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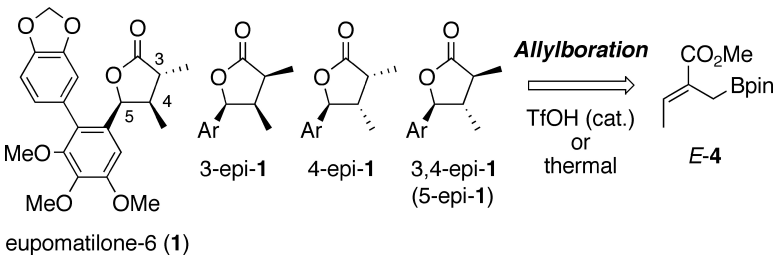
J. Am. Chem. Soc., **2005**, 127 (37), 12808-12809• DOI: 10.1021/ja054171l • Publication Date (Web): 25 August 2005



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Brønsted Acid-Catalyzed Allylboration: Short and Stereodivergent Synthesis of All Four Eupomatilone Diastereomers with Crystallographic Assignments

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Recent reports have highlighted the efficiency of simple Brønsted acids, notably, triflic acid, as catalysts that can facilitate difficult organic reactions and expand their substrate scope.[1] Contrary to the expectation that allylic boronates would undergo undesired processes, such as oligomerization or protodeboronation,[2] here, we report the surprising findings that triflic acid efficiently catalyzes the addition of deactivated allylboronates to aldehydes. This novel procedure was applied to the synthesis of all four diastereomers of eupomatilone-6 (**1**, Figure 1), a member of a structurally intriguing class of lignans isolated from the indigenous Australian shrub *Eupomatia bennettii*.[3] Eupomatilones exist under ambient conditions as equilibrating couples of biaryl atropisomers. Previous synthetic studies have raised ambiguities on the relative stereochemistry of the lactone's three substituents,[4−6] as originally assigned by NMR spectroscopy.[3] Our route to all four diastereomers of **1**, supported with thorough X-ray crystallographic evidence, provides closure on the eupomatilones' stereochemical determination.

The allylation of aldehydes with 2-alkoxycarbonyl allylboronates leads to α-*exo*-methylene γ-lactones reminiscent of the lactone unit of the eupomatilones.[7−12] These deactivated allylboronates, however, add very slowly under thermal conditions and require reaction temperatures over 100 °C. To optimize product yield in the addition of prototype allylboronate **2** to benzaldehyde (Table 1), we investigated the use of Lewis acids[9] and strong Brønsted acids. All Lewis acids tested, including $Sc(OTf)_3$ (entry 6), gave a slower reaction, and the superiority of bis(triflamide) and triflic acid in providing higher conversions was quickly evident. Also noteworthy is the concomitant lactonization of the intermediate hydroxy ester, which is most likely promoted by the acid catalyst. Due to easier handling of a liquid reagent, triflic acid was chosen for further optimization. The TfOH-catalyzed reaction was investigated at a lower temperature in view of using sensitive aldehydes. For example, reaction of **2** with hydrocinnamaldehyde, an aliphatic enolizable aldehyde, provided a high yield of lactone product at 0 °C (not shown). Further fine-tuning of reaction parameters and substrate stoichiometry led to the conditions of entry 8. Next, the addition of (*E*)-3-methyl allylboronate **4**[13] to 3,4,5-trimethoxybenzaldehyde (**5**), a combination of model substrates relevant to the eupomatilones, was tested under the optimal conditions (eq 1). The electron-rich, deactivated aldehyde **5** was found to be inert. To our surprise, however, the 2-bromo analogue **6**[14] reacted smoothly to give lactone **7**. To explain this key result, we speculate that the *ortho*-bromo substituent increases the electrophilicity of **6** by twisting the carbonyl group out of conjugation with the arene's π system and its deactivating methoxy substituents.

More intriguing is the *trans* stereochemistry of the lactone product, which is opposite to that expected from the allylboronate's *E* geometry. From **7**, heterogeneous hydrogenation led to **8** as the major diastereomer (Scheme 1). On the other hand, homogeneous hydrogenation conditions using Wilkinson's catalyst provided **10** as the major diastereomer (separable from **8**). This excellent level of selectivity in the reduction of the *exo*-methylene unit can be explained by C5 control in the case of heterogeneous conditions, with the catalyst's surface avoiding the face of the molecule bearing the remote but large C5 aryl group. With the smaller Wilkinson catalyst, the facial selectivity is controlled by the adjacent C4 methyl. Despite their double *ortho* substitution, both **8** and **10** were coupled very efficiently with commercial boronic acid **9** under Buchwald's conditions[15] to give 3,4-*epi*-**1** and 4-*epi*-**1**, respectively. All other attempted conditions and catalysts failed in this notoriously difficult substitution pattern for a Suzuki biaryl cross-coupling.

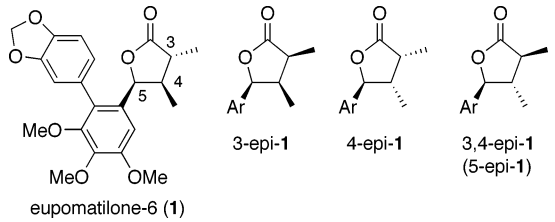
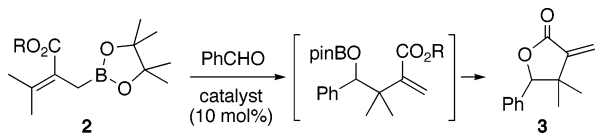


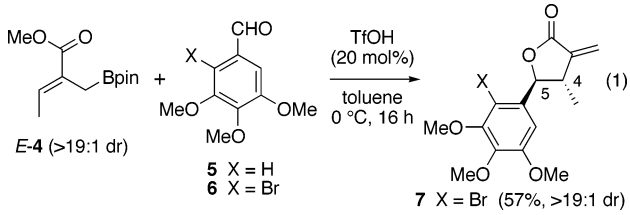
Figure 1. Eupomatilone-6 and its three unnatural diastereomers.

Table 1. Optimization of a Model Brønsted Acid-catalyzed Reaction between Deactivated Allylboronate **2** and Benzaldehyde[a]



entry	equiv of PhCHO	catalyst	conditions	yield (%)[b]
1	0.9	none	toluene, rt, 24 h	<5
2	0.9	CF_3CO_2H	toluene, rt, 24 h	77
3	0.9	Tf_2NH	toluene, rt, 24 h	99
4	0.9	TfOH	toluene, rt, 24 h	99
5	0.9	TfOH	toluene, 0 °C, 16 h	78
6	0.9	$Sc(OTf)_3$	toluene, 0 °C, 16 h	<5
7	1.5	TfOH	toluene, 0 °C, 16 h	96
8	2.0	TfOH	toluene, 0 °C, 16 h	99

[a] Standard conditions: reaction scale, approximately 0.4 mmol of allylboronate, 1.0 M solution. Entries 1−4, R = Et; entries 5−8, R = (−)-menthyl. [b] Isolated yields. pin = pinacolato ($OCMe_2CMe_2O$).



To access the two other diastereomers, a thermal allylboration between (*E*)-**4** and **6** was required (Scheme 2).[8] Unlike the TfOH-

† X-ray Crystallography Laboratory.

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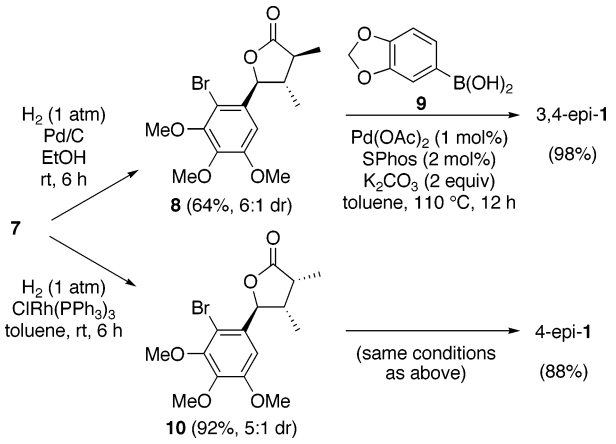
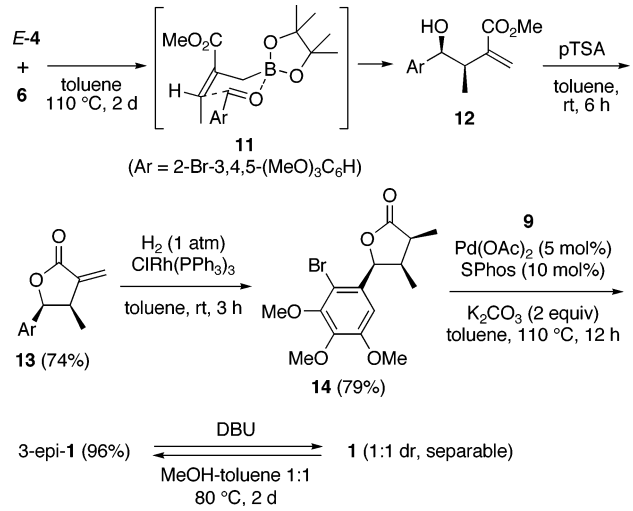
Scheme 1. Syntheses of 3,4-*epi*-**1** and 4-*epi*-**1**



Scheme 2. Syntheses of 3-*epi*-**1** and **1**



catalyzed variant, this reaction proceeded without isomerization to give the expected *syn*-hydroxy ester **12**, presumably via cyclic chairlike transition structure **11**. In this uncatalyzed variant, it was necessary to lactonize crude product **12** under mildly acidic conditions. The resulting α-*exo*-methylene lactone **13** was hydrogenated, then subjected to the Suzuki coupling with **9** to give 3-*epi*-**1** accompanied by a variable amount (5−20%) of the natural diastereomer (**1**). This result suggested that the "all-*cis*" 3-*epi*-**1** might be epimerized to the seemingly more stable 3,4-*trans* isomer **1**. This isomerization was best effected with DBU in methanol, however, only to give an equilibrium ratio of ca. 1:1 of the two separable epimers. With this, all four diastereomers of eupomatilone-6 (**1**) had been reached independently, and their stereochemistry was unambiguously proven through X-ray crystallographic analyses of aryl bromides **8**, **10**, and **14**, as well as 3,4-*epi*-**1** and 4-*epi*-**1**.[16] Our stereochemical assignments were correlated with the previously reported NMR spectroscopic data[3−6] and confirm Coleman's recent structural revision of **1**.[6]

The TfOH-catalyzed allylboration of **6** with (*E*)-**4** was key in accessing all four diastereomers of eupomatilone-6 (**1**). This new variant proceeds with ease at a temperature more than 100 °C lower than that of the corresponding uncatalyzed reaction. At this stage, the mechanism of the TfOH-catalyzed allylboration is not clear and is still under investigation. The stereochemistry of the process is intriguing as the reaction between (*Z*)-**4** and **6** also provided lactone **7** in >19:1 dr.[17] Yet, allylboronate (*E*)-**4** does not appear to undergo *E*-to-*Z* isomerization with TfOH. When 4,5-*cis* product **13** is treated with TfOH, isomerization to **7** occurs (possibly via a stable benzylic carbocation[18]), but much too slowly to account for this phenomenon.[17] With respect to the rate acceleration of the Brønsted acid, we tentatively favor an electrophilic boronate activation similar to that of the $Sc(OTf)_3$-catalyzed variant.[19]

In summary, we have reported a novel Brønsted acid-catalyzed allylboration method suitable for the most difficult, electronically deactivated allylboronate and aldehyde substrates. This method circumvents the use of metal ions, and rather employs a simple and cheap catalyst, triflic acid. Its usefulness as a complementary allylboration variant was demonstrated with a stereodivergent synthesis of all four diastereomers of eupomatilone-6, in only four or five steps from a common allylboronate. A thorough proof of stereochemistry supported by as many as five X-ray crystallographic structures brings an end to the ambiguity of the original stereochemical assignments. Further to the TfOH-catalyzed allylboration, our synthetic route featured a number of remarkable observations: the surprising reactivity of aldehyde **6**, the subtle reagent control observed in the hydrogenation of α-*exo*-methylene lactone **7**, and the success of a difficult case of Suzuki biaryl coupling using Buchwald's conditions. This work suggests that other reactions of boronic esters may be subject to Brønsted acid catalysis, and work to this effect is ongoing in our laboratory.

Acknowledgment. This work was funded by the Natural Sciences and Engineering Research Council (NSERC) of Canada, an AstraZeneca Chemistry Award to D.G.H., and the University of Alberta. We thank Dr. Jason Kennedy for advice, and Mr. Yuichiro Arimura for the preparation of (*E*)-**4**.

Supporting Information Available: Full experimental details, results of preliminary mechanistic studies, NMR spectral reproductions for all new compounds, and X-ray crystallographic data for **8**, **10**, **14**, 3,4-*epi*-**1**, and 4-*epi*-**1** (in CIF format). This material is available free of charge via the Internet at http://pubs.acs.org.

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JA054171L