VIP Homologation Very Important Paper

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Stereocontrolled Synthesis of 1,5-Stereogenic Centers through Three-Carbon Homologation of Boronic Esters**

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Abstract: *Allylic pinacol boronic esters are stable toward 1,3-borotropic rearrangement. We developed a Pd^{II}-mediated isomerization process that gives di- or trisubstituted allylic boronic esters with high E selectivity. The combination of this method with lithiation–borylation enables the synthesis of carbon chains that bear 1,5-stereogenic centers. The utility of this method has been demonstrated in a formal synthesis of (+)-jasplakinolide.*

Polyketide natural products are replete with carbon chains that bear 1,5-stereogenic centers connected by alkyl, di- or tri-substituted alkenyl groups (Figure 1).[1] Numerous ingenious

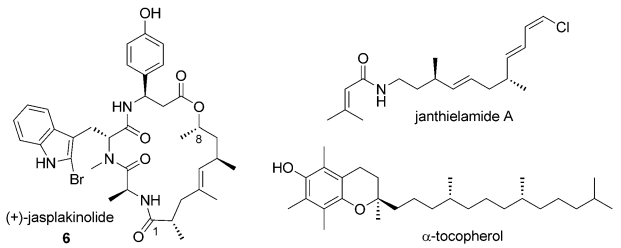
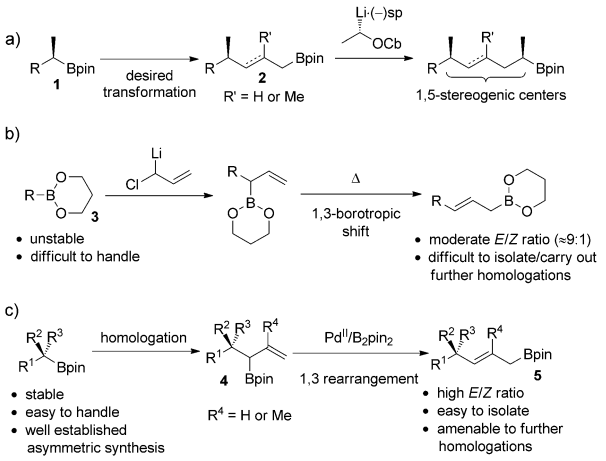


Figure 1. Examples of natural products that contain 1,5-stereogenic centers.

strategies have been devised for the synthesis of these natural products, but control of the double-bond geometry, especially in the case of tri-substituted alkenyl groups, can sometimes be challenging.[2] Recently, lithiation–borylation has emerged as a powerful tool to control the stereochemistry along a carbon chain and to build up multiple stereogenic centers with high stereocontrol.[3] In order to use lithiation–borylation to create compound arrays that bear 1,5-stereogenic centers, a three-carbon homologation of boronic ester **1** to an allylic boronic ester intermediate **2** would be required, which would then be set up for further homologations (Scheme 1 a). While there was one report of a three-carbon homologation of a boronic



Scheme 1. 1) Proposed strategy for the stereocontrolled synthesis of 1,5-stereogenic centers. 2) Previous work: Brown's three-carbon homologation of propylene glycol boronic esters. 3) This work: three-carbon homologation of pinacol boronic esters. pin = pinacol, Cb = N,N-diisopropylcarbamoyl, sp = (−)-sparteine.

ester, this homologation required the use of unstable and difficult-to-handle propylene glycol boronic esters **3** (Scheme 1 a).[4] Furthermore, these substrates perform poorly in lithiation–borylation processes, thus limiting their use in asymmetric synthesis. In contrast, pinacol boronic esters perform well in lithiation–borylation processes, and so we needed to find conditions under which such esters could be employed in three-carbon homologations.

In order to achieve our goal, we needed to 1) carry out a homologation to give allylic boronic ester **4** followed by 2) a diastereoselective 1,3-borotropic shift to give boronic ester **5** (Scheme 1 c). Both steps presented challenges. First of all, we needed to establish a general and efficient protocol for the homologation of a broad range of pinacol boronic esters to allylic boronic esters **4**.[5] Secondly, conditions for the key 1,3-borotropic shift needed to be identified to maximize the reaction efficiency and more importantly to control the olefin geometry. It is important to note that while less sterically hindered allylic boronic esters (and boranes)[6] are known to undergo a 1,3-borotropic shift upon heating, pinacol allylic boronic esters have been shown to be thermally stable.[7] Despite the limited precedence, we initiated a research program aimed at addressing this challenge, anticipating that its solution would be highly useful for the synthesis of many relevant molecules. Herein we describe the first three-carbon homologation of pinacol boronic esters, introducing a di- or tri-substituted alkenyl unit with high stereocontrol over the double-bond geometry. This methodology was

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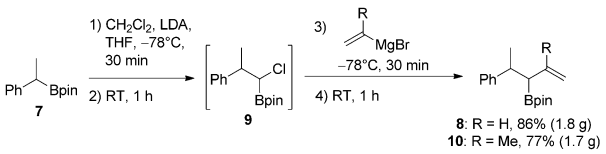
applied to the stereocontrolled synthesis of carbon chains that bear 1,5-stereogenic centers and to a formal synthesis of the natural product (+)-jasplakinolide (**6**).

We began our study by investigating the direct homologation of boronic ester **7** to allylic boronic ester **8** using 1-chloroallyllithium. Unfortunately, while this process had worked well for tertiary pinacol boronic esters,[5a] it worked poorly for secondary pinacol boronic esters, giving mixtures of the starting material, the desired product, and over-homologated products.[8] We then designed a two-step, one-pot protocol that consists of 1) a Matteson homologation[9] with dichloromethyl lithium to give **9**, followed by 2) the in situ treatment with vinyl magnesium bromide (Scheme 2). This procedure routinely gave boronic ester **8** in high yield and could be easily carried out on multi-gram scale. We also successfully applied this process to the synthesis of β-methyl-containing substrates **10** by using isopropenyl magnesium bromide in the second step. Furthermore, this protocol uses readily available and nontoxic reagents in contrast to previous methods.[5b,c]

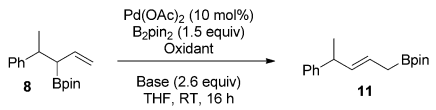


Scheme 2. One-pot Matteson homologation/alkylation of boronic ester **7**.

Having developed a very efficient method for the synthesis of **8**, we next examined the key 1,3 rearrangement (Table 1). We initially tested thermal and microwave conditions and confirmed that the 1,3-borotropic shift of the pinacol boronic ester does not occur. An alternative method was then required in order to achieve our goal. We drew inspiration from previous syntheses of allylic boronic esters through the Pd^0-catalyzed borylation of allylic carbonates[10] and allylic alcohols[11] with B_2pin_2. These reactions are believed to occur through the reductive elimination of a Bpin-bound π-allyl–Pd^{II} intermediate and generally result in high *E* selectivity. We reasoned that access to this intermediate directly from **8** by using a novel Pd^{II}-catalytic cycle would enable the required 1,3 rearrangement without the need for further manipulation of the boronic ester (e.g. oxidation and acylation). We turned this hypothesis into practice by treating boronic ester **8** with $Pd(OAc)_2$ and B_2pin_2. Under these reaction conditions, the rearranged product **11** was formed in an encouraging conversion of 12%, but a poor *E*/*Z* ratio (Table 1, entry 1). During these experiments, we observed the precipitation of catalytically inactive Pd black out of the solution. We reasoned that a stoichiometric oxidant may be required in order for the Pd to turn-over (see below). We were pleased to find that the addition of $CuCl_2$ gave **11** in good yield and remarkably high *E* selectivity (Table 1, entry 2). Further screening showed that the addition of basic Na_2HPO_4 was beneficial, thus leading to **11** essentially as a single diastereoisomer in high yield. Furthermore, the catalyst loading could be reduced to 2.5 mol% (Table 1, entry 3). A control experiment without $Pd(OAc)_2$ resulted in decomposition of **8**, product **11** was not observed (Table 1, entry 4; see the Supporting Information for full optimization details).

With this two-step, three-carbon homologation procedure in hand, we evaluated the scope of the process by testing a broad range of primary, secondary, and tertiary pinacol boronic esters (Table 2), all of which gave the desired allylic boronic esters with very high *E* selectivity.

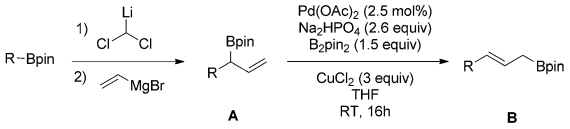
Table 1: Optimization of reaction conditions for the 1,3 rearrangement of boronic ester **8**.

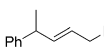
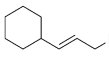
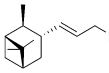
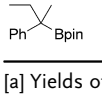
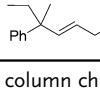


Entry	Oxidant ([equiv])	Base	Conv.[a] [%]	Yield[b] [%]	*E*/*Z* ratio[a]
1	–	–	12	n.d.	1:1
2	$CuCl_2$ (3)	–	100	57	>95:5
3[c]	**$CuCl_2$ (3)**	**Na_2HPO_4**	**100**	**94 (79)**	**>95:5**
4[d]	$CuCl_2$ (3)	Na_2HPO_4	–	–	n.d.

[a] Determined by GC-MS of the crude reaction mixture. [b] Determined by ^1H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard (yield of isolated product in parentheses). [c] 2.5 mol% $Pd(OAc)_2$. [d] No $Pd(OAc)_2$ was used. Entry in bold marks optimized reaction conditions. n.d. = not determined.

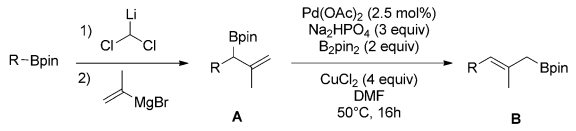
Table 2: Substrate scope.

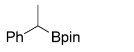
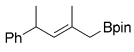
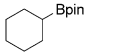
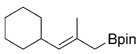
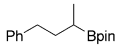
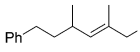
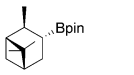
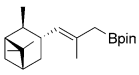
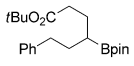
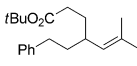
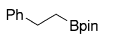
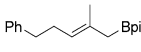
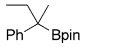
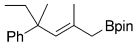


Substrate	Yield of **A** [%][a]	Yield of **B** [%][a]	*E*/*Z*[b]	Product
	86	79	>95:5	
	77	72	>95:5	
	86	84	>95:5	
	72	50	>95:5	
	65	64	>95:5	
	86	76	95:5	
	73[c]	79[d]	>95:5	

[a] Yields of isolated products after purification by column chromatography. [b] Determined by GC-MS of the crude reaction mixture. [c] Homologation carried out using 1-chloro allyllithium.[5a] [d] Reaction carried out for 4 days at RT.

Table 3: Substrate scope for β-methyl substituted allylic boronic esters.



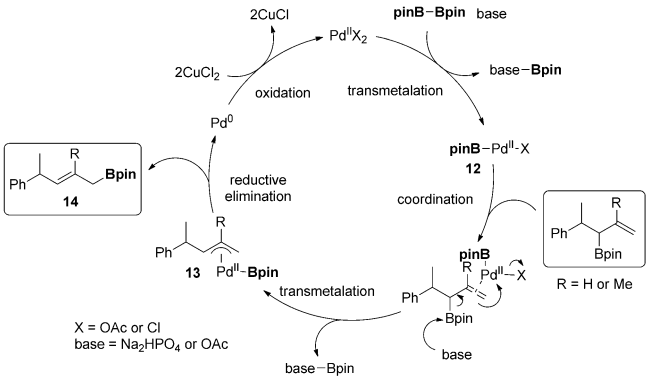
Substrate	Yield of **A** [%][a]	Yield of **B** [%][a]	*E*/*Z*[b]	Product
	77	79	>95:5	
	82	44[c]	>95:5	
	88	61	>95:5	
	67	68	>95:5	
	59	52[c]	>95:5	
	83	65	91:9	
	96[d]	49[c,e]	>95:5	

[a] Yields of isolated products after purification by column chromatography. [b] Determined by GC-MS of the crude reaction mixture. [c] 1.5 equiv B_2pin_2 and 2.6 equiv Na_2HPO_4 were used.[13] [d] Homologation carried out using 1-chloro-methallyl-lithium.[5a] [e] Reaction heated at 80 °C.

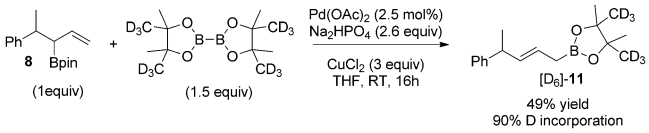
A highly diastereoselective 1,3 rearrangement could also be achieved for β-methyl-substituted boronic esters (Table 3). The optimization of the reaction conditions for these sterically more demanding and challenging substrates showed that heating to 50 °C and increasing the amount of reagents was required to achieve a full conversion. Changing the solvent from THF to DMF was necessary to maintain a high *E*/*Z* selectivity (see the Supporting Information for further details of the screening). Again this methodology worked well for a broad range of primary, secondary, and tertiary pinacol boronic esters, giving high *E*/*Z* ratios throughout. This methodology enabled the diastereoselective synthesis of a range of β-methyl-substituted allylic boronic esters, of which only a few examples have been reported to date.[12]

The proposed mechanism for the 1,3 rearrangement is shown in Scheme 3. A transmetalation between B_2pin_2 and $Pd(OAc)_2$ gives the Bpin-bound Pd^{II} intermediate **12**.[14] Coordination of Pd^{II} to the alkene of the substrate followed by base-aided transmetalation gives the key π-allyl-Pd^{II} intermediate **13**.[15] Reductive elimination[10a,11c] to give allylic boronic ester **14** followed by oxidation of Pd^0 back to Pd^{II} by $CuCl_2$ completes the cycle. We believe that the origin of the high *E*/*Z* selectivity is the preference of the π-allyl intermediate **13** to adopt an *E* configuration to minimize $A^{1,3}$ strain.

To determine whether the Bpin incorporated in the product originated from the external B_2pin_2 that was added or from the starting material, we carried out the 1,3 rearrangement using deuterium-labeled B_2pin_2 (Scheme 4). Treatment of boronic ester **8** and $[D_{12}]$-B_2pin_2 under the



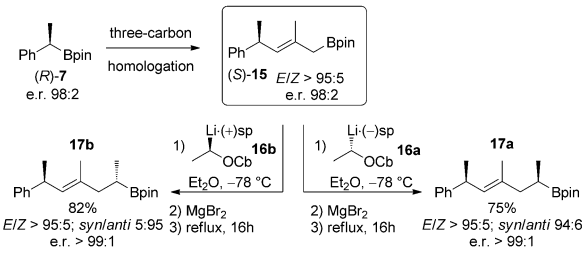
Scheme 3. Proposed mechanism of 1,3 rearrangement.



Scheme 4. Deuterium labeling study.

standard optimized conditions for the 1,3 rearrangement gave boronic ester $[D_6]$-**11** with 90% incorporation of D, thus showing that the Bpin incorporated in the product originated from the external B_2pin_2. Analysis of the crude reaction mixture by GC-MS showed that the excess of B_2pin_2 left at the end of the reaction was a mixture of $[D_{12}]$-B_2pin_2 and $[D_6]$-B_2pin_2, which is believed to be the source of 10% of the nondeuterated boronic ester **11** (see the Supporting Information for full details as well as further details of mechanistic studies).

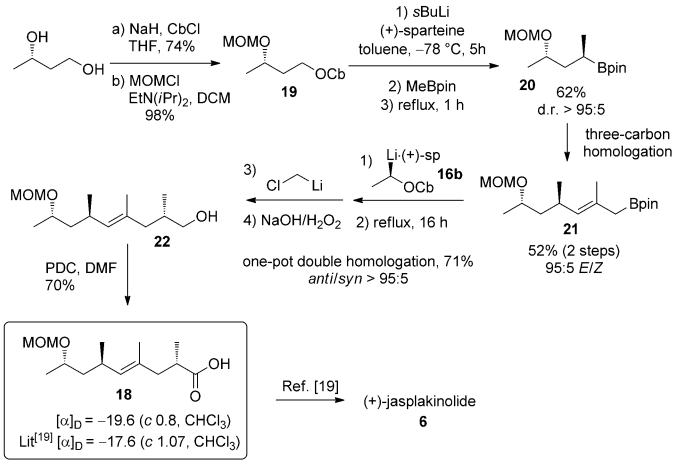
We then illustrated the power of this methodology by the diastereoselective synthesis of carbon chains that bear 1,5-stereogenic centers (Scheme 5). First of all we confirmed that our three-carbon homologation was compatible with enantioenriched substrates by preparing allylic boronic ester (*S*)-**15** from chiral boronic ester (*R*)-**7**[16] with no erosion of stereochemistry. Homologation of boronic ester (*S*)-**15** with lithiated carbamate **16a** gave *syn*-boronic ester **17a** in good yield and a d.r. of 94:6. The *anti* diastereomer **17b** was prepared in a similar yield and selectivity by carrying out the same homologation, but using the opposite enantiomer of



Scheme 5. Synthesis of boronic esters that contain 1,5-stereogenic centers.

lithiated carbamate **16b**, which is easily prepared by using (+)-sparteine[17] in place of (−)-sparteine. As we have access to both enantiomers of boronic ester **7**, this gives us the potential to easily make all four stereoisomers of boronic ester **17** at will.

To demonstrate the synthetic utility of our three-carbon homologation methodology, we carried out a synthesis of the C_{1-8} polyketide fragment **18** of (+)-jasplakinolide **6** (Scheme 6).[1b] Our synthesis began from commercially available (*S*)-(+)-1,3-butane diol by the selective carbamoylation of the



Scheme 6. Synthesis of carboxylic acid **18**.

primary alcohol followed by MOM protection of the secondary alcohol to give **19**. Lithiation–borylation of **19** with MeBpin gave **20** with high levels of selectivity. Subsequent three-carbon homologation worked well, giving allylic boronic ester **21** in good yield and an *E*/*Z* ratio of 95:5. Homologation with lithiated carbamate **16b**, followed by Matteson homologation[18]/oxidation gave alcohol **22** in 71% yield and excellent *anti*/*syn* selectivity in a one-pot double homologation sequence. Final oxidation with PDC completed the synthesis of carboxylic acid **18**, a known intermediate in the synthesis of (+)-jasplakinolide,[19] in just seven steps from (*S*)-(+)-1,3-butane diol. It is important to note that all of the stereogenic centers are formed under reagent control, and thus the same reaction sequence can potentially be applied to the synthesis of any of the eight stereoisomers of carboxylic acid **18**.

In summary, we have developed the first procedure for a three-carbon homologation of pinacol boronic esters. This method enables the highly diastereoselective synthesis of 1,5-related stereogenic centers along a carbon chain connected by di- or tri-substituted alkenes, a ubiquitous motif in natural products. This methodology was applied to a short synthesis of the C_{1-8} polyketide fragment of (+)-jasplakinolide.

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Keywords: 1,5-stereocenters · allylic boronic esters · asymmetric synthesis · lithiation–borylation · palladium

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[2] This is especially the case when RCM is employed. For a review, see: A. Fürstner, *Science* **2013**, *341*, 1229713. In the specific case of (+)-jasplakinolide, prepared by ring-closing metathesis, an approximately 1:1 mixture of *E*/*Z* isomers was obtained: a) R. Tannert, T.-S. Hu, H.-D. Arndt, H. Waldmann, *Chem. Commun.* **2009**, 1493 – 1495; b) R. Tannert, L.-G. Milroy, B. Ellinger, T.-S. Hu, H.-D. Arndt, H. Waldmann, *J. Am. Chem. Soc.* **2010**, *132*, 3063 – 3077.

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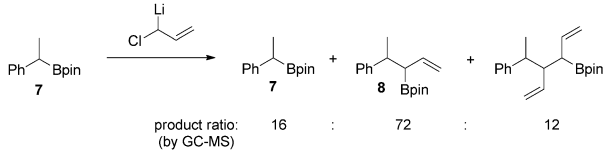

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