Organic LETTERS

Letter

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Synthesis of Functionalized Cyclic Boronates

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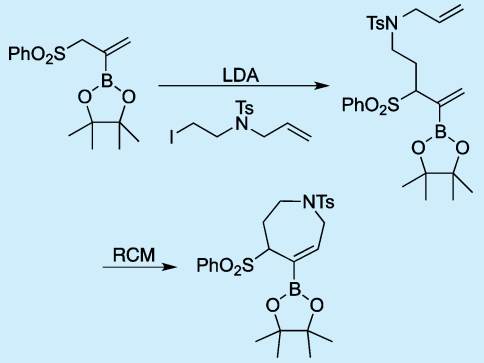
Supporting Information

ABSTRACT: Deprotonation of a simple borylated allylic sulfone and subsequent alkylation with certain unsaturated electrophiles provide substrates that are easily converted into functionalized alkenyl boronates with ring sizes from five- to seven-membered. A Chan—Lam reaction on one such substrate afforded an alkoxyallylic sulfone that was readily converted via a (4 + 3)-cycloaddition to a polycycle possessing the ABC ring substructure of ingenol.



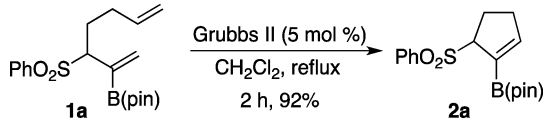
In recent work, we demonstrated that allyl sulfones bearing a boronic ester at the 2-position could be alkylated without decomposition of the Lewis acidic boron moiety.[1] The ability of the boronic ester to tolerate anion formation permitted the synthesis of alkylated products that could undergo further transformations. We were able to demonstrate in a single case that the alkylation product **1a** could be cyclized under metathesis conditions to produce the cyclopentene **2a** in very high yield. However, it was not known whether the scope of that process would permit a more general development of the reaction and whether we could begin to apply such products to synthetic chemistry. In this work, we demonstrate that functionalized cyclic systems bearing alkenylboron species are generated via ruthenium-catalyzed ring-closing metathesis (RCM) of alkylated products with good generality such that access to five- through seven-membered rings is almost always possible.

While inspired to pursue this study for a number of reasons, we were particularly interested in using relatively simple chemistry to prepare value-added chemicals in short order. Uniquely structured organoboron compounds and boronates in particular are in demand due to the popularity and power of the Suzuki—Miyaura coupling reaction,[2] whose application in organic synthesis is well-known and continuing to grow.

We began our studies with the readily available alkylation products derived from **3**.[1] Our initial attempts at generalizing the process leading to **2a** began with application of the reaction conditions depicted in Scheme 1 to other substrates. The results are summarized in Table 1.

Synthesis of the cyclohexene **2b** from **1b** proceeded uneventfully using the conditions that formed **2a**, but the yield was lower (Table 1, entry 1). Increasing the catalyst loading from 5% to 10% had little effect on the reaction outcome. For **1c**, under these "standard" reaction conditions, only starting material and the product of alkene isomerization

Scheme 1. RCM of a Boronate



and RCM, product **2b**, were obtained. It was clear that a more robust protocol for RCM was needed to effect the transformation. Increasing the reaction temperature to 110 °C (refluxing toluene) and using the Hoveyda—Grubbs second generation catalyst **4b**[3] led to complete conversion of starting material to the undesired isomerization product **2b** in 80% yield.

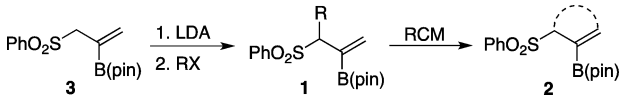
Perusal of the literature revealed that the likely cause of our problem was due to formation of ruthenium hydride species that catalyzed olefin isomerization.[4] The isomerization could be suppressed by addition of a catalytic amount of an oxidant. Using 10% benzoquinone in conjunction with **4b** allowed the formation of the seven-membered ring product **2c**; however, the isomerization product **2b** was still prevalent. After considerable experimentation, it was found that, for substrate **1c**, 2 equiv of the oxidant were required to block the formation of **2b** completely. An effort to increase the yield by dilution resulted in a stalled reaction with only partial conversion of starting material.

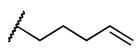
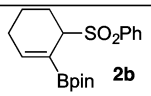
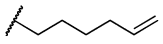
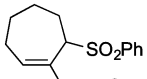
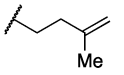
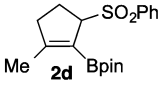
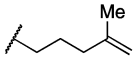
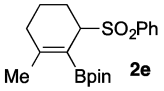
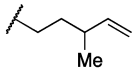
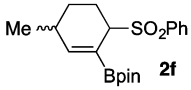
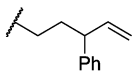
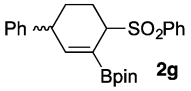
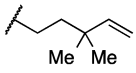
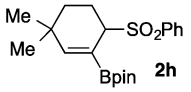
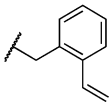
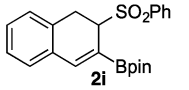
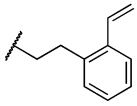
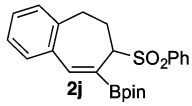
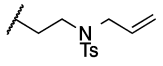
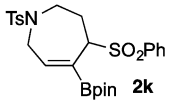
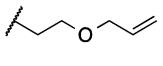
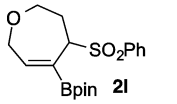
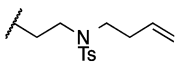
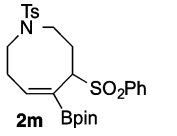
With a set of conditions in hand that effectively promoted ring closure of our less reactive olefins, we subjected a group of substrates to these conditions. Formation of trisubstituted cyclopentene **2d** was possible (Table 1, entry 3). However, formation of the corresponding cyclohexene (**2e**) failed (Table 1, entry 4). The creation of cyclohexenyl boronates bearing

Received: October 17, 2013
Published: December 5, 2013

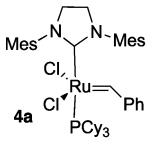
   dx.doi.org/10.1021/ol4029918 | *Org. Lett.* 2014, 16, 3–5

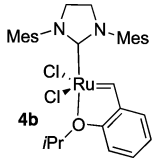
Table 1. RCM of Borylated Allylic Sulfones



entry	SM	R	product	yield (%)
1	**1b**		 **2b**	70[a]
2	**1c**		 **2c**	80[b]
3	**1d**		 **2d**	78[b]
4	**1e**		 **2e**	0[b]
5	**1f**		 **2f**	78[b]
6	**1g**		 **2g**	80[b]
7	**1h**		 **2h**	90[b]
8	**1i**		 **2i**	95[b]
9	**1j**		 **2j**	80[b]
10	**1k**		 **2k**	93[b]
11	**1l**		 **2l**	0[b]
12	**1m**		 **2m**	0[b]

[a]A 0.1 M solution of diene in CH_2Cl_2 was purged with argon and added to a pressure tube with 5 mol % of **4a**. The tube was sealed with a Teflon coated cap and heated for 2 h at 45 °C. [b]A 0.005 M solution of diene in toluene was purged with Ar and added to a pressure tube with 10 mol % of **4b**. The tube was sealed with a Teflon-coated cap and heated at 110 °C for 24 h.

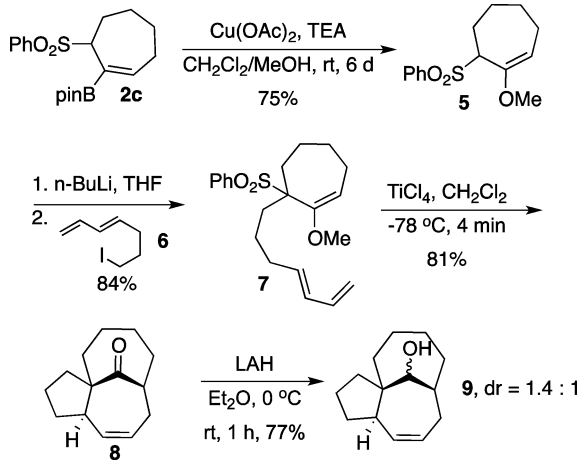




allylic substituents was very successful (Table 1, entries 5–7). Indeed, the yields of all of the products in these cases were higher than that of **2b**, likely as a consequence of conformational effects in the starting materials.[5] The synthesis of benzo-fused six- and seven-membered ring boronates also proceeded in high yield (Table 1, entries 8–9). Attempts to prepare heterocyclic boronates gave mixed results. While the synthesis of azepine derivative **2k** proceeded very well, the corresponding oxepine could not be prepared, starting material being largely recovered on attempts to effect the RCM of **1l**. While problems associated with metathesis reactions in systems bearing allylic heteroatoms are known,[6] this outcome was a surprise. Similar results were realized in the attempted RCM of **1m**, the eight-membered ring analogue of **2k** (Table 1, entry 12). It was also interesting to find no evidence of dimerization for either **1l** or **1m**. This suggests a lack of reactivity or sequestration of catalyst that is rapid and irreversible.

We were curious about the possibility of using cyclic boronates as precursors to cyclic alkoxyallylic sulfones, compounds we had developed as progenitors of alkoxyallylic cations that serve as dienophiles in intramolecular (4 + 3)-cycloaddition reactions.[7] To that end, treatment of **2c** with methanol in the presence of copper acetate afforded **5** in good yield, though the reaction was slow (Scheme 2).[8] Attempts to speed up the process resulted in lower yields of product. Another method exists to prepare compounds like **5**, but generally affords a lower yield of the desired seven-membered ring.[9] Deprotonation of **5** and alkylation with **6** afforded **7** in good yield. Activation of **7** with $TiCl_4$ gave an 81% yield of **8** as the primary product of the reaction.[10] The relative stereochemistry of the reaction was established by X-ray analysis of one of the stereoisomers of the reduction product **9**. This compound possesses a portion of the carbocyclic structure of ingenol, though it lacks the proper "in–out" stereochemistry of the natural product.[11]

Scheme 2. From Cyclic Boronate to (4 + 3)-Cycloadduct

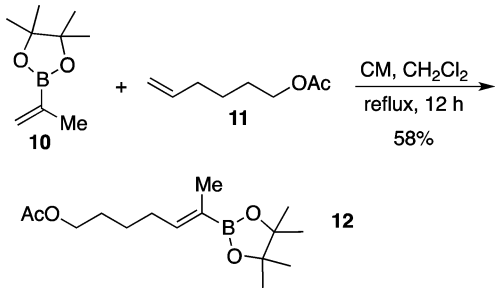


We also investigated the ability of sulfone **3** to undergo metathesis in an intermolecular fashion. Grubbs and co-workers reported that boronate **10** could undergo cross-metathesis with simple olefins in fair yields (Scheme 3).[12]

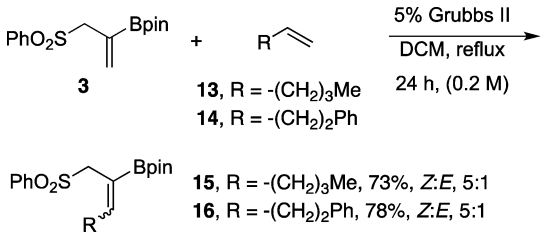
Under identical conditions, we found that **3** engaged productively in cross-metathesis with terminal, unfunctionalized monoolefins to produce products in good yield, but with low stereoselectivity. For example, using 1-hexene (**13**) and 4-phenyl-1-butene (**14**), the corresponding products **15** and **16** were isolated in 73% and 78% yield, respectively, as mixtures of stereoisomers (ca. 5:1 *Z*/*E*) (Scheme 4). However, all attempts to engage alkenes bearing allylic alcohol, allylic ether, allylic

dx.doi.org/10.1021/ol4029918 | *Org. Lett.* 2014, 16, 3–5

Scheme 3. Cross-Metathesis of a Vinyl Boronate

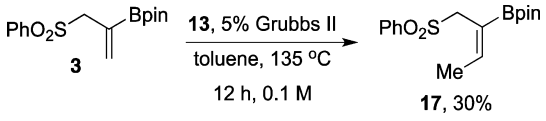


Scheme 4. Successful Cross-Metatheses of 3



amine, or protected amine functional groups in the reaction failed. Finally, it is worth mentioning that under harsher conditions, rapid isomerization of the olefin occurred, leading to the unexpected product **17** (Scheme 5). The fact that under

Scheme 5. Unusual Cross-Metathesis of 3



these conditions only the product **17** could be isolated suggests that isomerization, steric effects, and thermodynamic control favor the least substituted product possible. This is either starting material or the product shown, derived from the isomerized alkene.

In conclusion, we have developed a route to functionalized, cyclic boronates via a ring-closing metathesis reaction. While acknowledging some limitations, the preparation of precursors and execution of the ring closure is simple and should make available a much wider array of value-added boronates than those reported here. Further development of the process and applications of the chemistry are in development. Results will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, and copies of ^{1}H and ^{13}C NMR spectra. X-ray data on reduction product of **8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the National Science Foundation and the Department of Chemistry at the University of Missouri—Columbia. We thank Frontier Scientific for a gift of the precursor to **3**. We thank Materia for a gift of several metathesis catalysts. We thank Dr. Charles L. Barnes (Missouri—Columbia) for acquisition of X-ray data. We thank Ms. Carissa S. Hampton (Missouri—Columbia) for assistance in preparing this manuscript. Dedicated to the memory of Andrew Harmata (November 9, 1924–October 1, 2013).

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