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Enantioselective Synthesis of (*Z*)-1,2-*anti*-2,5-*anti*-Triol Monosilyl Ethers Using a Cross-Metathesis Allylboration Sequence

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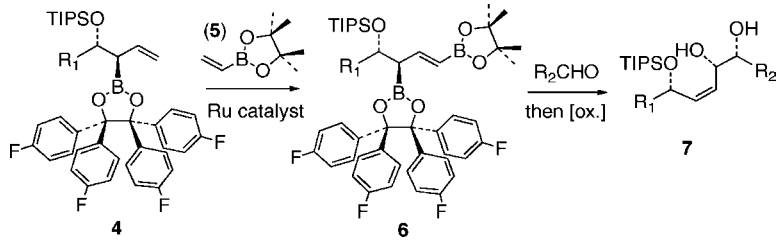
ABSTRACT



The enantioselective synthesis of (*Z*)-1,2-*anti*-2,5-*anti*-triol monosilyl ethers via a two-step sequence involving olefin cross-metathesis of *β*-alkoxyallylboronate 4 and subsequent allylboration of the derived bisboryl intermediate 6 provides triol monoethers 7 with good to excellent diastereoselectivity.

Stereodefined 1,2,5-triol subunits are present in many biologically active natural products. The zooxanthellamides, stagonolides, and annonaceous acetogenins are three classes of natural products in which this moiety is found.[1]

The boron-mediated allylation reaction has proven to be an important method for carbon−carbon bond formation.[2] This reaction proceeds with predictable control of stereochemistry via cyclic, chairlike transition states and has been widely applied in the synthesis of natural products. In recent years, our laboratory has focused on developing higher-order applications of the allylboration reaction in which two C−C bond forming events are performed in a single operation with a bifunctionalized allylboron reagent (i.e., the double allylboration reaction).[3,4] One limitation to this methodology, which provides 1,5-diols with excellent stereochemical control, is the general difficulty of synthesizing reagents that enable placement of additional substituents on the 1,5-diol scaffold as a direct result of the double allylboration event.

In an effort to expand the utility of the double allylboration reaction, we imagined that manipulation of the terminal olefin of boronate ester **3** via cross metathesis might provide a means to introduce additional functional-

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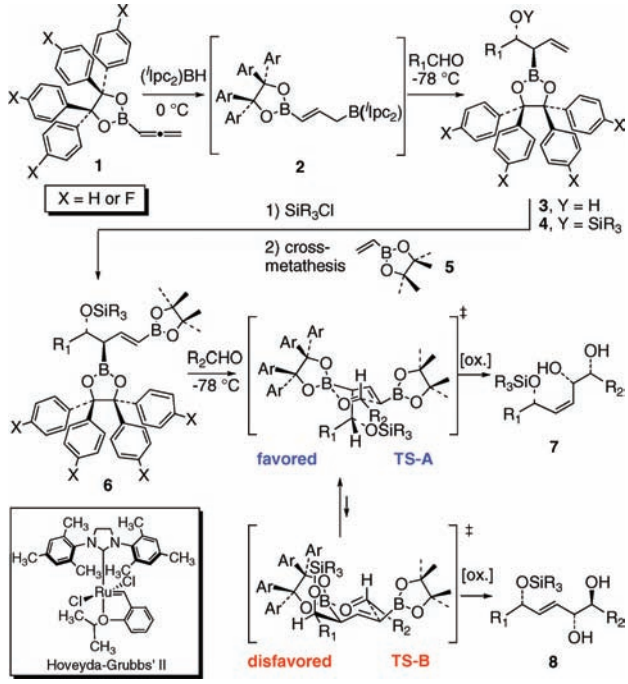
Scheme 1. Allylboration-Cross-Metathesis Allylation Sequence



ity (Scheme 1).[5] Owing to our long-standing interest in the synthesis of polyhydroxylated natural products,[6] we concentrated on metathesis partners that would enable us to access 1,2-*anti*-2,5-*anti* triols of type **7**. Specifically, we studied the cross metathesis reactions of silyl ether protected allylboronates **4** and pinacol vinyl boronate (**5**), which is a well-established metathesis coupling partner.[7] Accordingly, we report herein a highly diastereoselective synthesis of (*Z*)-1,2-*anti*-2,5-*anti*-1,2,5-triols **7** by the sequence summarized in Scheme 1.

Allylboronate **3a** ($R_1 = CH_2CH_2Ph$, X = H) was synthesized via the hydroboration of allene **1a** (X = H) with $^{l}Ipc_2BH$ followed by treatment of allylboronate **2** with hydrocinnamaldehyde at −78 °C.[3a,8] Initial attempts to effect cross metathesis reactions of silyl ethers **4a** (derived from **3a**) with pinacol vinylboronate **5** using Grubbs' second generation catalyst were unsuccessful.[9] The lack of reactivity was attributed to the steric bulk associated with the tetraphenyl-substituted dioxaborolane unit of **4a** ($R_1 = CH_2CH_2Ph$, X = H), along with the bulky pinacol boronate ester of the coupling partner **5**. Therefore, we turned to use of the more robust Hoveyda-Grubbs' second generation catalyst[10] in order to accommodate the increase in reaction temperature necessary to effect the cross metathesis reaction. However, treating a mixture of **4a** ($R_1 = CH_2CH_2Ph$, X = H, $-SiR_3$ = TBS), **5** and the second generation Grubbs-Hoveyda catalyst in toluene at 80 °C led to olefin 14−24% isomerization of **4a** to the corresponding vinylboronate after 24 h, presumably due to a Ru−H species generated in situ upon decomposition of the ruthenium catalyst.[11] Following an extensive screening of additives to suppress the olefin isomerization, tetrafluoro-1,4-benzoquinone was selected as the most effective reagent to prevent this side reaction.[12]

A third variable that had to be optimized to maximize selectivity for the (*E*)-olefin geometry in the cross metathesis product **6** is the size of the alcohol protecting group. Because it is known that steric bulk at the allylic position generally enhances selectivity for the (*E*)-olefinic metathesis product,[13] we studied the cross metathesis of a series of silyl ethers generated from **3a** ($R_1 = PhCH_2CH_2$, X = H) (Table 1).

Table 1. (*E*)-Selectivity in the Cross-Metathesis Reactions of Silyl Ether Derivatives of Allylboronate **3a**

entry[a]	R_3Si	*E*/*Z* ratio in **5**[b]
1	TMS	3:1
2	TES	6:1
3	TBS	8:1
4	TBDPS	16:1
5	TIPS	≥20:1

[a] Reactions were performed by treating silyl ethers derived from allylboronate **3a** ($R_1 = CH_2CH_2Ph$, X = H; 1.0 equiv) and pinacol vinyl boronate **5** (1.5 equiv) with the 2nd generation Hoveyda-Grubbs catalyst in toluene (0.5 M) at 80 °C for 24 h in the presence of tetrafluoro-1,4-benzoquinone (0.10 equiv). [b] Olefin geometry in **6** was determined by ^1H NMR analysis of the crude product.

These experiments led to the identification of the TIPS ether as the alcohol protecting group that gives greatest selectivity for (*E*)-**6**.

The results of cross-metathesis reactions of a range of allylboronate substrates are summarized in Table 2. In all cases, the selectivity for the (*E*)-olefinic product was excellent (≥20:1). Most of these reactions provided the vinylboronate products **6a**−**k** in 60−75% yield, along with some recovered **4a**−**k**. Presumably, these reactions did not proceed to

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(6) For representative examples, see: (a) Roush, W. R.; Straub, J. A.; VanNieuwenhze, M. S. *J. Org. Chem.* **1991**, *56*, 1636. (b) Roush, W. R.; Grover, P. T. *Tetrahedron* **1992**, *48*, 1981. (c) Hunt, J. A.; Roush, W. R. *J. Org. Chem.* **1997**, *62*, 1112. (d) Roush, W. R.; Hartz, R. A.; Gustin, D. J. *J. Am. Chem. Soc.* **1999**, *121*, 1990. (e) Heo, J.-N.; Holson, E. B.; Roush, W. R. *Org. Lett.* **2003**, *5*, 1697.

(7) (a) Morrill, C.; Grubbs, R. *H J. Org. Chem.* **2003**, *68*, 6031. (b) Blackwell, H. E.; O'Leary, D. J.; Chatterjee, A. K.; Washenfelder, R. A.; Bussman, D. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 58. (c) Esteban, J.; Costa, A. M.; Vilarrasa, J. *Org. Lett.* **2008**, *10*, 4843. (d) White, B. H.; Snapper, M. L. *J. Am. Chem. Soc.* **2003**, *125*, 14901. (e) Nicolaou, K. C.; Li, A.; Edmonds, D. J.; Tria, G. S.; Ellery, S. P. *J. Am. Chem. Soc.* **2009**, *131*, 16905.

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(9) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *38*, 2416.

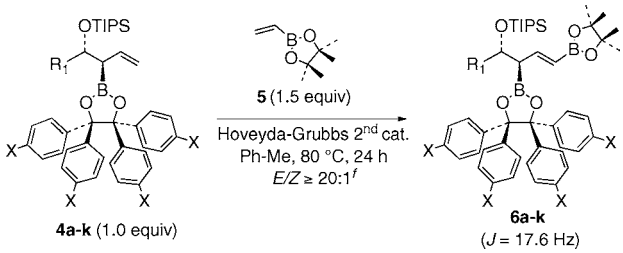
(10) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem.* **2000**, *122*, 8168.

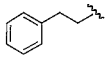
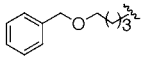
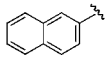
(11) (a) Hong, S. H.; Wenzel, A. G.; Salguero, T. T.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2007**, *129*, 7961. (b) Hong, S. H.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2004**, *126*, 7414.

(12) Hong, S. H.; Sanders, D. P.; Lee, C. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2005**, *127*, 17160.

(13) Grubbs, R. H. *Handbook of Metathesis*; Wiley-VCH: Weinheim Germany, 2003; Vol. 2.

Table 2. Cross-Metathesis Reactions of Allylboronates **4a**−**k**



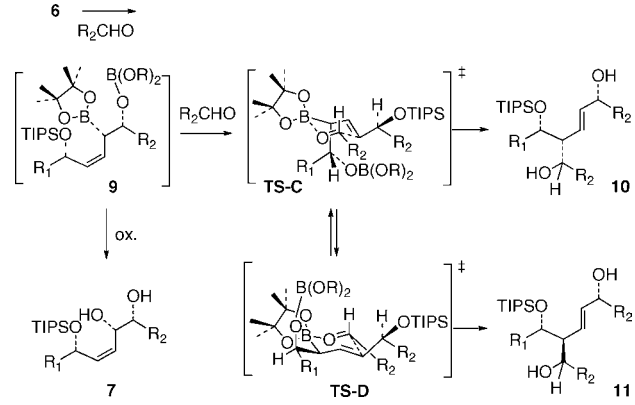
entry	R_1	product	catalyst (mol %)	additive[c] (mol %)	yield[d] / brsm[e] (%) (%)
1		**6a**[a]	10 10	10 none	56 / (90) 51 / (–)
		6b[b]	10 12	10 none	61 / (82) 74 / (–)
2		**6c**[b]	10	10	50 / (57)
3	TBDPSO 	**6d**[b]	10	10	69 / (87)
4		**6e**[b]	10	10	67 / (80)
5		**6f**[b]	10	none	52 / (–)
6		**6g**[b]	10 10	8 none	55 / (71) 67 / (–)
7		**6h**[b]	10 10	10 none	46 / (61) 88 / (–)
8		**6i**[b]	10 15	10 none	74 / (83) 75 / (–)
9		**6j**[b]	10 10	10 none	45 / (54) 43 / (–)
10		**6k**[b]	10	none	67 / (–)

[a] X = H. [b] X = F. [c] Tetrafluorobenzoquinone was added to prevent olefin isomerization. [d] Isolated yields of **6a**−**k**. [e] Yield based on recovered starting material. [f] Olefin geometry determined by ^{1}H NMR analysis of the crude reaction products.

completion owing to the high steric demands of the cross coupling partners—a consequence of the TIPS ether used to maximize selectivity for the (*E*)-olefin product in the metathesis reaction.

At the outset, we anticipated that the allylboration reactions of **6** would proceed via the chairlike transition state **TS-A** (see Scheme 1) with the α-silyloxy carbon chain residing in an axial position to avoid nonbonded steric interactions with the tetraphenyl-1,3,2-dioxaborolane unit of the reagent, which become quite significant in the alternative (disfavored) transition state **TS-B**.[3a] Accordingly, it was anticipated that this allylboration sequence would provide (*Z*)-1,2-*anti*-2,5-*anti*-1,2,5-triol monoethers **7** with excellent selectivity following oxidative workup. However, we recognized that a third allylboronate, **9**, would be produced in the allylboration of reactions of **6**, and that **9** could, in principle, react with a second equivalent of the aldehyde partner to provide double allylboration products of type **10** or **11** (Scheme 2). Indeed,

Scheme 2. Allylboronate Intermediate **9** May Undergo a Second Allylboration



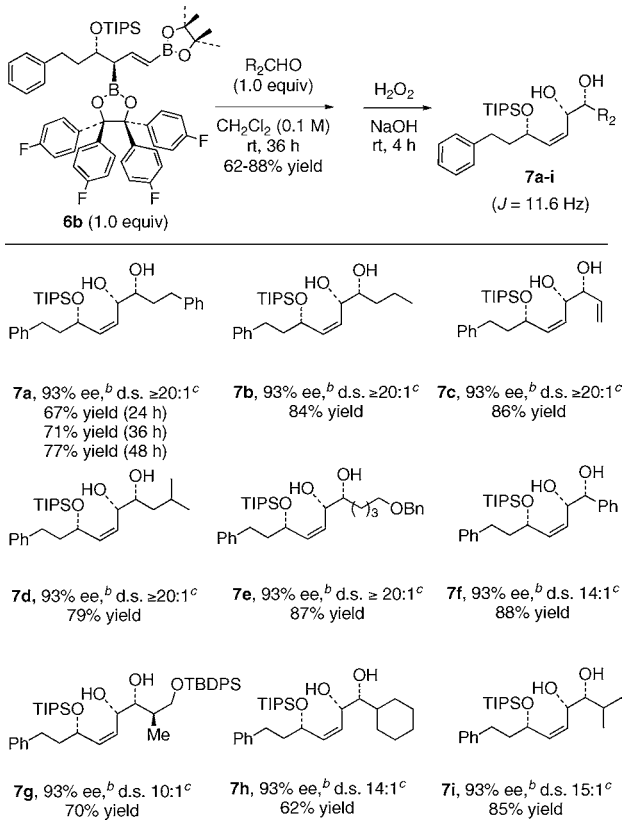
in experiments performed using **6a** (with the para substituent X = H), mixtures of **7** (major) and **10/11** were obtained when **6a** was treated with 1.0 equiv of aldehydes at various reaction temperatures and concentrations (data not shown). These results indicated that the reactivities of **6a** and **9a** (X = H) toward aldehydes are comparable.

Consequently, we directed our attention to adjusting the reactivity of the allylboronate functional group in **6** relative to that of the intermediate allylboronate species **9**. Based on earlier studies in which we observed that a *p*-nitrophenyl substituent on a 1,3,2-dioxaborolane increased the Lewis acidity of the allylboronate and correspondingly increased the rate of its reaction with aldehydes, compared to the parent allylboronate with a phenyl-substituted dioxaborolane,[14] we synthesized the tetra-*p*-fluorophenyl substituted allylboronate **6b** (X = F) by a sequence paralleling that used for the synthesis of **6a** (X = H). Treatment of **6b** with hydrocinnamaldehyde in CH_2Cl_2 (0.1 M) for 24 h, and subsequent workup with H_2O_2 and NaOH afforded triol **7a** in 67% yield with ≥20:1 d.s. Increasing the allylboration reaction period to 36 h provided **7a** in 71% yield, and while after 48 h the yield of **7a** was 77% (see Scheme 3). In all cases, the double allylboration products **10/11** were not observed. Thus, this proof of principle experiment established that the inductive effect of the *p*-fluoro substituents increased the reactivity of **6b** such that allylboration reactions of intermediate **9** were no longer competitive.

The scope of allylboration reactions of **6b** with additional aldehydes is presented in Scheme 3, and results of allylboration reactions of **6c**, **d**, **f**, **g** and **j** with hydrocinnamaldehyde are presented in Scheme 4. In the vast majority of cases (the one exception being the reaction of **6b** with hydrocinnama-

(14) Roush, W. R.; Banfi, L.; Park, J. C.; Hoong, L. K. *Tetrahedron Lett.* **1989**, *30*, 6457.

Scheme 3. Allylboration Reactions of **6b**—Scope of Aldehyde Substrates



[a] Unless indicated otherwise, all allylboration reactions were performed for 36, h at ambient temperature. [b] Determined by advanced Mosher ester analysis. [c] Diastereomer ratio determined by ^{1}H NMR analysis of the crude product.

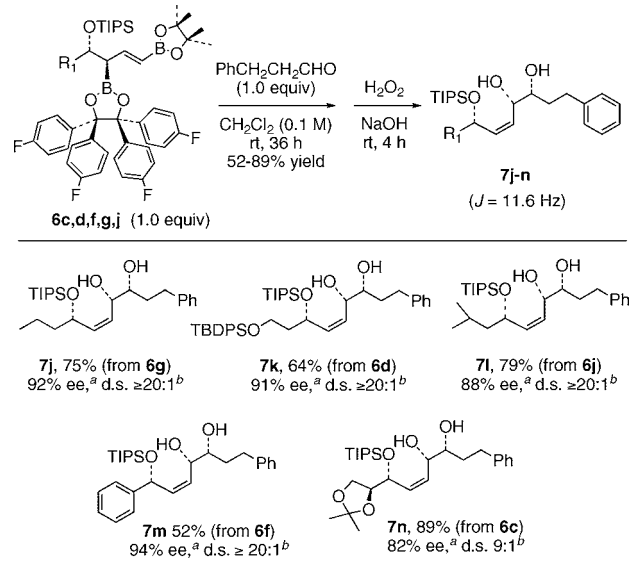
ldehyde in Scheme 3), the reactions were performed at ambient temperature for 36 h. The triol monoethers **7** were obtained in 52−89% yield, 82−93% e.e., and ≥14:1 d.s. for all examples except **7g** (10:1 d.s., Scheme 3) and **7n** (9:1 d.s., Scheme 4).

The relative and absolute stereochemistry of the triol monoethers presented in Schemes 3 and 4 were assigned via advanced Mosher ester analysis of the corresponding MPTA esters.[15,16]

(15) (a) Hoye, T. R.; Jeffrey, C. S.; Feng, S. *Nature Protoc.* **2007**, *2*, 2451. (b) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092. (c) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1968**, *90*, 3732.

(16) See Supporting Information for data.

Scheme 4. Allylboration Reactions of **6c**, **6d**, **6f**, **6g** and **6j** with Hydrocinnamaldehyde



[a] Determined by advanced Mosher ester analysis. [b] Diastereomer ratio determined by ^{1}H NMR analysis of the crude reaction product.

In summary, the allylboration-cross metathesis-allylboration sequence presented in Scheme 1 constitutes a convergent and highly enantio- and diastereoselective method for synthesis of (*Z*)-1,2-*anti*-2,5-*anti*-triol monosilyl ethers **7** with synthetically useful efficiency. This new method represents an expansion of our double allylboration methodology,[3] and defines a strategy for introduction of substituents at positions internal to the 1,5-diol motif. Applications of this new method in the synthesis of natural products, along with further extensions of the double allylboration methodology, are in progress and will be reported in due course.

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Supporting Information Available: Experimental procedures and tabulated spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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