiro Aoyama, Shū Kobayashi*

Graduate School of Pharmaceutical Sciences, The University of Tokyo, the HFRE Division, ERATO,
Science and Technology Agency (JST), Hongo, Bunkyo-ku, Tokyo 113-0033, Japan
Fax: (+81)-3-5684-0634, e-mail: skobayas@mol.f.u-tokyo.ac.jp

Received: March 31, 2005; Accepted: June 13, 2005

Abstract: Palladium–catalyzed cross–coupling reactions of allylic alcohols and arylboronic acids in water are described. The reactions proceeded smoothly in water at reflux using catalytic amounts of $[Pd(allyl)Cl]_2$ and PPh_3. Addition of a catalytic amount of a base allowed the reaction to proceed even at lower temperatures.

Keywords: allylic alcohols; allylic arenes; boronic acids; cross-coupling; palladium; water

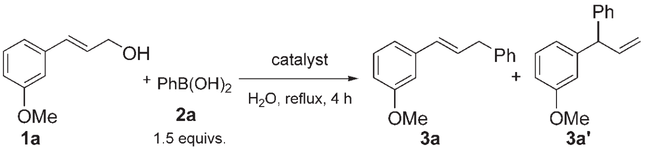
Catalytic reactions of allylic compounds mediated by π-allylpalladium complexes represent important carbon-carbon bond-forming reactions.[1] In most cases, allylic halides or allylic carboxylates, which are usually prepared from the corresponding allylic alcohols, have been used as allylating agents. If allylic alcohols can be used directly as allylating agents, preparation of the corresponding halides or carboxylates would no longer be required, thus the overall process of allylic alkylation would become highly efficient and atom-economical. In spite of their simple and efficient operation, allylic alcohols are rarely used as substrates in allylic alkylations because of the low tendency for hydroxide to act as a leaving group.[2,3] In our previous work, we have reported that palladium-catalyzed allylic substitution can proceed smoothly using allylic alcohols.[4] Remarkably, the reaction was successfully conducted in water.

Organic reactions in water have recently attracted much attention, not only because unique reactivity is often observed in water but also because water is a safe, environmentally benign, and economical substitute for conventional organic solvents.[5] Thus, development of atom-economical and synthetically useful reactions in water is one of the most important goals for modern synthetic chemistry.

Coupling reactions of allylic alcohols with arylboronic acids have been reported, but organic solvents were required.[3] Herein we disclose palladium–catalyzed cross–coupling reactions[6] utilizing water as a suspension medium. The key to a successful catalytic system was found to be the use of a catalytic amount of a base, although a stoichiometric amount of a base is usually needed for the Suzuki–Miyaura coupling. A catalytic amount of a base allowed the reaction to proceed even at lower temperatures.

Initially, 3-methoxycinnamyl alcohol was examined as an allylating agent for phenylboronic acid in the presence of a variety of catalysts in water (Table 1). Although the reaction hardly proceeded with rhodium catalysts[3a] (entries 1–3), the yield was greatly improved when catalytic amounts of palladium were employed in the presence of triphenylphosphine (entries 4, 6–9). In every case in which the reaction proceeded, a mixture of products (**3a** and **3a′**) was obtained. $Pd(PPh_3)_4$, combinations of $Pd_2(dba)_3 + PPh_3$ and $[Pd(allyl)Cl]_2 + PPh_3$ gave almost the same yields, while $[Pd(allyl)Cl]_2 + PPh_3$ gave a superior product ratio in favor of the non-branched alkene **3a**.

Table 1. Screening of transition metals.[a]



Entry	Catalyst [mol %]	Yield [%][b]	3a:3a′[c]
1	$RhCl_3$ (5)	<4	–
2	$[Rh(cod)Cl]_2$ (2.5)	N.D.	–
3	$Rh(PPh_3)_3Cl$ (5)	<2	–
4	$Pd(PPh_3)_4$ (5)	59	95:5
5	$Pd_2(dba)_3$ (2.5)	N.D.	–
6	$Pd_2(dba)_3$ (2.5), PPh_3 (15)	54	92:8
7	$PdCl_2$ (5), PPh_3 (15)	33	99:1
8	$Pd(OAc)_2$ (5), PPh_3 (15)	37	98:2
9	$[Pd(allyl)Cl]_2$ (2.5), PPh_3 (15)	52	98:2

[a] *Reaction conditions:* **1a** (0.4 mmol), **2a** (0.6 mmol), catalyst, H_2O (2.5 mL), 110 °C (bath temperature), 4 h.

[b] Yield of **3a** was determined by ^1H NMR spectroscopy after isolation as a mixture of **3a** and **3a′**.

[c] The ratio was determined by ^1H NMR spectroscopy.

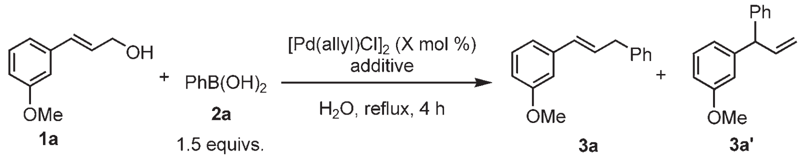
In order to examine catalyst loading and the effect of varying the phosphine ligands, $[Pd(allyl)Cl]_2$ was selected as the palladium source (Table 2). The reaction was found to proceed in good yield when the amount of palladium was decreased to 1 mol % (entries 1–3). The amount of the palladium could even be reduced to 0.5 mol % without losing the yield (entry 4). Although various phosphine ligands were investigated (entries 5–13), PPh_3 was found to be the most useful of those tried. Stability of the catalyst seems to play an important role, since a black deposit appeared at an early stage of the reaction when the yields were low.

Although the reaction proceeded successfully at reflux, the reaction rate dropped dramatically at 70 °C (Table 3, entries 1 and 2). In order to accelerate the reaction at milder temperatures, various additives were screened. A catalytic amount of a simple base was found to greatly accelerate the reaction (entries 3 and 4)

However, the reaction hardly proceeded at 50 °C even with sodium hydroxide (Table 3, entry 6). We then re-examined the amount of PPh_3, since an excess of PPh_3 was thought to inhibit the reaction. By reducing the amount of PPh_3 to 1 mol %, the reaction was found to proceed successfully at 50 °C. As a result, it was revealed that 1 mol % of PPh_3 was enough and was needed for the reaction. The reaction did not proceed when $Pd_2(dba)_3$ was tried as a catalyst, but the addition of PPh_3 along with $Pd_2(dba)_3$ allowed for a smooth reaction (entries 8 and 9). A similar tendency was also observed in our early examinations (Table 1, entries 5 and 6). Since the amount of sodium hydroxide seemed to affect the reaction, it too was examined once again (entries 10 and 11). One mol % of NaOH was sufficient, and a better yield was attained even at 40 °C. Finally, a range of phosphine ligands was tested in the presence of 1 mol % of NaOH (entries 13–16). Tri-*o*-tolylphosphine and triarylphosphines with electron-withdrawing substituents were found to be more effective than PPh_3. The product was obtained in 74% yield by using 2 mol % of the palladium source (entry 17).

Next, other substrates were examined at reflux (Table 4, conditions 1) or at 40 °C with NaOH (conditions 2). In general, reactions under reflux gave better results than the use of lower temperatures. At reflux, the reac-

Table 2. Effect of ligands.[a]



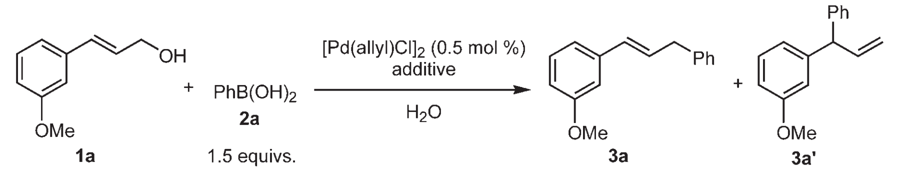
Entry	X [mol%]	Additive [mol %]	Yield [%][b]	**3a**:**3a'**[c]
1	2.5	PPh_3 (15)	52	98:2
2	1	PPh_3 (7.5)	69	98:2
3	0.5	PPh_3 (3)	83	98:2
4	0.25	PPh_3 (1.5)	83	96:4
5	0.5	$P(p\text{-}MeOC_6H_4)_3$ (3)	74	97:3
6	0.5	$P(p\text{-}Tol)_3$ (3)	31	97:3
7	0.5	$P(p\text{-}ClC_6H_4)_3$ (3)	27	98:2
8	0.5	P(2-naphthyl)$_3$ (3)	55	98:2
9	0.5	$P(o\text{-}Tol)_3$ (3)	3	92:8
10	0.5	PCy_3 (3)	13	–
11	0.5	P^tBu_3 (3)	<1	98:2
12	0.5	P(2-Furyl)$_3$ (3)	15	97:3
13	0.5	$P(m\text{-}NaO_3SC_6H_4)_3$ (3)	5	98:2

[a] *Reaction conditions:* **1a** (0.4 mmol), **2a** (0.6 mmol), catalyst, H_2O (2.5 mL), 110 °C (bath temperature), 4 h.

[b] Yield of **3a** was determined by ^1H NMR spectroscopy after isolation as a mixture of **3a** and **3a′**.

[c] The ratio was determined by ^1H NMR spectroscopy.

Table 3. Effect of the Brønsted bases.[a]

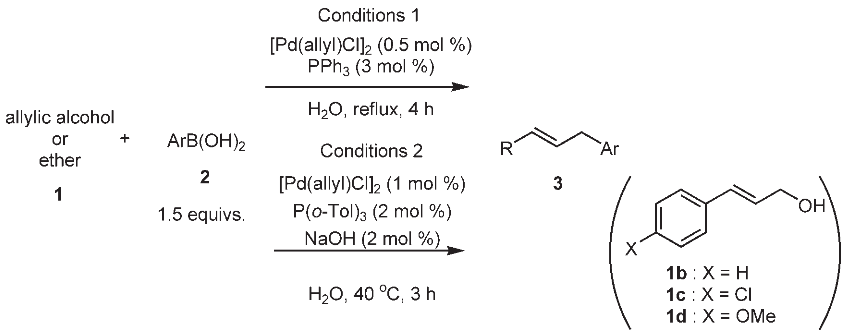


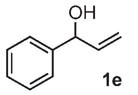
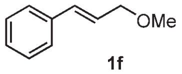
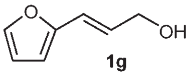
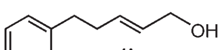
Entry	Temp [°C]	Time [h]	Additive [mol%]	Yield [%][b]	**3a**:**3a'**[c]
1	reflux	4	PPh_3 (3)	83	98:2
2	70	4	PPh_3 (3)	29	99:1
3	70	4	PPh_3 (3), NaOH (5)	78	93:7
4	70	4	PPh_3 (3), CH_3CO_2Na (5)	63	93:7
5	70	4	PPh_3 (3), $CH_3(CH_2)_{10}CO_2Na$ (5)	10	97:3
6	50	4	PPh_3 (3), NaOH (5)	<4	–
7	50	2	PPh_3 (1), NaOH (5)	34	93:7
8[d]	50	2	NaOH (5)	0	–
9[d]	50	2	PPh_3 (1), NaOH (5)	23	–
10	50	2	PPh_3 (1), NaOH (10)	28	92:8
11	50	2	PPh_3 (1), NaOH (1)	40	97:3
12	40	4	PPh_3 (1), NaOH (1)	36	96:4
13	40	4	P(*o*-Tol)$_3$ (1), NaOH (1)	61	97: 3
14	40	4	P(*p*-MeOC$_6$H$_4$)$_3$ (1), NaOH (1)	12	97:3
15	40	4	P(*p*-ClC$_6$H$_4$)$_3$ (1), NaOH (1)	62	98:2
16	40	4	P(*p*-FC$_6$H$_4$)$_3$ (1), NaOH (1)	64	97:3
17[e]	40	3	P(*o*-Tol)$_3$ (2), NaOH (2)	74	97:3

[a] *Reaction conditions:* **1a** (0.4 mmol), **2a** (0.6 mmol), catalyst, H_2O (2.5 mL).
[b] Yield of **3a** was determined with ^1H NMR spectroscopy after isolation as a mixture of **3a** and **3a**′.
[c] The ratio was determined with ^1H NMR spectroscopy.
[d] 0.5 mol % of $Pd_2(dba)_3$ was used.
[e] 1 mol % of $[Pd(allyl)Cl]_2$ was used.

tion proceeded faster with an allylic alcohol which has an electron-withdrawing group (entries 1–3). On the other hand, the products were successfully obtained with an allylic alcohol (**1d**) which has electron-donating group when reactions were conducted in the presence of NaOH. As for boron reagents, the reactions proceeded faster and gave better yields with an electron-donating group under the reflux conditions (entries 4–6). When the reaction was conducted at 40 °C, a boron reagent with an electron-donating substituent decomposed rapidly, and resulted in a lower yield (entry 4). The reactions hardly proceeded in the case of *p*-acetylphenylboronic acid and 4-biphenylboronic acid due to their low solubility in water. By adding 10 mol % of a surfactant, sodium dodecyl sulfate (SDS), the yields were slightly improved (entries 6 and 8). Cinnamyl alcohol (**1b**) and its isomer (**1e**) gave the same product with almost the same yields (entries 1 and 9). The reaction also proceeded with the methyl ether (**1f**). Since the corresponding alcohol could not be observed during the reaction, the ether might react directly. Whereas the substrate which contained a furan ring (**1g**) resulted in a low yield at reflux due to apparent decomposition, the yield was improved to 55% at 40 °C. When an allylic alcohol (**1h**) with an alkyl substituent at the 3-position was used in this reaction, the cross-coupling product was obtained albeit with low regioselectivity (entry 12).

Table 4. Substrate scope.



Entry	Allylic alcohol or ether	Ar	Conditions 1[a] Yield [%]	Conditions 2[b] Yield [%]
1	**1b**	Ph	82	66
2	**1c**	Ph	70	63
3	**1d**	Ph	50 (70)[c]	73
4	**1a**	p–MeOC$_6$H$_4$	89	17
5	**1a**	p–ClC$_6$H$_4$	72	54
6	**1a**	p-AcC$_6$H$_4$	73	12[d]
7	**1a**	o–MeC$_6$H$_4$	89	60
8	**1a**	p–PhC$_6$H$_4$	90	10[d]
9	 **1e**	Ph	76	67
10	 **1f**	Ph	83	61
11	 **1g**	Ph	38	55
12	 **1h**	Ph	71[e]	65[e]

[a] *Reaction conditions:* **1** (0.4 mmol), **2** (0.6 mmol), catalyst, H_2O (2.5 mL), 110 °C (bath temperature), 4 h.

[b] *Reaction conditions:* **1** (0.4 mmol), **2** (0.6 mmol), catalyst, H_2O (2.5 mL), 40 °C (bath temperature), 3 h.

[c] The reaction was conducted for 6 h.

[d] The reaction was conducted with 10 mol % of SDS.

[e] The total yield of two isomers. linear:branched = 2:1 (determined by ^{1}H NMR spectroscopy).

The role of NaOH remains unclear.[6a,7] Since the reactivity order of substituted allylic alcohols depends on the presence of NaOH, the rate-determining step of this reaction might be changed by the addition of NaOH. On the other hand, although a boron reagent with an electron-donating group gave a better yield at reflux, it decomposed rapidly with NaOH at 40 °C. From these results, it is speculated that NaOH acts as an activator for boron reagents. In the case of the reaction without NaOH, the transmetalation step is assumed to be the rate-determining step, and this assumption is consistent with a fact that the reaction proceeded rapidly with an alcohol substituted with an electron-withdrawing group (for example, Table 4, entry 2). On the other hand, in the presence of NaOH, formation of a π-allyl complex or the reductive elimination step is assumed to become the rate-determining step, and therefore, the reaction proceeded rapidly with an alcohol substituted with an electron-donating group (for example, Table 4, entry 3).

In summary, we have developed a catalytic system that enables cross-coupling reactions between allylic alcohols and arylboronic acids in water. Preparation of allyl halides or carboxylates is not needed, and thus the method is more atom-economical than conventional cross-coupling methods. It was also found that a Brønsted base such as NaOH accelerated the reaction dramatically, and enabled the reaction to proceed at milder temperatures. It is noteworthy that only a catalytic amount of a base is needed. Further investigations to clarify the role of NaOH are now in progress.

Experimental Section

Typical Experimental Procedure for the Cross–Coupling of Allylic Alcohol and Arylboronic Acid

To a mixture of $[Pd(allyl)Cl]_2$ (0.002 mmol) and P(*o*-Tol)$_3$ (0.004 mmol) was added water (2.5 mL), and the mixture was degassed and stirred under an argon atmosphere for 30 min at 40 °C. An aqueous solution of NaOH (1.0 M, 0.004 mmol, 4 μL), 3-methoxycinnamyl alcohol (0.4 mmol),[8] and $PhB(OH)_2$ (0.6 mmol) were added, and the mixture was degassed once more and stirred under argon at 40 °C for 3 h. The reaction mixture was quenched with 1 M HCl (1 mL), and the product was extracted with ethyl acetate. The organic phase was dried over Na_2SO_4 and evaporated. The resulting residue was purified with preparative TLC to afford the desired product.

***1-(3-Methoxycinnamyl)benzene* (3a):** colorless oil; ^{1}H NMR ($CDCl_3$): δ=3.54 (2H, d, *J*=6.0 Hz), 3.76 (3H, s), 6.29–6.45 (2H, m), 6.73–6.77 (1H, m), 6.89–6.95 (2H, m), 7.16–7.32 (6H, m); ^{13}C NMR ($CDCl_3$): δ=39.3, 55.2, 111.4, 112.9, 118.8, 126.2, 128.5, 128.7, 129.5, 129.6, 131.0, 139.0, 140.1, 159.8; IR (neat): ν=3027, 2946, 2833, 1600, 1579, 1493, 1453, 1267, 1155, 1044, 969, 769, 699 cm^{-1}; MS (FAB): *m/z*=225 (MH^+); anal. calcd. for $C_{16}H_{16}O$: C 85.68, H 7.19; found: C 85.53, H 7.37.

***1-[1-(3-methoxyphenyl)allyl]benzene* (3a′):** colorless oil; ^{1}H NMR ($CDCl_3$): δ=3.69 (3H, s), 4.62 (1H, d, *J*=7.1 Hz), 4.90–4.96 (1H, m), 5.12–5.16 (1H, m), 6.16–6.27 (1H, m), 6.67–6.72 (3H, m), 7.1–7.2 (6H, m); ^{13}C NMR ($CDCl_3$): δ=54.6, 55.1, 111.4, 114.6, 116.4, 121.0, 126.3, 128.4, 128.5, 129.3, 140.4, 143.1, 144.9, 159.6; IR (neat): ν=3016, 2939, 1600, 1488, 1265, 1151, 1047, 919, 781 700 cm^{-1}; MS (EI): *m/z*=224 (M^+); anal. calcd. for $C_{16}H_{16}O$: C 85.68, H 7.19; found: C 85.45, H 7.25.

Acknowledgements

This work was partially supported by a Grant-in-Aid for Scientific Research from Japan Society of the Promotion of Science. N. A. thanks the JSPS fellowship for Japanese Junior Scientists.

References and Notes

[1] a) *Handbook of Organopalladium Chemistry for Organic Synthesis*, Vol. 2, (Eds.: E.-I. Negishi, A. de Meijere), Wiley Interscience, New York, **2002**, pp. 1663–2027; b) J. Tsuji, *Palladium Reagents and Catalysts*; John Wiley & Sons, Chichester, **1995**.

[2] a) K. E. Atkins, W. E. Walker, R. M. Manyik, *Tetrahedron Lett.* **1970**, 3821–3824; b) J.-P. Haudegond, Y. Chaunin, D. Commereuc, *J. Org. Chem.* **1979**, *44*, 3063–3065; c) D. E. Bergbreiter, D. A. Weatherford, *J. Chem. Soc. Chem. Commun.* **1989**, 883–884; d) I. Shimizu, M. Toyoda, T. Terashima, M. Oshima, H. Hasegawa, *Synlett* **1992**, 301–302; e) M. Sakakibara, A. Ogawa, *Tetrahedron Lett.* **1994**, *35*, 8013–8014; f) H. Bricout, J.-F. Carpentier, A. Mortreux, *J. Mol. Catal. A: Chem.* **1998**, *136*, 243–251; g) X. Lu, X. Jiang, X. Tao, *J. Organomet. Chem.* **1988**, *344*, 109–118; h) K. Itoh, N. Hamaguchi, M. Miura, M. Nomura, *J. Chem. Soc. Perkin Trans. 1* **1992**, 2883–2835; i) I. Strary, I. G. Stará, P. Kocovsky, *Tetrahedron* **1994**, *50*, 529–537; j) Y. Tamaru, Y. Horino, M. Araki, S. Tanaka, M. Kimura, *Tetrahedron Lett.* **2000**, *41*, 5705–5709.

[3] For coupling reactions of allylic alcohols with boronic acid, see: a) G. W. Kabalka, G. Dong, B. Venkataiah, *Org. Lett*. **2003**, *5,* 893–895; b) H. Tsukamoto, M. Sato, Y. Kondo, *Chem. Commun.* **2004**, 1200–1201; c) M. Yoshida, T. Gotou, M. Ihara, *Chem. Commun.* **2004**, 1124–1125.

[4] K. Manabe, S. Kobayashi, *Org. Lett.* **2003**, *5*, 3241–3244.

[5] a) *Organic Synthesis in Water*, (Ed.: P. A. Grieco), Blackie Academic & Professional, London, **1998**; b) C.-J. Li, T.-H. Chen, *Organic Reactions in Aqueous Media*, Klewer Academic Publishers, Dordrecht, **1997**.

[6] For a review on coupling reactions using organoboron reagents, see: a) N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457–2483; b) A. Suzuki, H. C. Brown, *Organic Syntheses via Boranes*, Aldrich Chemical Company, Inc., Milwaukee, **2003**, Vol. 3.

[7] K. Matos, J. A. Soderquist, *J. Org. Chem.* **1998**, *63*, 461–470.

[8] *trans*-3-Methoxycinnamyl alcohol was prepared by the reduction of ethyl *trans*-3-methoxycinnamate using $LiAlH_4$ in the presence of $AlCl_3$. **trans-*3-Methoxycinnamyl alcohol* (1a):** colorless oil; ^{1}H NMR ($CDCl_3$): δ=1.85 (1H, s), 3.80 (3H, s), 4.30 (2H, d, *J*=5.7 Hz), 6.30–6.39 (1H, m), 6.55–6.60 (1H, m), 6.78–6.98 (3H, m), 7.22–7.25 (1H, m); ^{13}C NMR ($CDCl_3$): δ=55.2, 63.5, 111.8, 113.3, 119.1, 128.9, 129.6, 130.8, 138.2, 159.8; IR (neat): ν=3342, 3006, 2936, 2835, 160, 1579, 1491, 1289, 1156, 1096, 1047, 970, 771, 688 cm^{-1}; MS (FAB): *m/z*=165 (MH^+); anal. calcd. for $C_{10}H_{12}O_2$: C 73.15, H 7.37; found: C 72.87, H 7.29.