Single-pot triple catalytic transformations based on coupling of *in situ* generated allyl boronates with *in situ* hydrolyzed acetals†

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***In situ* hydrolyzed acetals were coupled with *in situ* generated allyl boronates in a one-pot procedure, affording regio- and stereodefined homoallyl alcohols, epoxides and amino alcohols.**

Application of organoboronates has revitalized the field of selective allylation reactions in modern organic synthesis.[1–3] The selective synthesis based on this chemistry requires access to highly regio- and stereoselective methods[1–4] for preparation of functionalized allyl boronates. However, purification of the functionalized allyl boronates is often problematic.

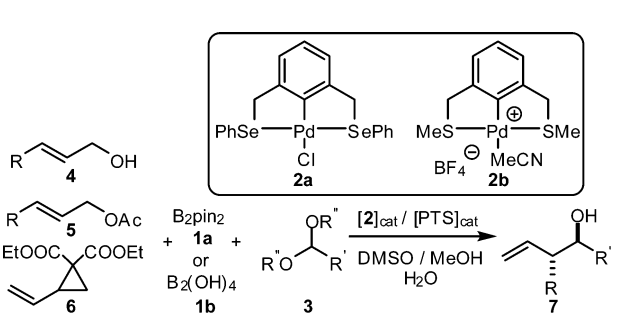
Usual problems are the oxidation of the allylic carbon under solvent-free conditions[3a,c] and the elimination of the boronate group during chromatography. These purification problems may become the most important obstacles using allyl boronates in organic synthesis. A possible solution to this problem is the design of single-pot transformations involving catalytic generation of transient organoboronates. We[3] and other groups[4] have recently demonstrated that palladium, iridium and ruthenium catalysis can be used for efficient synthesis of organoboronates, which are subsequently reacted further in a one-pot sequence.

As a part of our research program focused on development of one-pot reactions based on catalytically generated allyl boronates,[3a–c] we have studied the possibility to employ *in situ* hydrolyzed acetals as aldehyde components for the process. This approach is particularly useful when the acetals are more stable or more easily accessible than the requisite aldehydes. Indeed, we have found (Scheme 1, Table 1) that under the reaction conditions of pincer-complex[5] (**2a,b**) catalyzed boronation with bis(pinacolato)diboron (**1a**) or diboronic acid (**1b**), various acetals (**3a–f**) can readily be hydrolyzed by water in the presence of catalytic amounts of *p*-toluenesulfonic acid (PTS). In these processes, a broad variety of allylic substrates, including allyl alcohols (**4**), acetates (**5**) and vinyl cyclopropanes (**6**), can be employed and the overall reaction results in regio- and stereodefined homoallyl alcohols (**7**), which are useful building blocks in organic synthesis (Scheme 3). A typical reaction could be performed as a real one-pot process by mixing diboronate **1**, catalyst **2**, acetal **3** and allylic substrate **4–6** in a mixture of DMSO, MeOH and water. This mixture was reacted at 70 °C for 24 h, and then the homoallyl alcohol product was isolated in good to excellent yields. Acetals of common aromatic aldehydes such as **3a** work very well in these reactions. However, the synthetic power of the process can be best demonstrated by application of acetals **3b–f**. The aldehydes formed by hydrolysis of these acetals are either difficult to handle (**3b,c**), unstable (**3d**) or difficult to access (**3e,f**). As the reaction conditions of the boronation and allylation are fully compatible with the *in situ* hydrolysis of these acetals, their handling and purification can be avoided by use of the operationally simple one-pot approach.

The above described procedure involves three individual reactions performed in concert (Scheme 2). The first process is based on our catalytic boronation method[3d,e] using inexpensive substrates **4–6**, including allyl alcohols, to give allyl boronates. Formation of these species are accelerated[3e] by catalytic amounts of PTS, and the catalytic boronation can also be performed in the presence of water.[3a] These reaction components can also be employed for hydrolysis of acetals **3**. The aldehydes formed in this process immediately react with the allyl boronate in a highly regio- and stereoselective process.[1a,b] This also ensures that unstable or highly reactive aldehydes formed from **3c–f** do not accumulate in the reaction mixture, ensuring a smooth reaction without decomposition and catalyst inhibition. Accordingly, the homoallylic product **7** is formed as a single regio- and stereoisomer, without significant generation of by-products.

Overall, the reaction can be classified as cooperative concerted catalysis[6] involving a catalytic action by **2** on the allylic substrate and by PTS on both the allylic substrate[3e] (**4–6**) and on acetal **3**, followed by coupling of the transient allyl boronate and aldehyde intermediates (Scheme 2). Accordingly, the presented new one-pot procedure involves three perfectly synchronized catalytic actions, of which two are catalyzed by PTS and one is catalyzed by pincer complex **2**.

The reaction is highly cost and eco-efficient. Because of the one-pot approach, all discrete reactions share the same solvent and at least two purification steps can be avoided. Furthermore, the reaction proceeds with a good atom economy and



Scheme 1 Single-pot synthesis of homoallyl alcohols.

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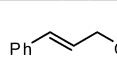
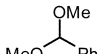
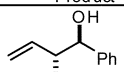
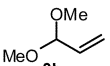
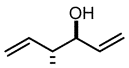
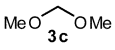
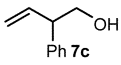
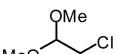
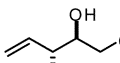
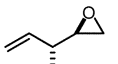
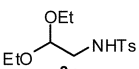
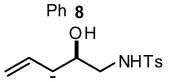
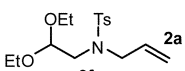
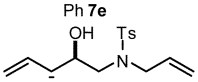
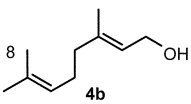
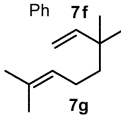
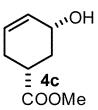
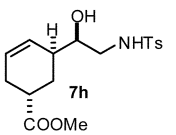
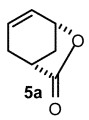
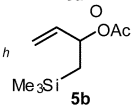
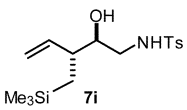
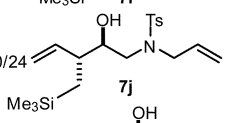
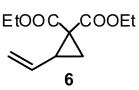
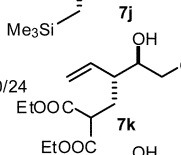
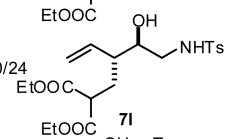
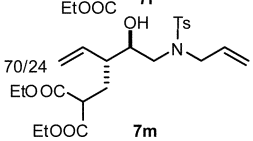
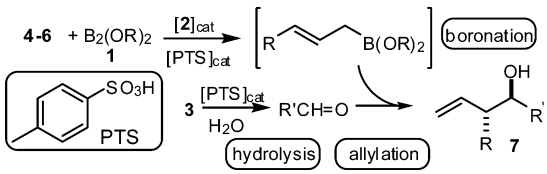
† Electronic supplementary information (ESI) available: Detailed experimental procedures and characterization of the products. ^{1}H and ^{13}C NMR spectra of the reported products. See DOI: 10.1039/b804920c

Table 1 Selective allylation of *in situ* hydrolyzed acetals with allyl alcohols, acetates and vinylcyclopropane[a]

Entry	Substrate	Acetal	Cat	Cond.[b]	Product	Yield[c]
1[d]	 **4a**	 **3a**	**2a**	50/16	 **7a**	89
2[e]	**4a**	 **3b**	**2a**	50/16	 **7b**	81
3	**4a**	 **3c**	**2a**	70/24	 **7c**	85
4[f]	**4a**	 **3d**	**2a**	70/24	 **7d**	78
5[f,g]	**4a**	**3d**	**2a**	70/24	 **8**	68
6	**4a**	 **3e**	**2a**	70/24	 **7e**	92
7	**4a**	 **3f**	**2a**	70/24	 **7f**	89
8	 **4b**	**3c**	**2a**	70/24	 **7g**	74
9	 **4c** COOMe	**3e**	**2b**	70/24	 **7h** COOMe	76
10	 **5a**	**3e**	**2b**	70/16	**7h**	73
11[h]	 **5b**	**3e**	**2b**	70/24	 **7i**	78
12[h]	**5b**	**3f**	**2b**	70/24	 **7j**	73
13	 **6**	**3d**	**2b**	70/24	 **7k**	59
14	**6**	**3e**	**2b**	70/24	 **7l**	74
15	**6**	**3f**	**2b**	70/24	 **7m**	69

[a] Unless otherwise stated allyl substrate **4–6**, **1a**, **3**, PTS (20 mol%) and catalyst **2** (5 mol%) in a mixture of DMSO/MeOH/H_2O were stirred for the times and temperatures given. [b]*Conditions*: Temperature (°C)/time (h). [c]Isolated yield. [d]5 mol% of PTS was used without any water. [e]Sequential one-pot reaction was performed. [f]50 mol% of PTS was employed. [g]After *in situ* formation of **7d** KOH was added. [h]**1b** and 20 mol% of LiOAc was employed in a sequential one-pot reaction.



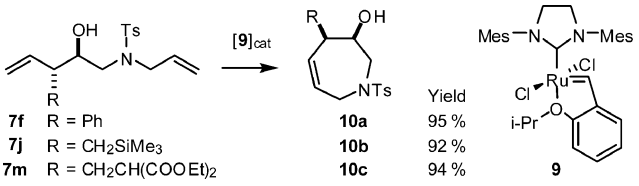
Scheme 2 Three individual reactions in a one-pot process.

the by-products are harmless boronic acid/esters and alcohols. The reaction is versatile, and it can be employed for operationally simple advanced functionalization of allylic substrates. For example, homologization of allyl alcohols (entries 3 and 8) can be performed using dimethoxy methane **3c**. This reagent is easier to handle and less toxic than formaldehyde, and the corresponding process can be performed under relatively mild conditions.

Chloro-substituted acetal **3d**, which is easy to handle and inexpensive, was employed to prepare chlorohydrins **7d** and **7k** (entries 4 and 13). Chlorohydrins are widely used to elaborate epoxide functional groups. Indeed, chlorohydrin **7d** formed by the described procedure (entry 4) can easily be converted to the corresponding epoxide **8** (entry 5) without isolation. This procedure, involving hydrolysis of **3d**, boronation of **4a**, their coupling, affording **7d** and the subsequent epoxide formation, can be considered as a four-step one-pot sequence. Protected amino aldehydes **3e,f** reacted smoothly under standard reactions conditions (entries 6–7, 9–12 and 14–15) providing ready access to various stereodefined amino alcohols **7e,f,h–j,l–m**. In this process, deprotection of the aldehyde is not necessary prior to the allylation reaction.

Although the majority of the reactions could be performed as the above described real one-pot procedure, in a few cases a sequential approach had to be applied. Acrylaldehyde formed by hydrolysis of **3b** inhibited catalyst **2**, and therefore **3b** was added after completion of the catalytic boronation process (entry 2). Likewise, silyl substituted substrate **5b** undergoes rapid Peterson elimination even under mild acidic conditions, and therefore PTS and acetals **3e** and **3f** had to be added after boronation of **5b** (entries 11 and 12). Interestingly, the corresponding allyl boronate[3d] with an allylsilane functional group is stable under the mildly acidic conditions of the acetal hydrolysis and the densely functionalized products **7i,j** are formed in high yields.

The coupling reactions work well with various allylic substrates. Both primary (**4a,b**) and secondary allyl alcohols (**4c**) can be employed, affording the homoallyl alcohol products in high yields. The reactions proceed with excellent regio- and stereoselectivity in all cases. In the reactions with **4c** and **5a**, the product comprises three stereocenters, yet **7h** could be obtained as a single diastereomer, indicating that both the boronation and allylation processes are highly selective. Because of the mild acidic reaction conditions, several functional groups, including COOR and $SiMe_3$ are tolerated. In general, allyl alcohols are the preferred substrates over allyl acetates in preparation or *in situ* formation of functionalized allyl boronates,[3a] because of the high reaction rate and simplicity of the processes. However, there are some exceptions. For example, activated acetate **5a** reacted much faster (16 h) than the corresponding alcohol **4c** yielding the same final product **7h**



Scheme 3 Synthesis of stereodefined azepines by RCM.

(24 h). As the reaction of **5a** (entry 10) is conducted in the presence of MeOH, it is reasonable to expect that **5a** is first solvolyzed to **4c** followed by the boronation and subsequent coupling process. However, the shorter reaction time required for **5a** (entry 10), *vs*. that for **4c** as substrate indicates that probably the boronation of **5a** is faster than its methanolysis to **4c**.

In the case of silyl substituted substrates, the reaction proceeded smoothly with acetate **5b** as the allyl source. However, the corresponding allyl alcohol could not be boronated because of extensive elimination reactions, even when the reaction was conducted without PTS. On the other hand, under neutral conditions **1a** was not suitable as a boronate source, and therefore in these reactions (entries 11 and 12) diboronic acid **1b** was employed. Vinylcyclopropane derivative **6** could be efficiently used as the allyl source under our typical reaction conditions (entries 13–15) affording carbethoxy functionalized homoallyl alcohols **7k–m**.

The stereo- and regiodefined products obtained in the above described operationally simple procedures are useful intermediates for advanced organic synthesis.[7] This can be demonstrated by synthesis of stereodefined heterocyclic compounds[7] from **7f, 7j** and **7m** using Hoveyda–Grubbs catalyst[8] **9** (Scheme 3). This ring closing metathesis reaction[8] does not affect the stereocenters of the dienes, thus it can be employed for synthesis of stereodefined azepines **10a–c**, which are analogs of potent glycosidase and protein kinase inhibitors.[7a]

In summary, we have devised a new one-pot procedure for allylation of *in situ* hydrolyzed acetals using simple substrates, such as allyl alcohols, acetals and vinylcyclopropane. This procedure involves three individual processes under the same reaction conditions: boronation of the allyl sources, hydrolysis of the acetals and highly selective carbon-carbon bond formation by the *in situ* generated allyl boronates and aldehydes. This sequence of cooperative processes involves three perfectly synchronized catalytic actions by PTS and palladium-pincer complex **2**. The reaction is particularly useful for *in situ* generation and application of unstable and sensitive aldehydes. The reaction has a broad synthetic scope and a high level of functional group tolerance. The produced densely functionalized homoallyl alcohols are useful building blocks for natural products and drug intermediates.

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Notes and references

1. (*a*) *Boronic Acids*, ed. D. G. Hall, Wiley, Weinheim, 2005; (*b*) J. W. J. Kennedy and D. G. Hall, *Angew. Chem., Int. Ed.*, 2003, **42**, 4732; (*c*) S. Darses and J.-P. Genet, *Chem. Rev.*, 2008, **108**, 288; (*d*) D. G. Hall, *Synlett*, 2007, 1644; (*e*) K. J. Szabó, *Synlett*, 2006, 811; (*f*) H. E. Burks and J. P. Morken, *Chem. Commun.*, 2007, 4717.
2. (*a*) L. Carosi and D. G. Hall, *Angew. Chem., Int. Ed.*, 2007, **46**, 5913; (*b*) V. Rauniyar and D. G. Hall, *Angew. Chem., Int. Ed.*, 2006, **45**, 2426; (*c*) H. Lachance, X. Lu, M. Gravel and D. G. Hall, *J. Am. Chem. Soc.*, 2003, **125**, 10160; (*d*) E. M. Flamme and W. R. Roush, *J. Am. Chem. Soc.*, 2002, **124**, 13644; (*e*) U. Schneider and S. Kobayashi, *Angew. Chem., Int. Ed.*, 2007, **46**, 5909; (*f*) S. Lou, P. N. Moquist and S. E. Schaus, *J. Am. Chem. Soc.*, 2007, **129**, 15398; (*g*) R. Wada, T. Shibuguchi, S. Makino, K. Oisaki, M. Kanai and M. Shibasaki, *J. Am. Chem. Soc.*, 2006, **128**, 7687; (*h*) R. D. Pace and G. W. Kabalka, *J. Org. Chem.*, 1995, **60**, 4838; (*i*) H. Ito, S. Ito, Y. Sasaki, K. Matsuura and M. Sawamura, *J. Am. Chem. Soc.*, 2007, **129**, 14856; (*j*) E. Canales, E. Hernandez and J. A. Soderquist, *J. Am. Chem. Soc.*, 2006, **128**, 8712.
3. (*a*) N. Selander, A. Kipke, S. Sebelius and K. J. Szabó, *J. Am. Chem. Soc.*, 2007, **129**, 13723; (*b*) V. J. Olsson and K. J. Szabó, *Angew. Chem., Int. Ed.*, 2007, **46**, 6891; (*c*) N. Selander, S. Sebelius, C. Estay and K. J. Szabó, *Eur. J. Org. Chem.*, 2006, 4085; (*d*) S. Sebelius, V. J. Olsson and K. J. Szabó, *J. Am. Chem. Soc.*, 2005, **127**, 10478; (*e*) V. J. Olsson, S. Sebelius, N. Selander and K. J. Szabó, *J. Am. Chem. Soc.*, 2006, **128**, 4588; (*f*) S. Sebelius, V. J. Olsson, O. A. Wallner and K. J. Szabó, *J. Am. Chem. Soc.*, 2006, **128**, 8150.
4. (*a*) S. D. Goldberg and R. H. Grubbs, *Angew. Chem., Int. Ed.*, 2002, **41**, 807; (*b*) J. A. Jernelius, R. R. Schrock and A. H. Hoveyda, *Tetrahedron*, 2004, **60**, 7345; (*c*) J. D. Sieber and J. P. Morken, *J. Am. Chem. Soc.*, 2006, **128**, 74; (*d*) N. F. Pelz, A. R. Woodward, H. E. Burks, J. D. Sieber and J. P. Morken, *J. Am. Chem. Soc.*, 2004, **126**, 16328.
5. (*a*) *The Chemistry of Pincer Compounds*, eds. D Morales-Morales and C. M. Jensen, Elsevier, Amsterdam, 2007; (*b*) M. Albrecht and G. van Koten, *Angew. Chem., Int. Ed.*, 2001, **40**, 3750; (*c*) M. E. v. d. Boom and D. Milstein, *Chem. Rev.*, 2003, **103**, 1759; (*d*) J. Dupont, C. S. Consorti and J. Spencer, *Chem. Rev.*, 2005, **105**, 2527; (*e*) R. B. Bedford, *Chem. Commun.*, 2003, 1787. For synthesis of **2a,b** see ref 3*a* and; (*f*) Q. Yao, E. P. Kinney and C. Zheng, *Org. Lett.*, 2004, **6**, 2997; (*g*) J. Dupont, N. Beydoun and M. Pfeffer, *J. Chem. Soc., Dalton Trans.*, 1989, 1715.
6. (*a*) J. Min, Y. Na, H. Han and S. Chang, *Chem. Soc. Rev.*, 2004, **33**, 302; (*b*) J.-C. Wasilke, S. J. Obrey, R. T. Baker and G. C. Bazan, *Chem. Rev.*, 2005, **105**, 1001; (*c*) D. E. Fogg and E. N. d. Santos, *Coord. Chem. Rev.*, 2004, **248**, 2365; (*d*) G. Poli and G. Giambastini, *J. Org. Chem.*, 2002, **67**, 9456; (*e*) C. Kammer, G. Prestat, T. Gaillard, D. Madec and G. Poli, *Org. Lett.*, 2008, **10**, 405.
7. (*a*) I. Nakamura and Y. Yamamoto, *Chem. Rev.*, 2004, **104**, 2127; (*b*) A. Fürstner and O. R Thiel, *J. Org. Chem.*, 2000, **65**, 1738; (*c*) H. Li, Y. Blériot, C. Chantereau, J.-M. Mallett, M. Sollugoub, Y. Zhang, E. Rodríguez-García, P. Vogel, J. Jiménez-Barbero and P. Sinaÿ, *Org. Biomol. Chem.*, 2004, **2**, 1492; (*d*) H. K. Lee, J. H. Im and S. H. Jung, *Tetrahedron*, 2007, **63**, 3321.
8. (*a*) T. M. Trnka and R. H. Grubbs, *Acc. Chem. Res.*, 2001, **34**, 18; (*b*) S. B. Garber, J. S. Kingsbury, B. L. Gray and A. H. Hoveyda, *J. Am. Chem. Soc.*, 2000, **122**, 8168.

