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Direct Boronation of Allyl Alcohols with Diboronic Acid Using Palladium Pincer-Complex Catalysis. A Remarkably Facile Allylic Displacement of the Hydroxy Group under Mild Reaction Conditions

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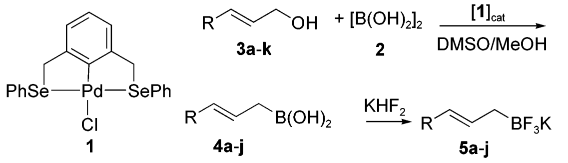
Allyl alcohols are one of the most readily available substrates in palladium-catalyzed allylic displacement reactions.[1] Unfortunately, the hydroxy group is one of the most reluctant leaving groups in substitution reactions, and therefore, application of harsh reaction conditions and employment of Lewis acids or other additives are required in these processes.[1c−j] However, employment of these reaction conditions and reagents precludes the efficient synthesis of unstable allyl metal derivatives, such as allyl boronates, in high isolated yields.

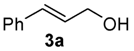
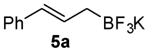
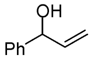
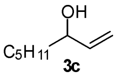
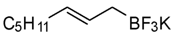
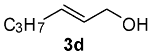
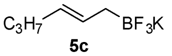
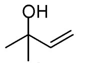
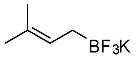
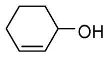
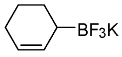
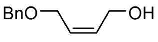
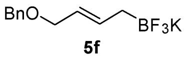
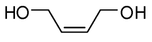
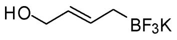
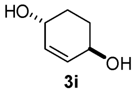
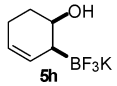
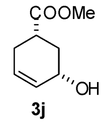
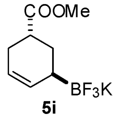
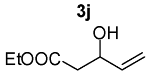
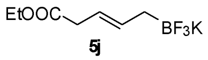


(1)

We have now found that hydroxy to boronate substitution can be achieved under mild conditions using a wide variety of allyl alcohols (**3a**−**k**) and diboronic acid (also called tetrahydroxydiboron, **2**) with 5 mol % pincer-complex[2] **1**[2a] in a mixture of DMSO and MeOH (eq 1). This reaction can be employed for regio- and stereoselective synthesis of allyl boronic acids **4a**−**j**.[3a,b,4a] As allyl boronic acids are not sufficiently stable under solvent-free conditions,[3a,4a] compounds **4a**−**j** were converted[3b−f,4a] to their trifluoro(allyl)borate derivatives **5a**−**j** (Table 1), which are useful precursors in Lewis acid and transition metal catalyzed allylation reactions.[3b,c,4d] Because of the mild reaction conditions and the use of the highly selective[4] (and readily available[2a]) pincer-complex catalyst **1**, the isolated yields of the allyl boronate products are very high (Table 1). Commonly used palladium(0) sources, such as $\mathrm{Pd_2(dba)_3}$ and $\mathrm{Pd(PPh_3)_4}$, were found to be inefficient as catalysts in the presented reactions.

The boronation reactions (eq 1) proceed with excellent regioselectivity, as isomeric allyl alcohols **3a** and **3b** give the same regioisomer **5a**. Similarly, both branched alcohol **3c** and linear alcohol **3d** provide linear allyl boronates **5b** and **5c**, respectively. Unsubstituted cyclic alcohol **3f** reacted smoothly, providing the corresponding boronate **5e** in excellent yield. Allylic substitution with hydroxy or benzyloxy groups leads to increased reactivity, as boronation of **3g**−**i** proceeded at a temperature (20−40 °C) lower than that of the corresponding reaction of the alkyl-substituted analogues **3c**−**f** (40−60 °C). The relatively low temperature is also essential for the high isolated yields of the products since allyl hydroxy boronates **4g**,**h**/**5g**,**h** very easily undergo hydroxy boronate elimination to give the corresponding 1,3-diene. Compounds **3g**,**h** reacted with excellent regioselectivity to give linear products **5f**,**g**. Interestingly, substitution of **3h** resulted in monoboronated product **5g**; thus the reaction can be employed for desymmetrization of bisallyl alcohols. Using harsher reaction conditions to obtain the diboronated product leads to extensive formation of butadiene.

Table 1. Palladium-Catalyzed Direct Boronation of Allyl Alcohols[a]

entry	substrates	cond. [°C/h]	products	yield[b]
1	 **3a**	40/16	 **5a**	92
2[c]	 **3b**	40/7	**5a**	86
3	 **3c**	50/16	 **5b**	90
4	 **3d**	50/16	 **5c**	94
5	 **3e**	50/16	 **5d**	98
6	 **3f**	60/16	 **5e**	92
7	 **3g**	40/21	 **5f**	87
8[c]	 **3h**	20/16	 **5g**	74
9[d]	 **3i**	40/16	 **5h**	87
10[e]	 **3j**	50/24	 **5i**	82
11[e]	 **3k**	40/20	 **5j**	77

[a] Unless otherwise stated, the reactions of **2** and the corresponding substrates were conducted in the presence of **1** (5 mol %) in a mixture of DMSO and MeOH. After the indicated reaction times, aqueous $\mathrm{KHF_2}$ was added. [b] Isolated yield. [c] Pure MeOH used as solvent. [d] A mixture of DMSO and water was used as solvent. [e] *p*-Toluenesulfonic acid (2.5 mol %, entry 11, or 5 mol %, entry 10) was used as cocatalyst.

Substitution of cyclic substrate **3i** provides a single diastereomer **5h**, indicating that the boronation reaction is both regio- and stereoselective (entry 9).

The substitution pattern of **5h** clearly shows that the reaction proceeds with allyl rearrangement and with trans stereoselectivity. For acyclic primary dialcohol **3h**, the boronation reaction affords the corresponding linear product **5g**; however, in case of cyclic analogue **3i**, the directing effect of the hydroxy group leads to formation of the 1,2-substituted product **5h**. Formation of this regioisomer is particularly surprising since usual palladium-catalyzed reactions via allyl−palladium complexes bearing electron-

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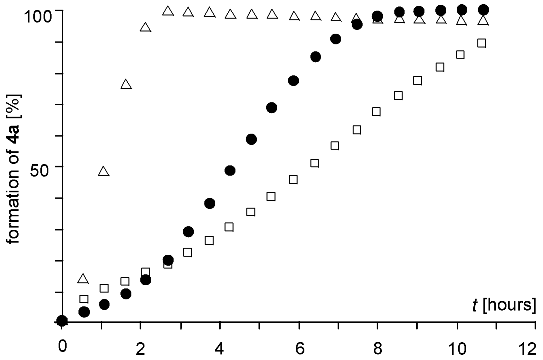


Figure 1. Formation of **4a** from **3a** (●, △) and cinnamyl acetate (□) using **2** and 5 mol % of **1** in DMSO-d_6/MeOH-d_4 mixture at 55 °C. Effects of addition of 5 mol % PTS (△).

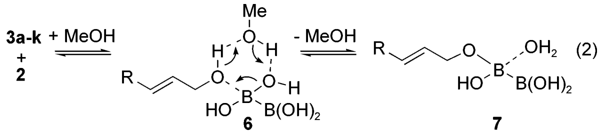
withdrawing substituents usually give the other regioisomer, the 1,4-substituted product.[1a,5]

In the presence of COOR groups (**3j**,**k**), the rate of boronation reaction drops considerably. However, we found that addition of catalytic amounts (3−5 mol %) of strong acids, such as *p*-toluene sulfonic acid (PTS), considerably accelerated the conversion of **3j**,**k**, affording the corresponding boronated products **5i** and **5j**. Again **5i** was obtained as a single diastereomer, clearly indicating that the boronation reactions proceed with high trans regioselectivity.

We found that using a DMSO/MeOH mixture is indispensable to obtain high reaction rates and high yields. When the reactions were performed in pure DMSO, a very slow reaction with low conversion (about 5−20%) of the allyl alcohol substrate occurred. On the other hand, catalyst **1** is poorly soluble in pure MeOH, and therefore, only the most reactive allyl alcohols **3h**,**i** react under mild conditions using MeOH as solvent (entry 8). As mentioned above, allyl hydroxy boronates tend to decompose to 1,3-dienes. This decomposition is particularly fast for **4h** in MeOH, decreasing the yield of the boronation reaction. We found that in a DMSO/water mixture the rate of consumption of **3i** is slower than that in MeOH; however, the corresponding boronated product **4h**/**5h** could be obtained in high yield (entry 9), indicating that **4h** is stable in the presence of water as cosolvent.

To gain insight into the activation of the hydroxy group, we carried out competitive boronation experiments (Figure 1) monitored by ^{1}H NMR. We have previously shown[4a] that cinnamyl acetate and **2** in the presence of catalytic amounts of **1** afford cinnamyl boronic acid **4a**. Surprisingly, under the same reaction conditions, cinnamyl alcohol **3a** was converted significantly faster to boronic acid **4a** than was cinnamyl acetate. Thus, **3a** was converted quantitatively to **4a** in 8 h, while its acetate derivative was still present in the reaction mixture after 11 h.[6] Addition of 5 mol % of PTS had a dramatic effect on the rate of the reaction, as boronation of **3a** was complete in 2 h accounting for a 4-fold acceleration of the reaction. Allylboronic acid **4a** was surprisingly stable[7b] in the presence of PTS, as in 9 h only 5% of **4a** was decomposed (Figure 1).

The above studies clearly indicate that under the employed reaction conditions the hydroxy group of the allyl alcohol is converted to an excellent leaving group, which is easier to displace than an acetate. A possible explanation is that **2** acts as a Lewis acid catalyst by interacting with the free electron pairs of the oxygen of **3a**−**k**. A similar activation is suggested in the Tamaru reaction employing BEt_3 for activation of allyl alcohols.[1c−e] On the other hand, boronic acids are far less efficient Lewis acids than are alkyl (or halo) boranes. Therefore, we envision another type of activation of the hydroxy group involving formation of allyl boronic acid ester **7** (eq 2). This esterification is probably facilitated by inclusion of a methanol molecule in the six-membered ring TS (**6**) of the process. In **7**, the hydroxy group is converted to a better leaving group, and moreover, the cleavage of the B−B bond is also facilitated by coordination of the water molecule produced in the esterification. Application of small amounts of PTS (entries 10 and 11, Figure 1) is supposed to catalyze the ester formation.



In summary, we have shown that allyl alcohols can be converted to allyl boronates using **2** and catalytic amounts of **1**. Functionalized allyl boronates are very useful precursors in natural product and advanced organic synthesis,[3a−d,7a,b] which explains the great current interest to find efficient synthetic methods for preparation of these species.[4a,7] The above presented robust catalytic transformation employs the least expensive allylic precursors reported for synthesis of functionalized allyl boronates, and therefore, this method is also a good example for the synthesis of highly value-added chemicals.

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Supporting Information Available: Experimental procedures as well as characterization and NMR spectra of the products. This material is available free of charge via Internet at http://pubs.acs.org.

References

(1) (a) Tsuji, J. *Palladium Reagents and Catalysis. New Perspectives for the 21st Century*; Wiley: Chichester, UK, 2004. (b) Marshall, J. A. *Chem. Rev.* **2000**, *100*, 3163. (c) Tamaru, Y. *Eur. J. Org. Chem.* **2005**, 2647. (d) Kimura, M.; Futamata, M.; Mukai, R.; Tamaru, Y. *J. Am. Chem. Soc.* **2005**, *127*, 4592. (e) Kimura, M.; Horino, Y.; Mukai, R.; Tanaka, S.; Tamaru, Y. *J. Am. Chem. Soc.* **2001**, *123*, 10401. (f) Takahara, J. P.; Masuyama, Y.; Kurusu, Y. *J. Am. Chem. Soc.* **1992**, *114*, 2577. (g) Ozawa, F.; Okamoto, H.; Kawagishi, S.; Yamamoto, S.; Minami, T.; Yoshifuji, M. *J. Am. Chem. Soc.* **2002**, *124*, 10968. (h) Ozawa, F.; Ishiyama, T.; Yamamoto, S.; Kawagishi, S.; Murakami, H. *Organometallics* **2004**, *23*, 1698. (i) Starý, I.; Stará, I. G.; Kocovský, P. *Tetrahedron* **1994**, *50*, 529. (j) Bergbreiter, D. E.; Weatherford, D. A. *J. Chem. Soc., Chem. Commun.* **1989**, 883.

(2) (a) Yao, Q.; Kinney, E. P.; Zheng, C. *Org. Lett.* **2004**, *6*, 2997. (b) Albrecht, M.; Koten, G. v. *Angew. Chem., Int. Ed.* **2001**, 3750. (c) Slagt, M. Q.; Rodríguez, G.; Grutters, M. M. P.; Gebbink, R. J. M. K.; Klopper, W.; Jenneskens, L. W.; Lutz, M.; Spek, A. L.; Koten, G. v. *Chem.—Eur. J.* **2004**, *10*, 1331. (d) van der Boom, M. E.; Milstein, D. *Chem. Rev.* **2003**, *103*, 1759.

(3) (a) Roush, W. R.; Walts, A. E.; Hoong, L. K. *J. Am. Chem. Soc.* **1985**, *107*, 8186. (b) Batey, R. A.; Thadani, A. N.; Smil, D. V.; Lough, A. J. *Synthesis* **2000**, 990. (c) Batey, R. A.; Quach, T. D. *Tetrahedron Lett.* **2001**, *42*, 9099. (d) Li, S.-W.; Batey, R. A. *Chem. Commun.* **2004**, 1382. (e) Kabalka, G. W.; Venkataiah, B.; Dong, G. *J. Org. Chem.* **2004**, *69*, 5807. (f) Vedejs, E.; Chapman, R. W.; Fields, S. C.; Lin, S.; Schrimpf, M. R. *J. Org. Chem.* **1995**, *60*, 3020.

(4) (a) Sebelius, S.; Olsson, V. J.; Szabó, K. J. *J. Am. Chem. Soc.* **2005**, *127*, 10478. (b) Kjellgren, J.; Sundén, H.; Szabó, K. J. *J. Am. Chem. Soc.* **2004**, *126*, 474. (c) Kjellgren, J.; Sundén, H.; Szabó, K. J. *J. Am. Chem. Soc.* **2005**, *127*, 1787. (d) Solin, N.; Wallner, O. A.; Szabó, K. J. *Org. Lett.* **2005**, *7*, 689. (e) Solin, N.; Kjellgren, J.; Szabó, K. J. *J. Am. Chem. Soc.* **2004**, *126*, 7026.

(5) (a) *Comprehensive Organic Synthesis*; Godleski, S. A., Ed.; Pergamon Press: New York, 1991; Vol. 4. (b) Szabó, K. J. *Chem. Soc. Rev.* **2001**, *30*, 136. (c) Bäckvall, J.-E.; Nyström, J.-E.; Nordberg, R. E. *J. Am. Chem. Soc.* **1985**, *107*, 3676.

(6) For other substrates, application of acetates is even less efficient. For example, dialcohol **3i** readily provides **5h** (entry 9); however, the corresponding diacetate is completely unreactive under the same reaction conditions.

(7) (a) Hall, D. G. *Boronic Acids: Preparation and Application in Organic Synthesis and Medicine*; Wiley: Weinheim, Germany, 2005. (b) Yu, S. H.; Ferguson, M. J.; McDonald, R.; Hall, D. G. *J. Am. Chem. Soc.* **2005**, *127*, 12808. (c) Ishiyama, T.; Ahiko, T.-a.; Miyaura, N. *Tetrahedron Lett.* **1996**, *37*, 6889. (d) Sebelius, S.; Wallner, O. A.; Szabó, K. J. *Org. Lett.* **2003**, *5*, 3065. (e) Ito, H.; Kawakami, C.; Sawamura, M. *J. Am. Chem. Soc.* **2005**, *127*, 16034.

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