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Palladium-Catalyzed Coupling of Allyl Acetates with Aldehyde and Imine Electrophiles in the Presence of Bis(pinacolato)diboron

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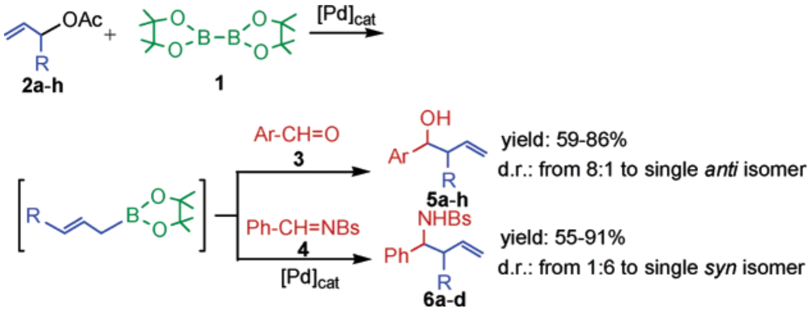
ABSTRACT



An efficient one-pot procedure was developed for palladium-catalyzed electrophilic substitution of allyl acetates (2a–h) in the presence of bis(pinacolato)diboron (1). These reactions proceed with an excellent regioselectivity and with a remarkably high stereoselectivity. The catalytic transformations take place via palladium-catalyzed formation of allyl boronates, which subsequently react with aldehyde (3) and sulfon-imine (4) electrophiles to afford homoallylic alcohols (5a–h) and amines (6a–d), respectively. A particularly interesting mechanistic feature is that the allylic substitution of the transient allyl boronate with sulfon-imine requires palladium catalysis. This finding indicates that the formation of the homoallylic amine derivatives (6a–d) involves bis-allylpalladium intermediates.

Palladium catalysis offers an attractive synthetic approach for stereo- and regioselective allylation of electrophilic substrates.[1] These reactions usually proceed in two consecutive steps. The first step is a palladium-catalyzed formation of an allylmetal species from allyl halides or allyl acetates and an organometallic reagent[2,3] (such as $SnCl_2$, $ZnEt_2$, Et_3B, $(SnMe_3)_2$, etc.). Usually, the allyl-metal intermediates are sufficiently reactive for direct coupling with electrophiles.[2] However, less reactive species such as transient trialkyl-allyl stannanes require a second palladium-catalyzed step to accomplish the allylation of the electrophile.[3] The organometallic reagents employed in these reactions have to comply with two important requirements: (1) they must be compatible with several reactive functionalities to ensure a broad synthetic scope for the catalytic transformations, and (2) the transient allylmetal compound must undergo highly regio- and stereoselective coupling with the electrophile.

We have now found that bis(pinacolato)diboron (**1**) is an organometallic reagent that largely satisfies the above requirements. Thus, functionalized allyl acetates (**2**) could be reacted with aldehyde (**3**) or imine (**4**) electrophiles in the presence of **1** and catalytic amounts of $Pd_2(dba)_3$ affording the corresponding homoallylic alcohol (**5**) or amine (**6**) products with high regio- and stereoselectivity (Scheme 1 and Table 1).

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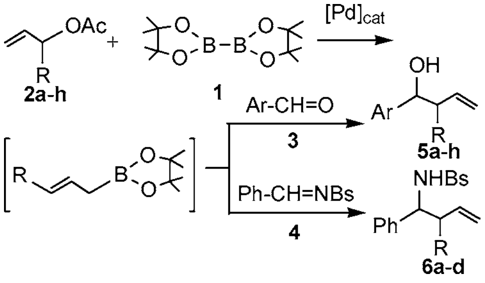
10.1021/ol035052i CCC: $25.00

Scheme 1



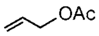
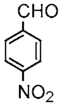
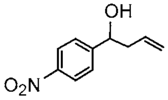
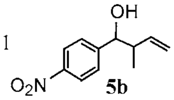
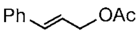
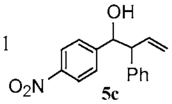
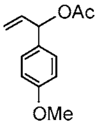
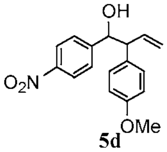
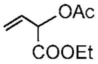
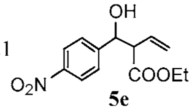
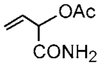
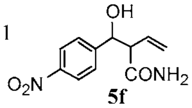
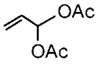
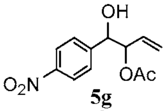
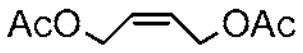
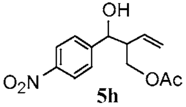
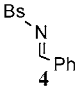
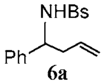
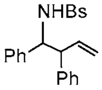
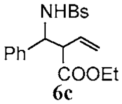
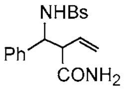
In a typical reaction, the corresponding electrophile **3** or **4** (0.30 mmol) and $Pd_2(dba)_3$ (6 mol % palladium) were dissolved in DMSO (3 mL). Thereafter, the allylic substrate **2a−h** (0.36 mmol) was added, and this mixture was stirred for 10 min at room temperature under Ar. After addition of diboron reagent **1** (0.36 mmol), the reaction mixture was stirred at the allotted temperatures and times listed in Table 1. The products (**5**, **6**) were isolated by column chromatography using a pentane−EtOAc eluent.

The reactions usually could be carried out under mild conditions at room temperature or at slightly elevated temperatures (40 °C). The synthetic scope of the reaction is broad due to a high level of functional group tolerance. Many functionalities, including NO_2, COOEt, OAc, and $CONH_2$, remained unchanged under the applied reaction conditions. A particularly attractive feature of this catalytic transformation is that nitro-benzaldehyde (**3**) can be used as a coupling component. Under the applied reaction conditions, **3** resists both Cannizzaro reaction and change of the nitro functionality, which may take place under basic conditions and on using low-valent metals.[4a,b] The catalytic transformations proceeded with very high regioselectivity, affording the branched allylic isomer. The diastereoselectivity of the reactions is also remarkably high. In several cases (entries 2, 7, 8, and 10), only a single diastereomer was formed. It is interesting to note that recent publications on synthesis of analogues of **5g** (entry 7) and **5h** (entry 8) particularly emphasized the difficulties concerning the highly stereoselective preparation of these types of compounds.[4a,c]

When high reaction temperatures (> 60 °C) were employed, amorphous palladium(0) was precipitated from the reaction mixture, thereby deactivating the catalyst. We have tried to stabilize the catalyst by addition of various phosphines (e.g., PPh_3 and $P(OPh)_3$) or activated alkenes (e.g., maleic anhydride and COD). However, these additives strongly retarded or inhibited the catalytic process. It was found that precipitation of palladium black could be suppressed most efficiently by lowering the reaction temperature and by elongation of the reaction time.

Mechanistic Aspects. Miyaura and co-workers[5a] have shown that allyl acetates react with diboron reagent **1** in a palladium-catalyzed transformation affording allyl boronates (eq 1). It was found[5a] that this catalytic transformation is

Table 1. Pd-Catalyzed Allylic Substitution of Allyl Acetates **2a−h** in the Presence of Bis(pinacolato)diboron

entry	allyl	electrophile	method[a]	product	d.r.[b]	yield[c]
1	 **2a**	 **3**	60/4	 **5a**	-	71
2	 **2b**	**3**	60/21	 **5b**	s.d.[d]	81
3	 **2c**	**3**	40/21	 **5c**	33:1[d]	86
4	 **2d**	**3**	40/21	 **5d**	10:1[d]	83
5	 **2e**	**3**	20/21	 **5e**	8:1[d]	75
6	 **2f**	**3**	20/21	 **5f**	8:1[d]	61
7	 **2g**	**3**	20/91	 **5g**	s.d.[d]	74
8	 **2h**	**3**	40/21	 **5h**	s.d.[d]	59
9	**2a**	 **4**	60/4	 **6a**	-	80
10	**2c**	**4**	20/72	 **6b**	s.d.[e]	91
11	**2e**	**4**	20/21	 **6c**	1:11[e]	55
12	**2f**	**4**	20/21	 **6d**	1:6[e]	75

[a] All reactions were conducted in DMSO in the presence of **1** using 6 mol % Pd catalyst. The allotted temperatures and times are given in °C/h. [b] Diastereomer ratio (anti/syn) determined by ^1H NMR spectroscopy. [c] Isolated yield. [d] Major diastereomer has anti configuration.[4a−d] [e] Major diastereomer has syn configuration.[9a,b] Bs = benzenesulfonyl; s.d. = single diastereomer

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(5) (a) Ishiyama, T.; Ahiko, T.-a.; Miyaura, N. *Tetrahedron Lett.* **1996**, 6889. (b) Yamammoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207. (c) Hoffmann, R. W. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 555. (d) Brown, H. C.; Racherla, U. S.; Pellechia, P. J. *J. Org. Chem.* **1990**, *55*, 1868.

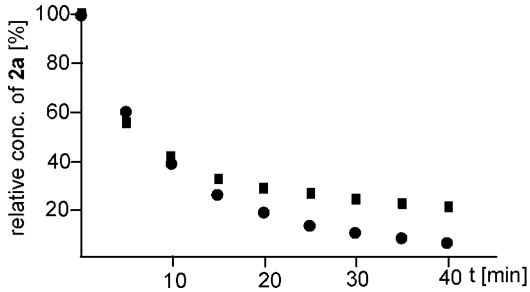
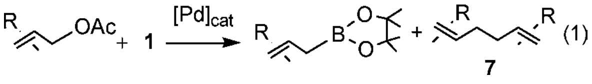
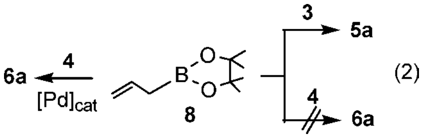


Figure 1. Palladium-catalyzed transformation of **2a**[6] in the presence (●) and absence (■) of aldehyde **3**.

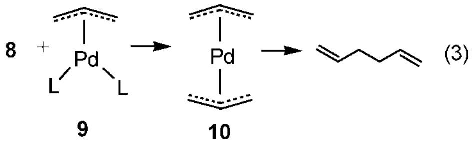
usually accompanied by formation of the allyl−allyl coupling product **7**.



It is reasonable to assume that the first step of the above-presented allylic substitution reaction (Scheme 1) is palladium-catalyzed formation of the transient allyl boronate. However, it is interesting to note that allyl−allyl coupling products (such as **7**) were not observed in any of the reactions presented in Table 1. It is well established that allyl boronates undergo direct allylboration with aldehydes and other electrophiles.[5b−d] In these reactions, the carbonyl group of the aldehyde coordinates to the boron atom, which reacts as an internal Lewis acid due to its low-lying vacant p_π-orbital.[5c] Indeed, allyl boronate **8** smoothly reacted with aldehyde **3** (eq 2) under the applied reaction conditions (Scheme 1) in the *absence* of palladium catalyst. Accordingly, the catalytic allylic substitution of allyl acetates (**2a**−**h**) with aldehyde **3** can be considered as a palladium-catalyzed formation of transient allyl boronates followed by direct coupling with the electrophile (i.e., **3**).



Performing the reaction as a one-pot sequence has several advantages. (1) Isolation of the reactive allyl boronate intermediates (entries 5−8) can be avoided. (2) Allyl−allyl coupling does not take place in the presence of electrophiles. (3) The palladium-catalyzed conversion of allyl acetate (**2a**) is faster in the presence of **3** than in the parent reaction (eq 1). To further explore feature 3, we have studied the rate of consumption of **2a** in the presence and in the absence of aldehyde **3** (Figure 1).[6] In the beginning of the reaction ($t <$ 10 min) the rate of conversion of **2a** does not depend on **3**. However, when the conversion exceeds 50%, the catalytic transformation of **2a** is faster in the presence of **3** than in the absence of it. This indicates that accumulation of allyl boronate **8** inhibits the catalytic process.



It is well-known that homocoupling product **7** readily forms from bis-allylpalladium complexes.[7a,b] Therefore, appearance of the allyl−allyl coupling product (**7**) in the absence of aldehyde **3** indicates that a bis-allylpalladium intermediate (**10**) is generated under catalytic conditions (eq 3).

The possible intermediacy of bis-allylpalladium complex **10** in the above-presented catalytic process (Scheme 1) is also indicated by the reactions involving imine **4** (entries 9−12). In contrast to aldehyde **3**, sulfon-imine **4** cannot be allylboronated with **8** in the *absence* of palladium catalyst (eq 2). Accordingly, the boron atom does not exert an internal Lewis acid reactivity as in the reactions with aldehyde types of substrates.[5c] On the other hand, we have found that in the presence of $Pd_2(dba)_3$ catalyst, allyl boronate **8** smoothly reacts with **4** affording **6a**. A similar reactivity was reported for palladium-catalyzed allylic substitution of trialkyl-allyl stannanes with aldehydes and imines.[3,8] In these reactions, the bis-allypalladium intermediate (**10**) is formed from allyl stannanes and **9** (cf. eq 3).

It was shown that bis-allylpalladium complexes readily react with electrophiles under catalytic conditions.[3,7,8] Although the catalytic allylic substitution via bis-allylpalladium complexes is a well-known reaction for trialkyl-allyl stannanes, as far as we know, this is the first study reporting a similar reactivity for allyl boronates.

The high stereoselectivity is a synthetically useful feature of the presented allylic substitution reaction. The reactions with aldehyde **3** selectively provide (entries 2−8) the anti diastereomer. This stereoselectivity can be explained by the selective formation of the trans isomer of the allyl boronate intermediate in the initial palladium-catalyzed step. The subsequent reaction of the *trans*-allyl boronates with aldehydes leads to formation of the anti diastereomer.[5c] The major diastereomer formed in the reactions with sulfon-imine **4** has syn configuration. A similar syn diastereoselectivity was reported for the formation of **6b** from **4** and cinnamyl bromide in indium- and zinc-mediated reactions.[9a] Although understanding the mechanism of the stereochemistry requires further studies, we believe that the nature of the steric and

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(6) These reactions were performed in the presence of **1** and a catalytic amount of $Pd_2(dba)_3$ in DMSO-d_6 at 50 °C.

(7) (a) Nakamura, H.; Bao, M.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2001**, *40*, 3208. (b) Goliaszewski, A.; Schwartz, J. *Tetrahedron* **1985**, *41*, 5779.

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electronic interactions governing the stereoselection can be similar in the indium-mediated and in the present palladium-catalyzed process.[9a]

In summary, we have shown that aldehyde (**3**) and sulfon-imine (**4**) electrophiles can be allylated by allyl acetates in the presence of **1** and a catalytic amount of $Pd_2(dba)_3$. The catalytic reaction proceeds with a remarkable high regio- and stereoselectivity providing the branched allylic isomer. Mechanistic studies show that the first step of the reaction is a palladium-catalyzed formation of transient allyl boronates. Subsequently, aldehyde **3** reacts directly with the allyl boronate to afford homoallylic alcohols as products. However, the reaction of sulfon-imine **4** with the allyl-boronate intermediate requires palladium catalysis, indicating that bis-allylpalladium intermediates may be involved in the reaction.

Acknowledgment. This work was supported by the Swedish Research Council (VR).

Supporting Information Available: Characterization and ^{13}C NMR spectra of new compounds **5g**, **5h**, and **6d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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