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ω-Alkenylallylboronates: Design, Synthesis and Application to the Asymmetric Allylation / RCM Tandem Sequence

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Dedicated to Professor Santos Fustero

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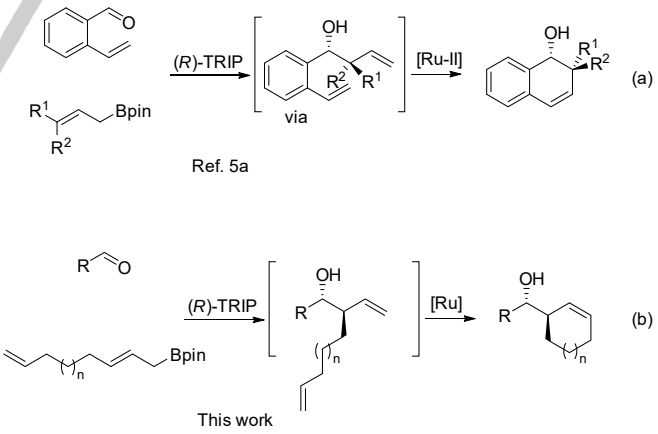
Abstract: the synthesis of allylboronates bearing an alkenyl moiety appended at a remote position is described for the first time. For that aim, the palladium-catalyzed borylation of the corresponding allylic alcohols was used as the key step. The required allylic alcohols were in turn obtained in 3-4 step sequences. The presence of an extra alkenyl moiety at a strategic position allows triggering a tandem asymmetric allylation/RCM reaction sequence that efficiently affords different sized cycles featuring two consecutive stereocenters and an exocyclic alcohol function. Products are obtained in moderate to excellent yields and high enantioselectivities, in most of the cases.

The asymmetric construction of cyclic backbones from acyclic precursors represents a longstanding challenge in organic synthesis. The simultaneous control over both endo- and exocyclic stereocenters results in an especially difficult task. Among stereoselective methodologies, the allylboration of carbonyl compounds shows a number of interesting features due to the highly ordered chair-like transition state that accounts for a stereospecific transformation rendering complete control over the relative configuration of the two contiguous stereocenters set up when the allylborating reagent bears substitution at the γ-position.[1,2] In 2010, Antilla described for the first time the chiral Brønsted acid-catalyzed asymmetric allylboration of aldehydes.[3,4] During the following decade, a number of synthetic applications were developed by others and us.[5] Among them, our first contribution in the fied described the tandem allylboration / ring-closing metathesis (RCM) reaction sequence for the asymmetric construction of cyclic homoallylic alcohols (Scheme 1a).[5a] For that aim, an extra alkenyl functionality was introduced in a strategic remote position of the aldehyde counterpart. Thus, different sized carbocycles bearing one or two endocyclic stereocenters were achieved in high yields and excellent diastereo- and enantioselectivities, in most cases. The viability of the relay catalysis process Brønsted acid catalyzed asymmetric allylboration / RCM reaction sequence allowed us to envision a new related process, described herein (Scheme 1b).[6,7] Following this, in 2015, we described for the first time the use of an allylboronate bearing an extra functionality pending at the γ position.[8] Since then, other groups have shown interest in this field giving rise to a number of interesting synthetic applications.[9] Herein, the introduction of an extra alkenyl functionality in a remote position of the allylboronate instead of the aldehyde results in the formation of two contiguous stereocenters, now one endocyclic and the second exocyclic. Moreover, for this new process the alcohol function would occupy an exocyclic position.



Scheme 1. Precedents and new strategy.

Our first challenge was the synthesis of the hitherto unknown ω-alkenylallylboronates **1**.[10] Building upon our own experience,[8] we decided to rely on an allylic alcohol borylation of commercially available (*E*)-octa-2,7-dien-1-ol **2a** (Scheme 2).[11] The key allylic borylation afforded model substrate **1a** in moderate yield (Scheme 2). It is worth noting that despite the starting allylic alcohol **2a** was used as a 6:1 mixture of *E*/*Z* isomers product **1a**

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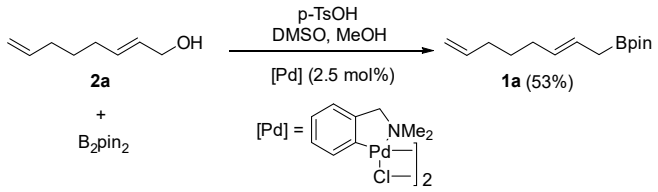
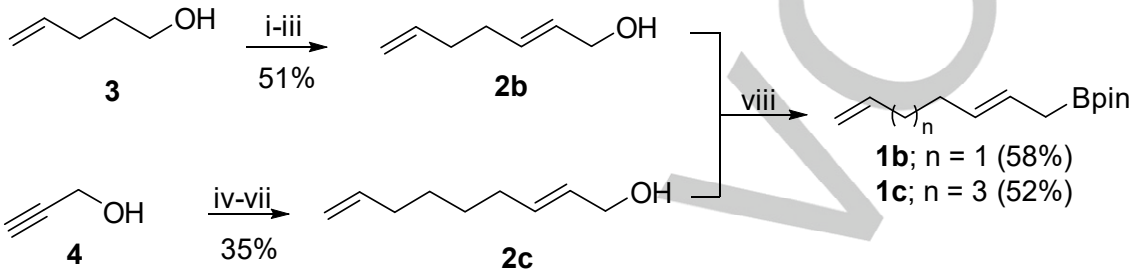
was obtained exclusively as the corresponding *E*-isomer. This result may be explained by the intermediacy of a palladium π-allyl complex responsible for the observed stereochemistry scrambling.[12]

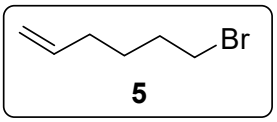


Scheme 2. Synthesis of model substrate.

Once the viability of the synthesis of the allyborating agent **1a** was stablished, we aimed to synthesize other ω-alkenylallylboronates **1b,c** that would afford other ring sizes. First, the synthesis of this previously unknown allylboronate class will be outlined (Scheme 3). The precursors for 5- and 7-membered carbocycles **1b,c** were both synthesized by allylic borylation of the corresponding known ω-alkenylallylic alcohols **2b,c** which were in turn prepared from commercially available 4-penten-1-ol **3** and propargyl alcohol **4** in three and four steps, respectively (Scheme 3).[14,15]

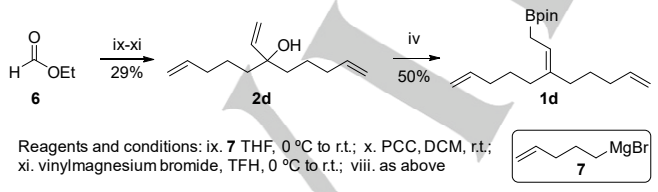


Reagents and conditions: i. DMSO, oxallyl chloride, CH_2Cl_2,Et_3N, -78ºC; ii. Ph_3P=C(H)CO_2Me; iii. DIBAL-H, CH_2Cl_2,-78ºC,2h; iv. DHP, PTSA (5% mol), CH_2Cl_2, 0ºC to rt; v. n-BuLi, THF, 0 ºC / **5**, DMSO; vi.p-TsOH, MeOH; vii. $LiAlH_4$, THF, 0 ºC then reflux; viii. B_2pin_2, [Pd] (2.5 mol%), DMSO/MeOH, p-TsOH, 50 ºC



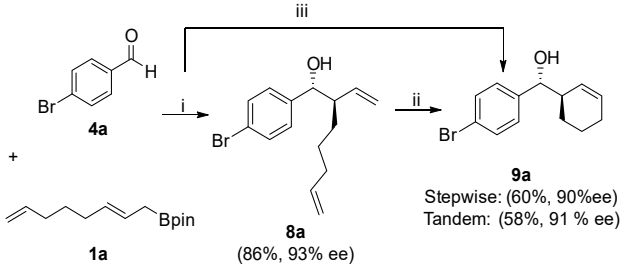
Scheme 3. Synthesis of ω-alkenylallylboronates **1b,c**.

Trying to increase the complexity of our tandem process, we designed bis ω-alkenylallylboronate **1d** (Scheme 4). We envisioned that the presence of two alkenyl chains in the open chain intermediate may result in a diastereoselective RCM subsequent step, that could be regarded as a pseudodesymmetrization process. **1d** was obtained in moderate yield using otherwise identical conditions that for the rest of the allylboronates **1a-c** using alcohos **2d**. **2d** was in turn synthesized in three simple steps starting from ethyl formate **6** (Scheme 4).



Scheme 4. Synthesis of ω-bisalkenylallylboronate **1d**.

With model substrate **1a** in our hands, we evaluated the viability of our asymmetric allylation / RCM strategy, first in a stepwise manner. To our delight, the allylboration step afforded product **8a** in good chemical yield, as a single diastereoisomer and in high enantioselectivity without modifying the standard conditions ((*R*)-TRIP, toluene, - 30 ºC).[13] Similarly, the RCM using second generation Grubbs' catalyst ([Ru-II]) afforded final product **9a** in moderate yield and with a minor erosion of the optical purity (Scheme 5). Our experience allowed us being optimistic about success of the one-pot transformation under relay catalysis conditions. Indeed, when the reaction is conducted in the presence of both catalysts at -30 ºC in toluene overnight, followed by stirring at room temperature for 6 extra hours, product **9a** is obtained in an improved yield and enantioselectivity (Scheme 5). It is worth noting that our methodology gives rise to the *threo* diastereoisomer that is the minor diastereoisomer formed in the allylation of carbonyl compounds using either classic cyclic allylmetal additions[16] or in a more recent photoredox asymmetric allylation with cyclic alkanes.[17]



Reagents and conditions: i. (R)-TRIP (5 mol%), toluene, -30ºC, overnight ii. [Ru-II] (5 mol%), rt iii.(R)-TRIP / [Ru-II] (5 mol%), toluene, -30ºC, overnight then rt

Scheme 5. Validation of both the stepwise and the relay catalysis strategies.

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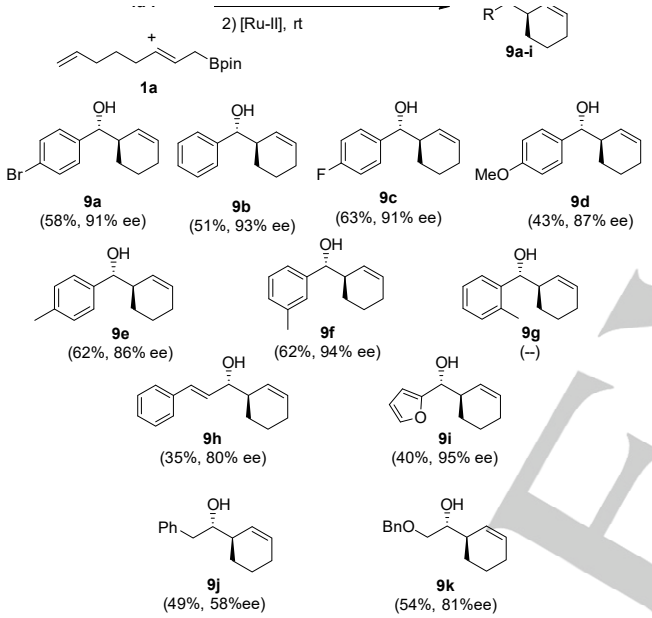
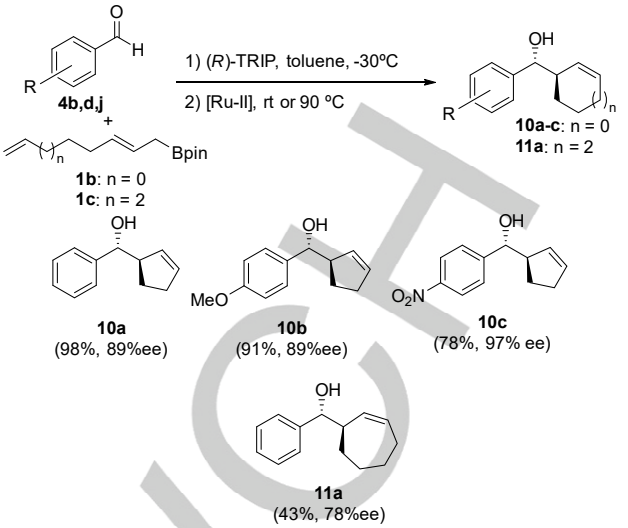
Once our relay catalysis strategy has been stablished, we turned to study the scope of this new transformation (Scheme 6). Aromatic aldehydes bearing both electron-withdrawing (**9a,c**) and electron-donating substituents (**9d**) afforded the product in good yield and high enantioselectivity (Scheme 6). Regarding substitution pattern, while the introduction of substituents at the para and metha positions did not compromise chemical yield neither enantioselectivity (**9e,f**), the presence of a substituent in the ortho position completely inhibited the reaction (**9g**) (Scheme 6). Moreover, alkenyl as well as heteroaromatic aldehydes could also be succesfully employed (**9h,i**). While the use of cinnamaldehyde resulted in a moderate drop both in chemical yield and enantioselectivity (**9h**), furfuraldehyde behaved very well in terms of enantiocontrol, although the yield was also moderately lower (**9i**) (Sheme 6). Finally, aliphatic aldehydes were also used affording the corresponding products (**9j,k**) in moderate yields and enantioselectivities (Scheme 6).



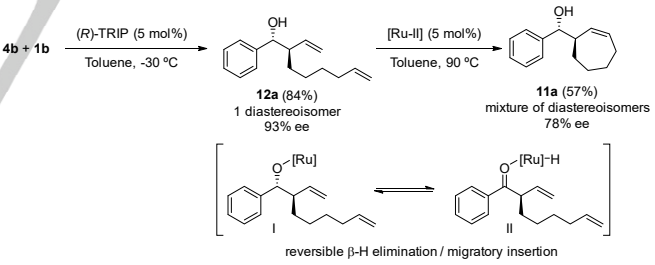
Scheme 6. Scope for the asymmetric allylation/ RCM tandem process using **1a**.

Next, the extension of the asymmetric allylboration/RCM tandem sequence was explored using the new ω-alkenylallylboronates **1b,c** (Scheme 7). Reagent **1b** successfully afforded five-membered products **10a-c** in excellent yields and high enantioselectivities (Scheme 7). Seven-membered derivative **11a** was obtained starting from reagent **1c** in moderate yield and enantioselectivity as mixture of diastereoisomers (Scheme 7).



Scheme 7. Use of ω-alkenylallylboronates **1b,c** in the asymmetric allylboration/RCM tandem sequence.

We believe that the decreased enantioselectivity observed for seven-membered rings may be explained by the higher temperature at which the RCM step must be conducted in these cases (Scheme 7). The ability of ruthenium species to catalyze transfer hydrogenation reactions is well-documented.[18] We believe that the formation of a ruthenium alcoxyde ***I*** may result in a reversible β-hydride elimination / migratory insertion sequence, accounting for the loss in stereochemical integrity. In order to shed some light on this issue, the corresponding ring-opened intermediate was isolated. To our delight, intermediate **12a** was obtained in high yield, as a single diastereoisomer and in an excellent 93% ee, showing that the erosion of optical purity observed was due to the RCM step, as expected (Scheme 8).



Scheme 8. Study of the loss of optical integrity in seven-membered ring derivatives **10a,b**.

Finally, we challenged our methodology towards the asymmetric allylboration / psudodesymmetring RCM tandem process using bisalkenylated allylboronate **1d**. Unfortunately, the final product **13** was obtained in low yield, a moderate 5:1 diastereomeric ratio and a poor 36% ee (Scheme 9). Noteworthy, this is one of the rare examples of chiral Børnsted acid-catalyzed allylboration using a γ,γ-disubstituted boronate.[19] This fact may account both for the low reactivity and the poor enantioselectivity obtained.

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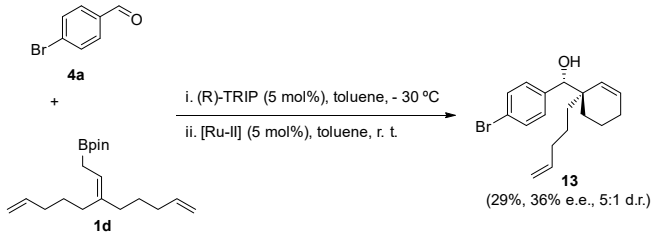

Scheme 9. Use of ω-alkenylallylboronate **1d** in the asymmetric allylboration/RCM tandem sequence.

In conclusion, allylboronates functionalized at a remote position with an extra alkenyl moiety have been synthesized for the first time, using a unified strategy based on the borylation of the corresponding dienyl allylic alcohols. Their participation in a tandem chiral Brønsted acid-catalyzed allylboration / ring-closing metathesis tandem process has then been studied affording several sized-cyclic alcohols, bearing the hydroxyl group at an exocyclic position. The corresponding 5- and 6-membered analogs are obtain in good chemical yields, as single diastereosimers and in high ee's. However, 7-membered rings are obtained with poorer results, due to the high temperature required for RCM in this case that results in partial epimerization. The use of a bis alkenylated allylboronate does not allow to carry out the pseudo desymmetrization of the two chains efficiently. Further efforts aimed at the synthesis of heterocyclic derivatives are currently under study and will be reported in due course.

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Keywords: asymmetric allylborylation • ring-closing metathesis • relay catalysis • functionalized allylboronates

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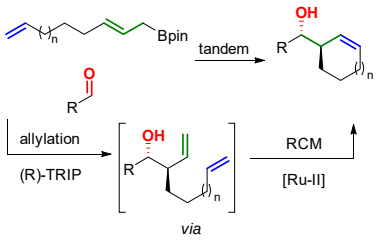

The synthesis of ω-alkenylallylboronate derivatives is described for the first time. In addition, their performance in the chiral Brønsted acid-catalyzed allylboration / RCM tandem sequence is studied. Hence, cyclic alcohols displaying the hydroxyl functionality at an exocyclic position and two consecutive stereocenters are obtained as single diastereoisomers and in high degree of enantioselectivity, in most of the cases.

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