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Highly Selective and Robust Palladium-Catalyzed Carbon–Carbon Coupling between Allyl Alcohols and Aldehydes via Transient Allylboronic Acids

Nicklas Selander,[a] Sara Sebelius,[a] Cesar Estay,[a] and Kálmán J. Szabó*[a]

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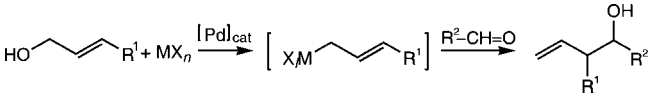
The highly regio- and stereoselective coupling of allyl alcohols with aldehydes could be achieved with 5 mol-% of SeCSe pincer complex catalyst and *p*-toluenesulfonic acid in the presence of diboronic acid. The transformations have a broad synthetic scope, and the high yields were obtained without the use of an inert atmosphere and carefully dried solvents.

Catalytic allylation of the carbonyl carbon of aldehydes with allyl alcohols is one of the most attractive transformations in palladium chemistry.[1,2a–2d] In practical implementations, the allylation reaction is initiated by a palladium-catalyzed conversion of allyl alcohols to allylmetal species. This conversion is mediated by $SnCl_2$,[2a] BEt_3,[2b] Et_2Zn[2c] and indium[2d] salts (Scheme 1). Subsequently, the allylmetal species undergoes electrophilic allylation with the aldehyde substrate.[2e–2g] As these transformations involve a two-step procedure with a Lewis acid and/or reductive organometallic reagent, the functional group tolerance of the reaction is usually limited. With the use of functionalized allyl alcohols, a further issue is the control of the stereoselectivity of the process, which is highly dependent on the applied organometallic reagent and on the steric bulk of the allylic substituent. Although there are many excellent procedures described in the literature,[1,2a–2d] it is still a challenge to find highly selective and robust methods for the palladium-catalyzed coupling of various allyl alcohols (including both cyclic and acyclic ones) with aliphatic and aromatic aldehydes.



Scheme 1. Allylation of aldehydes by in situ generated allylmetal species. M = Sn, B, Zn and In.

We have now found that allyl alcohols **1a**–**g** react readily with aldehydes **2a**–**i** in the presence of diboronic acid (**3**), catalytic amounts (5 mol-%) of easily accessible pincer complex catalyst **4**[2h] and *p*-toluenesulfonic acid (**5**) (Schemes 2, 3 and 4; Tables 1 and 2). These reactions can be performed as an operationally simple one-pot sequence under mild conditions (typically 40 °C–50 °C) in a DMSO/MeOH mixture. Allylation of the aldehyde substrates occurs via the allylboronic acids formed from the allyl alcohols and **3** (Scheme 5). When the reaction is carried out in the absence of the aldehyde component, allylboronic acids **7** can be observed and isolated after conversion to their corresponding allyl boronates.[3] Because transient allylboronic acids **7**[3] and the other reactants, including catalyst **4**, are stable in the presence of air, moisture, weak acids and bases, the reactions can be carried out without the use of an inert atmosphere and in standard quality solvents. Diboronic acid (**3**) is a nonreductive reagent with very weak (if any) Lewis acid character, and therefore, many functionalities, including ethoxycarbonyl/methoxy (Scheme 3; Table 2, Entries 2–10), nitro (Table 1, Entry 5; Table 2, Entries 5 and 8) and cyano groups (Tables 1 and 2, Entry 4), are tolerated. Palladium catalyst **4** is compatible with all of these groups and aromatic bromides as well (Tables 1 and 2, Entry 3). Allylation of **2e** (Tables 1 and 2, Entry 6) represents a particularly good example of the functional group tolerance of this reaction, as the aldehyde functionality of **2e** could be selectively converted without affecting its keto moiety.

The regioselectivity[4] of the reaction is excellent as both linear, **1a**, and branched, **1b**–**d**, allyl alcohols give the branched allylic products **6a**–**j**. At elevated temperatures and with the use of 50 mol-% of **5**, product **6k** undergoes lactonization[5c] to provide **6l** as a final product of the one-pot sequence (Scheme 3).

In the described processes (Schemes 2, 3 and 4), homoallylic alcohol products **6a**–**i** and **6m**–**v** were obtained as single diastereomers. The reactions of acyclic allyl alcohols **1a**–**c** afford the *anti* products, as the transformations proceed via allylboronic acids **7**,[3] in which the geometry of the double bond is *trans*.[4] The reaction proceeds readily and

[a] Dept. Organic Chemistry, Stockholm University, 10691 Stockholm, Sweden
E-mail: kalman@organ.su.se

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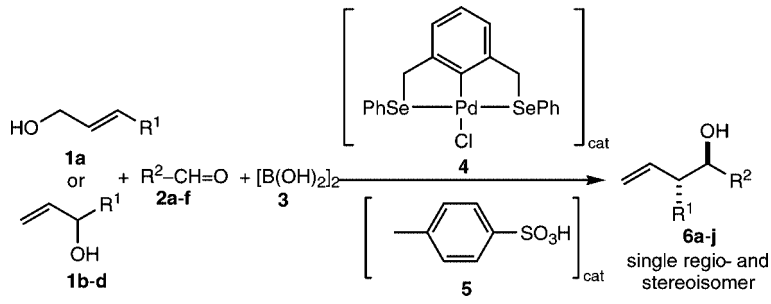
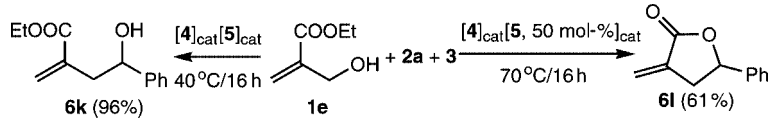
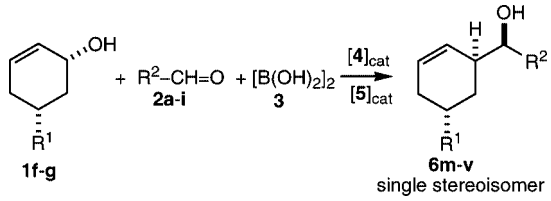


Scheme 2.



Scheme 3.



Scheme 4.

with high diastereoselectivity even for cyclic allyl alcohols **1f**–**g**. In these reactions, the double bond in the cyclic allylboronic acid intermediate has a *cis* geometry,[3] and thus the new carbon–carbon bond forms with *syn* diastereoselectivity.[4] It is remarkable that selective tandem stereocontrol of the reaction can be achieved from **1g** to provide the product as a single diastereomer out of the four diastereomeric products that are possible (Table 2, Entries 2–10). The excellent stereoselectivity is a consequence of the highly ster-

Table 1. Allylation of aldehydes with acyclic allyl alcohols (Scheme 2).[a]

Entry	Alcohol	R^1	Aldehyde	R^2	Conditions[b]	Product	Yield[c] [%]
1	**1a**	Ph	**2a**	Ph	40/16	**6a**	88
2[d]	**1a**	Ph	**2a**	Ph	40/48	**6a**	96
3	**1a**	Ph	**2b**	4-Br–C_6H_4	40/16	**6b**	93
4	**1a**	Ph	**2c**	4-CN–C_6H_4	40/16	**6c**	72
5	**1a**	Ph	**2d**	4-NO_2–C_6H_4	40/16	**6d**	78
6	**1a**	Ph	**2e**	4-CH_3CO–C_6H_4	40/16	**6e**	75
7	**1a**	Ph	**2f**	*n*-pentyl	50/16	**6f**	70
8	**1b**	*n*-pentyl	**2a**	Ph	50/16	**6g**	86
9	**1b**	*n*-pentyl	**2f**	*n*-pentyl	50/16	**6h**	76
10	**1c**	CH_2OBn	**2a**	Ph	40/16	**6i**	96
11	**1d**	vinyl	**2a**	Ph	60/16	**6j**	82

[a] Unless otherwise stated, the reactions of **1**, **2** and **3** were conducted in the presence of catalytic amounts of **4** and **5** (both 5 mol-%) in a DMSO/MeOH mixture. [b] Temperature [°C]/Time [h]. [c] Isolated yield. [d] Compound **5** was not used.

Table 2. Coupling of cyclic allyl alcohols with aldehydes (Scheme 4).[a]

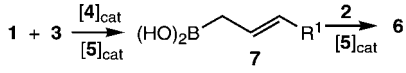
Entry	Alcohol	R^1	Aldehyde	R^2	Conditions[b]	Product	Yield[c] [%]
1	**1f**	H	**2a**	Ph	60/16	**6m**	98
2	**1g**	COOMe	**2a**	Ph	50/36	**6n**	93
3	**1g**	COOMe	**2b**	4-Br–C_6H_4	50/36	**6o**	72
4	**1g**	COOMe	**2c**	4-CN–C_6H_4	50/36	**6p**	75
5	**1g**	COOMe	**2d**	4-NO_2–C_6H_4	50/36	**6q**	73
6	**1g**	COOMe	**2e**	4-CH_3CO–C_6H_4	50/36	**6r**	78
7	**1g**	COOMe	**2f**	*n*-pentyl	50/36	**6s**	71
8	**1g**	COOMe	**2g**	3-NO_2–C_6H_4	50/36	**6t**	73
9	**1g**	COOMe	**2h**	H[d]	50/36	**6u**	78
10	**1g**	COOMe	**2i**	Me[e]	50/36	**6v**	72

[a] Unless otherwise stated, the reactions of **1**, **2** and **3** were conducted in the presence of catalytic amounts of **4** and **5** (both 5 mol-%) in a DMSO/MeOH mixture. [b] Temperature [°C]/Time [h]. [c] Isolated yield. [d] Paraformaldehyde was used. [e] Paracetaldehyde was used.

eoselective formation of the allylboronic acid intermediate[3] and the subsequent selective coupling with the aldehyde substrate.[4,5]

The reaction presented works smoothly with both aromatic and aliphatic aldehydes. As aliphatic aldehydes such as **2f** are somewhat less reactive than their aromatic counterparts **2a**–**e**, a higher reaction temperature (50 °C) was required for the allylation of **2f** compared with that of aromatic substrates **2a**–**e** (40 °C). Remarkably, even paraformaldehyde (**2h**) and paracetaldehyde (**2i**) could be used as aldehyde sources (Scheme 4; Table 2, Entries 9–10), and thus the presented one-pot sequence can be employed for the homologation of allyl alcohols.

The reactions were performed in the presence of catalytic amounts of *p*-toluenesulfonic acid (**5**). It was shown[3a] that under the applied reaction conditions the formation of allylboronic acids **7** is considerably accelerated in the presence of **5**, particularly when the allyl alcohol substrates contain carboxy substituents (**1e** and **1g**). Furthermore, Hall and coworkers[5c,5d] have shown that Brønsted acids catalyze the coupling reaction of allylboronates with aldehydes. Thus, **5** catalyzes both crucial steps (Scheme 5) of the coupling reaction. Nevertheless, certain reactions proceed even in the absence of acid catalyst **5**, for example coupling of **1a** with **2a** (Table 1, Entry 2). However, this process (Entry 2) takes much longer (48 h) than the corresponding reaction (Entry 1) in the presence of **5** (16 h). On the other hand, in the presence of allylic carboxy substituents (**1e** and **1g**) or a nitro substituent in the aldehyde component (**2d**), only traces of the coupling products are formed without the use of **5**.



Scheme 5.

In summary, we have developed a versatile one-pot reaction for the selective allylation of aldehydes with allyl alcohols, which can be carried out under mild conditions without the use of an inert atmosphere. The described procedure is environmentally benign as the byproduct of the catalytic reaction is the nontoxic boronic acid; the process is also economical as it employs inexpensive allyl alcohols as reagents.

Experimental Section

Allyl alcohol **1** (0.15 mmol) was dissolved in a DMSO/MeOH mixture (0.3:0.3 mL) followed by the addition of diboronic acid (**3**) (0.18 mmol), pincer complex **4** (0.0075 mmol, 5 mol-%), *p*-toluenesulfonic acid (**5**) (0.0075 mmol, 5 mol-%) and aldehyde **2** (0.18 mmol). This reaction mixture was stirred for the allotted temperatures and times listed in Table 1 and Table 2, and thereafter quenched with water and extracted with diethyl ether. After evaporation of the ether phase, product **6** was purified by silica gel column chromatography. The reactions do not require an inert atmosphere or carefully dried solvents. A detailed experimental procedure and characterization of the products is given in the Supporting Information.

Supporting Information (see footnote on the first page of this article): Detailed experimental procedures, characterization of the products as well as ^{1}H- and ^{13}C NMR spectra of **6a-v**.

Acknowledgments

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