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Triflic Acid-Catalyzed Additions of 2-Alkoxycarbonyl Allylboronates to Aldehydes. Study of Scope and Mechanistic Investigation of the Reaction Stereochemistry

Tim G. Elford, Yuichiro Arimura, Siu Hong Yu, and Dennis G. Hall*

Department of Chemistry, University of Alberta, Edmonton, Alberta, Canada, T6G 2G2

dennis.hall@ualberta.ca

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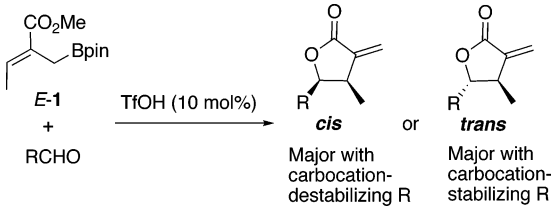

The substrate scope and the effect of substrate on the observed inversion of stereoselectivity in the triflic acid-catalyzed allylboration reaction between 2-alkoxycarbonyl allylboronates and aldehydes are presented. A mechanistic investigation is described so as to confirm the involvement of a carbocation intermediate as the source of stereochemical inversion. This methodology allows a facile access to β,γ-disubstituted five-membered ring lactones with an *exo*-methylene at the α-position.

Introduction

In the past few years, several reports have highlighted the efficiency of simple Brønsted acids as catalysts that can facilitate difficult organic reactions and expand their substrate scope.[1] Strong organic acids like triflic acid and triflimide are remarkably effective in promoting various polar additions and cycloadditions and are very convenient to use. These strong Brønsted acids are soluble in a wide range of organic solvents, and they can be prepared and employed in an anhydrous form. Our laboratory has recently described the first examples on the use of strong Brønsted acids to catalyze additions of allylic boronates to aldehydes.[2] Although strong Lewis acids had previously been reported to catalyze these additions,[3−6] it is quite surprising that allylic boronates can tolerate strong protic conditions susceptible to promote undesired processes such as oligomerization or protodeboronation.[3] Indeed, we found that triflic acid is particularly efficient at catalyzing the additions of very deactivated 2-alkoxycarbonyl allylboronates to aldehydes. This new variant proceeds with ease at a temperature more than 100 °C lower than the corresponding uncatalyzed reactions.[2] The novel triflic acid-catalyzed procedure was applied to the synthesis of all four diastereomers of eupomatilone-6,[2] a new natural product member of a structurally intriguing class of lignans isolated from the indigenous Australian shrub *Eupomatia bennettii*.[7] In this synthesis, the *E*-configured allylboronate *E*-**1** was found, unexpectedly, to provide the *trans* lactone product **3** upon addition to aldehyde **2** (eq 1). Indeed, according to the expected six-membered transition structure **4** (cf., eq 2), the trans stereochemistry of product **3** is opposite to that expected from the allylboronate's *E* geometry. In fact, the thermal uncatalyzed addition between *E*-**1** and **2** (eq 2) afforded the expected cis-configured lactone **6** (after an acid-promoted lactonization on open intermediate **5**). The fact that the related *Z*-configured allylboronate *Z*-**7** (the ethyl ester analogue of *Z*-**1**) provided the expected trans lactone **3** under triflic acid catalysis[2] (eq 3) suggested that isomerization had occurred somewhere along the reaction pathway between *E*-**1** and **3** (eq 1). In this

* Corresponding author. Tel.: (780) 492-3141. Fax: (780) 492-8231.

(1) Recent examples: (a) Williams, A. L.; Johnston, J. N. *J. Am. Chem. Soc.* **2004**, *126*, 1612−1613. (b) Zhang, L.; Kozmin, S. A. *J. Am. Chem. Soc.* **2004**, *126*, 10204−10205. (c) Mahoney, J. M.; Smith, C. R.; Johnston, J. N. *J. Am. Chem. Soc.* **2005**, *127*, 1354−1355. (d) Zhang, Y.; Hsung, R. P.; Zhang, X.; Huang, J.; Slafer, B. W.; Davis, A. *Org. Lett.* **2005**, *7*, 1047−1050. (e) Nakashima, D.; Yamamoto, H. *Org. Lett.* **2005**, *7*, 1251−1253.

(2) Yu, S. H.; Ferguson, M. J.; McDonald, R.; Hall, D. G. *J. Am. Chem. Soc.* **2005**, *127*, 12808−1280.

(3) Hall, D. G. *Boronic Acids−Preparation, Applications in Organic Synthesis and Medicine*; Hall, D. G., Ed.; Wiley-VCH: Weinheim, 2005; Ch. 1.

(4) Kennedy, J. W. J.; Hall, D. G. *J. Am. Chem. Soc.* **2002**, *124*, 11586−11587.

(5) Kennedy, J. W. J.; Hall, D. G. *J. Org. Chem.* **2004**, *69*, 4412−4428.

(6) Ishiyama, T.; Ahiko, T.-a.; Miyaura, N. *J. Am. Chem. Soc.* **2002**, *124*, 12414−12415.

(7) (a) Carroll, A. R.; Taylor, W. C. *Aust. J. Chem.* **1991**, *44*, 1615−1626. (b) Carroll, A. R.; Taylor, W. C. *Aust. J. Chem.* **1991**, *44*, 1705−1714.

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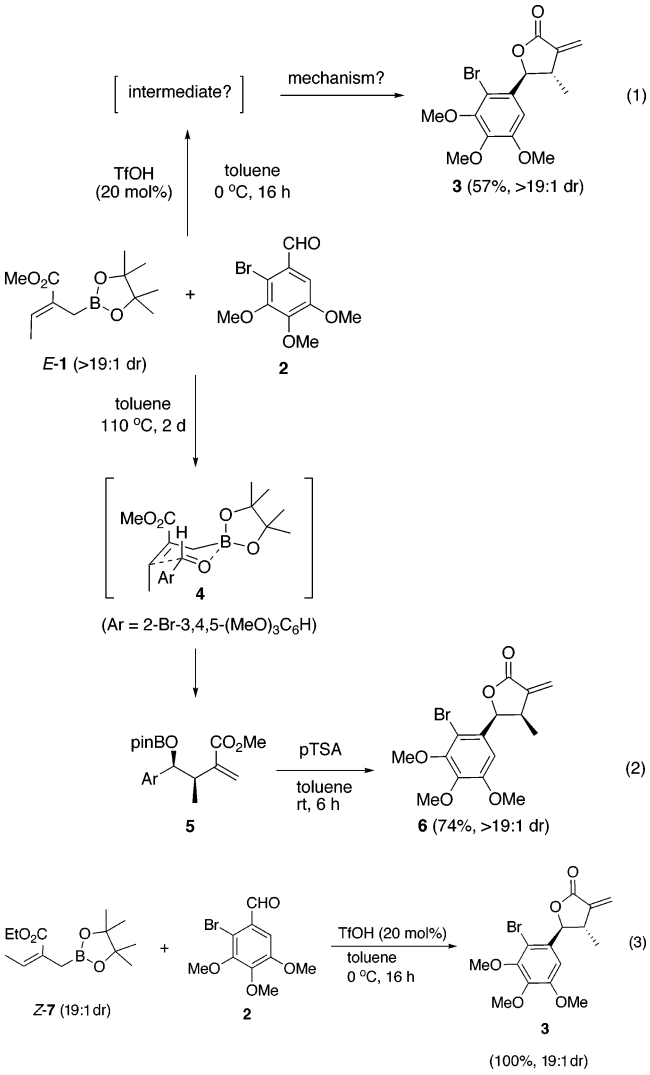
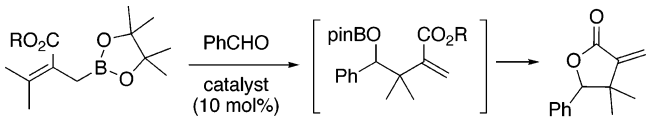


paper, we describe an investigation of the origin of the unexpected stereochemistry in the triflic acid-catalyzed additions of 2-alkoxycarbonyl allylic boronates. We also present a study on the scope of substrates for this reaction as well as a full comparison with the thermal, uncatalyzed conditions. These α-*exo*-methylene-γ-lactone products are of interest because they could be used as building blocks for the synthesis of several natural products. The stereoselective synthesis of such building blocks is quite significant[8,9] and could lead to a wide variety of natural product derivatives to be screened for their biological properties. Natural products containing this α-*exo*-methylene-γ-lactone core are known to possess significant biological activity.[8] As well, derivatives of α-*exo*-methylene-γ-lactones have shown significant antitumor properties.[10] The biological importance of this class of compounds is well-documented due to their cytotoxic, allergenic, anti-inflammatory, phytotoxic, and antimicrobial properties.[11] Hence, there is a great need for a stereospecific route to this class of compounds that would allow for chemical diversity to be easily introduced along the synthetic pathway.

Results and Discussion

1. Development of Optimal Protic Acid-Catalyzed Conditions. The allylation of aldehydes with 2-alkoxycarbonyl allylboronates leads to α-*exo*-methylene-γ-lactones.[4,5,12−15] 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 **8** to benzaldehyde (Table 1), we investigated the use of Lewis acids[4] and strong Brønsted acids.[2] 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. Because of the easier handling and measurement of liquid reagents, triflic acid was chosen for further optimization. The TfOH-catalyzed reaction was investigated at a lower temperature in view of using sensitive aldehydes. Further fine-tuning of reaction parameters and substrate stoichiometry led to the conditions of entry 8.

TABLE 1. Optimization of a Model Brønsted Acid-Catalyzed Reaction between Deactivated Allylboronate 8 and Benzaldehyde to Give Lactone Product 9[a]



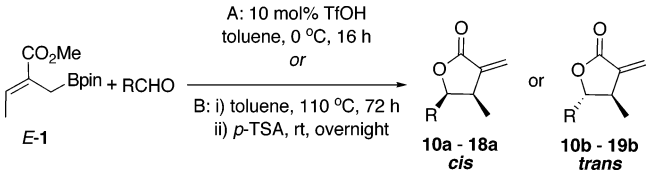
Entry	equiv of PhCHO	catalyst	conditions	yield (%)[b]
1	0.9	none	toluene, rt, 24 h	<5
2	0.9	CF_3CO_2H	toluene, rt, 24 h	77
3	0.9	Tf_2NH	toluene, rt, 24 h	99
4	0.9	TfOH	toluene, rt, 24 h	99
5	0.9	TfOH	toluene, 0 °C, 16 h	78
6	0.9	$Sc(OTf)_3$	toluene, 0 °C, 16 h	<5
7	1.5	TfOH	toluene, 0 °C, 16 h	96
8	2.0	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 and entries 5−8: R = methyl. [b] Isolated yields.

2. Scope of Substrate. Thermal versus Triflic Acid-Catalyzed Conditions. Once the conditions for the triflic acid-catalyzed allylboration reaction had been optimized, we next turned our attention to determining the substrate scope for the aldehyde. Our interest in this investigation was 3-fold. First, do all aldehydes display the reversal of cis/trans selectivity that was observed in the synthesis of **3** (cf. eq 1), or is there some governing factor that allows for only certain *trans*-lactones to be formed? Second, what types of aldehydes are amenable as substrates for this reaction so as to be a general reaction? Third, how do triflic acid-catalyzed reactions compare with the corresponding thermal (uncatalyzed) variant? To address these issues, various model aldehydes were chosen and reacted with

(8) Hoffmann, H. M. R.; Rabe, J. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 110.
(9) Bandichhor, R.; Nosse, B.; Reiser, O. *Top. Curr. Chem.* **2005**, *243*, 43−72.
(10) Matsuda, F.; Ohsaki, M.; Yamada, K.; Terashima, S. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 2123−2131.
(11) Janecki, T.; Blaszcyk, E.; Studzian, K.; Janecka, A.; Krajewska, U.; Rozalski, M. *J. Med. Chem.* **2005**, *48*, 3516−3521.
(12) Chataigner, I.; Lebreton, J.; Zammatio, F.; Villiéras, J. *Tetrahedron Lett.* **1997**, *38*, 3719−3722.
(13) Kennedy, J. W. J.; Hall, D. G. *J. Am. Chem. Soc.* **2002**, *124*, 898−899.
(14) Ramachandran, P. V.; Pratihar, D.; Biswas, D.; Srivastava, A.; Reddy, M. V. R. *Org. Lett.* **2004**, *6*, 481−484.
(15) Kabalka, G. W.; Venkataiah, B.; Dong, G. *J. Org. Chem.* **2004**, *69*, 5807−5809.

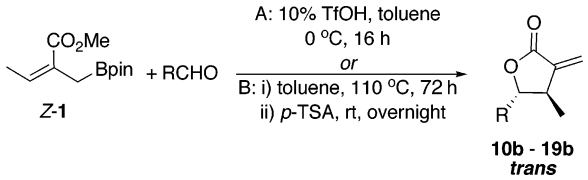
TABLE 2. Reaction of *E*-1 with Various Aldehydes under Thermal or TfOH-Catalyzed Conditions



entry	aldehyde	conditions[a]	product[b]	d.r.[c]	yield (%)[d]
1	*p*-$NO_2C_6H_4CHO$	A	**10a**	>19:1	53
2	*p*-$NO_2C_6H_4CHO$	B	**10a**	>19:1	90
3	*p*-BrC_6H_4CHO	A	**11b**	>19:1	62
4	*p*-BrC_6H_4CHO	B	**11a**	>19:1	79
5	*p*-$MeOC_6H_4CHO$	A	**12b**	>19:1	62
6	*p*-$MeOC_6H_4CHO$	B	**12a/12b**	1:1	62
7	*o*-MeC_6H_4CHO	A	**13b**	>19:1	49
8	*o*-MeC_6H_4CHO	B	**13a**	>19:1	80
9	*p*-MeC_6H_4CHO	A	**14b**	>19:1	59
10	*p*-MeC_6H_4CHO	B	**14a**	>19:1	48
11	C_6H_5CHO	A	**15b**	>19:1	58
12	C_6H_5CHO	B	**15a**	>19:1	67
13	*E*-$CH_3CH{=}CHCHO$	A	**16b**	>19:1	79
14	*E*-$CH_3CH{=}CHCHO$	B	**16a**	>19:1	92
15	$H_{11}C_5C{\equiv}CCHO$	A	**17a**	>19:1	63
16	$H_{11}C_5C{\equiv}CCHO$	B	**17a**	>19:1	51
17	$PhCH_2CH_2CHO$	A	**18a**	>19:1	46
18	$PhCH_2CH_2CHO$	B	**18a**	>19:1	59
19	*c*-$C_6H_{11}CHO$	A	**19a**	>19:1	11
20	*c*-$C_6H_{11}CHO$	B	**19a**	>19:1	66

[a] Conditions used: (A) TfOH, 0 °C for 16 h or (B) 110 °C for 72 h followed by *p*-TSA at room temperature overnight. [b] Relative configuration was determined by cycle NOE experiments (see Supporting Information). [c] The d.r. were determined from ^{1}H NMR spectra of crude products. [d] Yield is isolated yield after flash chromatography. *p*-TSA = para-toluenesulfonic acid, TfOH = triflic acid, d.r. = diastereomeric ratio and pin = $OCMe_2CMe_2O$.

TABLE 3. Reaction of *Z*-1 with Various Aldehydes under Thermal or TfOH-Catalyzed Conditions



entry	aldehyde	conditions[a]	product[b]	d.r.[c]	yield (%)[d]
1	*p*-$NO_2C_6H_4CHO$	A	**10b**	>19:1	52
2	*p*-$NO_2C_6H_4CHO$	B	**10b**	3.6:1	61
3	*p*-BrC_6H_4CHO	A	**11b**	>19:1	59
4	*p*-BrC_6H_4CHO	B	**11b**	3.1:1	53
5	*p*-$MeOC_6H_4CHO$	A	**12b**	>19:1	40
6	*p*-$MeOC_6H_4CHO$	B	**12b**	5.7:1	57
7	*o*-MeC_6H_4CHO	A	**13b**	>19:1	49
8	*o*-MeC_6H_4CHO	B	**13b**	6.1:1	49
9	*p*-MeC_6H_4CHO	A	**14b**	>19:1	91
10	*p*-MeC_6H_4CHO	B	**14b**	>19:1	71
11	C_6H_5CHO	A	**15b**	>19:1	78
12	C_6H_5CHO	B	**15b**	>19:1	66
13	*E*-$CH_3CH{=}CHCHO$	A	**16b**	>19:1	26
14	*E*-$CH_3CH{=}CHCHO$	B	**16b**	5.3:1	58
15	$H_{11}C_5C{\equiv}CCHO$	A	**17b**	2.7:1	46
16	$H_{11}C_5C{\equiv}CCHO$	B	**17b**	5.2:1	62
17	$PhCH_2CH_2CHO$	A	**18b**	>19:1	44
18	$PhCH_2CH_2CHO$	B	**18b**	2.5:1	40
19	*c*-$C_6H_{11}CHO$	A	**19b**	>19:1	71
20	*c*-$C_6H_{11}CHO$	B	**19b**	2.9:1	47

[a] Conditions used: (A) TfOH, 0 °C for 16 h or (B) 110 °C for 72 h followed by *p*-TSA at room temperature overnight. [b] Relative configuration was determined by cycle NOE experiments (see Supporting Information). [c] The d.r. were determined from ^{1}H NMR spectra of crude products. [d] Yield is isolated yield after flash chromatography. d.r. = diastereomeric ratio and pin = $OCMe_2CMe_2O$.

both *E*-**1** and *Z*-**1** under thermal and acid-catalyzed conditions. The results from these reactions are summarized in Tables 2 and 3.

From these results, a comparison between the isomeric allylboronates *E*-**1** and *Z*-**1** can be made. For both of these allylboronates, there was no clear trend as to which one gave better yields for a given aldehyde. While some reactions gave high yields of lactones from *E*-**1** (entries 2, 8, and 14 in Table 2), others were not nearly as successful and gave lower yields. However, the same situation occurred with *Z*-**1**, where some aldehydes gave significantly higher yields than others. It is also useful to note that, while most of the aldehydes used were aromatic or straight-chain aliphatic ones, branched aldehydes are also suitable substrates for this reaction. Specifically, the use of cyclohexanecarboxaldehyde (entries 19 and 20 in Tables 2 and 3) as well as *o*-tolualdehyde (entries 7 and 8 in Tables 2 and 3) demonstrated that more sterically hindered aldehydes are suitable for use in the triflic acid-catalyzed allylboration reaction. α,β-Unsaturated aldehydes are also suitable substrates as evidenced by the successful addition of both *E*-**1** and *Z*-**1** onto crotonaldehyde and 2-octynal (entries 13−16 in Tables 2 and 3). One reaction was attempted using *E*-**1** with cinnamaldehyde under triflic acid-catalyzed conditions. No product was isolated, and a nearly quantitative amount of starting materials (*E*-**1** and aldehyde) was recovered. Likewise, model ketones did not react even at room temperature.

More interesting is the trend that is observed when one looks at the relative stereochemistry of these lactone products. While all reactions with *Z*-**1** led to the corresponding *trans*-lactones as major diastereomer, some of the allylborations using *E*-**1** did in fact give the opposite selectivity and produced the *trans*-lactone as well. However, this is not always the case. Some of the aldehydes did produce the initially expected *cis*-lactone when reacted with *E*-**1**. Thus, it is apparent that not all aldehydes are prone to give the reverse selectivity as previously observed when using *E*-**1** and aldehyde **2** in the synthesis of **3** (eq 1). From the electronic nature of these aldehydes, it would seem that aldehydes with a group (R) capable of stabilizing a carbocation at the 5-position (γ) in the resulting lactones (entries 3, 5, 7, 9, 11, and 13 in Table 2) give unexpected results (i.e., *trans*-lactones), while others that are less effective at stabilizing a carbocation (entries 1, 15, 17, and 19 in Table 2) lead to the expected *cis*-lactones when subjected to the triflic acid-catalyzed conditions. For example, the *p*-nitrophenyl group (entry 1 in Table 2) would destabilize the benzylic carbocation formed at the γ-position, and it does lead to the observed *cis*-lactone being formed exclusively.

For all new lactones that were synthesized, cycle NOE experiments were used to determine the relative stereochemistry between the methyl group at the 4-position and the R group at the 5-position (see Supporting Information for a listing of values). Because of the puckering of the five-membered lactones, the same correlations could sometimes be seen in both isomers. When this was the case, the size of the correlation had to be compared. These were very different in magnitude and allowed for definitive assignments of the relative stereochemistry (see Supporting Information for comparison of values). Typical correlations can be seen in Figure 1. As one can see, protons

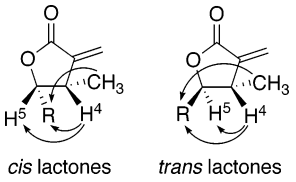


FIGURE 1. Typical cycle NOE correlations.

present on the R group of the lactone (i.e., the substituent originating from the aldehyde) were also useful in obtaining NOE data to allow for stereochemical assignments.

It is also interesting to look at the proton NMR data for these lactones and compare some of the chemical shifts between the different cis and trans isomers. The proton at the 4-position was, in all cases studied, further upfield in the *trans*-lactone than the corresponding proton in the *cis*-lactone. Furthermore, the proton at the 5-position was also further upfield in the *trans*-lactone than the corresponding proton in the *cis*-lactone. These results, summarized in the Supporting Information, further confirm the relative stereochemical assignments.

Once this pattern had been established, the relative stereochemistry of subsequently formed lactones was assigned based on the relative position of these peaks in the ^{1}H NMR. Cycle NOE experiments were eventually performed and did in fact confirm all of our assignments. This chemical shift pattern may prove to be a useful way of assigning relative stereochemistry in 5-membered *exo*-methylene lactones that are of similar structure without the need to run time-consuming NOE experiments. With regard to the current study on the triflic acid-catalyzed allylboration reaction, we next turned our attention toward investigating the mechanism of this reaction in an attempt to understand why allylboronate *E*-**1** leads to *trans*-lactones **11b**−**16b** and to determine the nature of the observed reversal of stereoselectivity.

3. Mechanistic Investigation into the Origin of Isomerization. Several questions remained in understanding the mechanism of the triflic acid-catalyzed reaction, such as whether a carbocation was being formed or not, how the triflic acid was turning over, and what the intermediate leading to the observed reversal of stereoselectivity was. As first reported by our group,[2] and further suggested by others,[16] we initially suspected that the open borate intermediate must be forming a carbocation, which would then be trapped by the nearby ester group to form the observed five-membered lactones (Figure 2).

From our work on the substrate scope, we immediately noticed that only allylboronate *E*-**1** gave an inversion of the expected stereochemistry in the lactone products, while products obtained using *Z*-**1** did not show this reversal. Thus, there must be an intermediate, possibly carbocation **A** in Figure 2, which when *E*-**1** is used allows for a conformational change in the molecule (A to B, Figure 2) and subsequent formation of the *trans*-lactone. With the reasonable assumption that the *trans*-lactone is the kinetically favored product, the same intermediate could also be present when *Z*-**1** is used but still lead to the expected product stereochemistry. Also from the substrate scope (Tables 2 and 3), if one takes a close look at the electronic nature of the aldehydes used, those with a group (R) that would stabilize a carbocation on the resulting adduct are the ones that are observed to give the unexpected stereochemistry. Any aldehydes that contained electron-withdrawing groups or could not stablize a nearby carbocation (e.g., alkyl and propargyl) did not display the reversal of stereochemistry. From these observations, we strongly hinted that the lactonization must be going through a carbocation (i.e., S_N1) mechanism, but conclusive proof needed to be found. A recent follow-up of our original paper[2] by another group[16] concludes that an S_N1 mechanism is operative for lactonizations under strong Lewis acid conditions but offers no evidence for it nor addresses several key issues.

3.1. Control Experiments to Address the Possibility of Lactone Isomerization. On the basis of the acidic conditions used in this allylboration reaction, we were initially aware that it could be the lactones themselves that were isomerizing via a reversible S_N1 mechanism. Because of the eclipsing bulky substituents in the *cis*-lactones, the *trans*-lactones are likely to be thermodynamically favorable. Thus, in the presence of triflic acid, it might be possible that the initially formed *cis*-lactone product was opening up to form a carbocation, which was reorientating itself by C−C bond rotation (i.e., A to B in Figure 2) to alleviate the steric strain of the nearby bulky groups, and then closing back up to form the observed *trans*-lactones. Under this hypothesis, aldehydes with a group (R) that could stabilize the carbocation would undergo this inversion of stereoselectivity. To assess whether it was the lactone products isomerizing instead of the open borate intermediate (Figure 2), we studied three different lactones. We started with the *cis*-lactones that

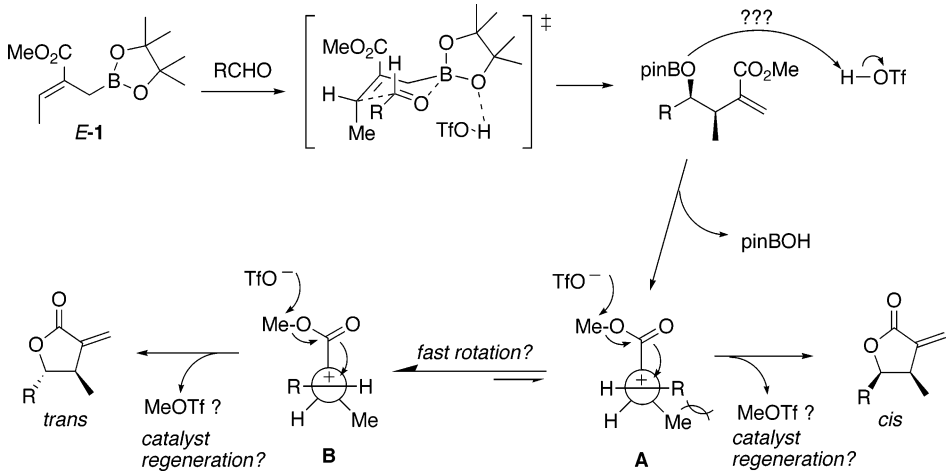
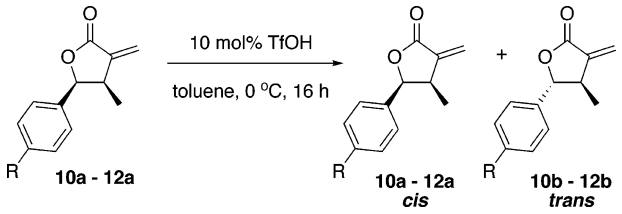


FIGURE 2. Early mechanistic hypotheses and questions that required investigation.

TABLE 4. Attempts of Isomerization of *cis*-Lactones to *trans*-Lactones as Possible Source for Reversed Stereochemistry



Entry	initial lactone	ratio of lactone products (**a**/**b**)[a]
1	**10a** R = NO_2	100:0
2	**11a** R = Br	74:26
3	**12a** R = OMe	5:95

[a] Ratio of products determined by ^{1}H NMR of crude reaction mixture.

had the *p*-nitro phenyl group (**10a**), the *p*-bromo phenyl group (**11a**), and the *p*-methoxy phenyl group (**12a**). Each of these *cis*-lactones was subjected to the same conditions used in the catalyzed allylboration reaction, that is, 0 °C for 16 h with 10 mol% triflic acid. ^{1}H NMR spectra of crude products were obtained after the typical workup, and the ratio of cis/trans isomers was measured (Table 4).

When **10a** was subjected to these conditions, there was no isomerization observed. This can be rationalized because of the severe electron-withdrawing nature of the *p*-nitrophenyl group. The resulting benzylic carbocation would be highly destabilized by any buildup of charge, and the lactone would immediately reform before any rotation/isomerization could occur. Thus, none of *trans*-lactone **10b** is observed. The complete opposite is true for **12a**. Here, the *p*-methoxyphenyl group stabilizes a benzylic carbocation, and this allows for the cis isomer to completely isomerize to the more stable *trans*-lactone. These two results are consistent to those obtained in Table 2. However, the result from entry 2 in Table 4 provides new information that rules out the notion that isomerization of the lactone products is at the origin of the inverted stereochemistry observed in many cases. Even though there is partial isomerization of lactone **11a** to **11b** observed under the reaction conditions, it is clearly not enough to explain the full isomerization observed previously for the allylboration/lactonization leading to **11b** in Table 2 (entry 3). Hence, lactone isomerization cannot be the sole mechanism affording this observed reversal of stereochemistry, and the main origin of this isomerization must occur prior to lactone formation.

3.2. Study of Isotopic Labeling for Tracking Down the Aldehyde Oxygen. We next decided to use oxygen-18 labeling of aldehydes to probe the location of the aldehyde oxygen throughout the reaction with respect to the suspected intermediacy of a carbocation in the isomerization event. If the aldehydes were labeled with oxygen-18 and then reacted with *E*-**1**, it would be possible to determine if the oxygen from the aldehyde ended up being incorporated into the lactones. We chose 4-nitrobenzaldehyde and 4-bromobenzaldehyde so as to make a good comparison between extremes of electronic properties. These two different oxygen-18 labeled aldehydes were made according to a previously reported literature method[17] using 10% ^{18}O-enriched water. The oxygen-18 labeled aldehydes were confirmed by high-resolution mass spectrometry (3−4% ^{18}O incorporation, see Supporting Information for details). These aldehydes were subjected to the normal triflic acid-catalyzed allylboration reaction conditions, and the lactones were purified in the typical fashion. Once isolated, they were analyzed by mass spectrometry to determine if there were elevated levels of oxygen-18. The normal isotopic distribution of oxygen includes 0.20% of naturally occurring oxygen-18. On the basis of the results from the mass spectrometry analysis, the two lactones coming from 4-nitrobenzaldehyde and 4-bromobenzaldehyde showed a level of oxygen-18 that was not distinguishable from the naturally occurring level. This experiment was performed twice, with the same conclusion that the oxygen from the aldehyde was not present in the final isolated lactone in each case. These results further supported our hypothesis that the triflic acid-catalyzed allylboration reaction proceeds through a carbocation intermediate where the aldehyde oxygen is eventually lost via the ionization process. In a control experiment, the oxygen-18 labeled *p*-nitrobenzaldehyde was also subjected to the thermal allylboration conditions with *E*-**1**. In this lactone product the oxygen-18 labeling could be detected at a level similar to the starting aldehyde.

3.3. Isolation of Open Intermediates and Investigation of Their Isomerization. To further confirm our findings, we next turned our investigation toward the exact nature of the open intermediate leading to a carbocation. To this end, we set out to isolate the open form of the allylboration product. Previous work in our group had found that a decrease in the temperature for the thermal allylboration reaction could prevent lactonization from occurring.[5] Using this information, we synthesized the corresponding acyclic methyl esters of three different aldehydes, 4-nitrobenzaldehyde (**20**), 4-bromobenzaldehyde (**21**), and 4-methoxybenzaldehyde (**22**). These model substrates were reacted under thermal allylboration conditions with both *E*-**1** and *Z*-**1** in an attempt to obtain both the cis and the trans acyclic methyl esters. Four of the methyl esters were isolated and purified (Figure 3).

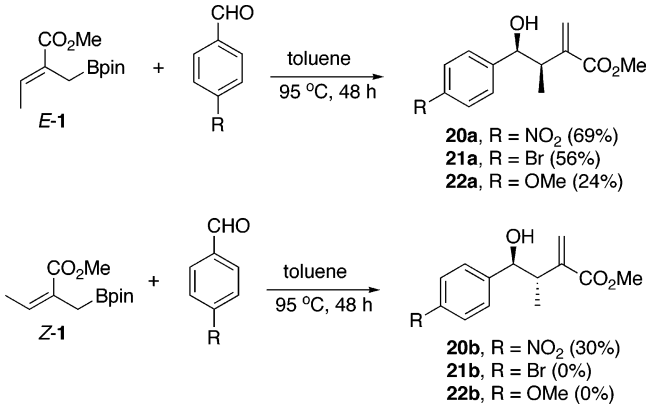
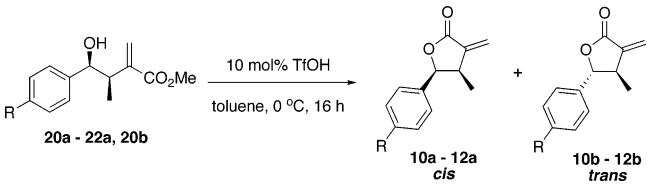


FIGURE 3. Synthesis of *cis*- and *trans*-acyclic methyl hydroxy esters.

All three aldehydes reacted with *E*-**1** to give the corresponding *cis*-methyl ester products. The assignments of stereochemistry were done on the basis of coupling constants and comparison of chemical shifts in the proton NMR between the methyl esters and their corresponding lactones. This stereochemical outcome is also consistent with standard allylboration chemistry based on a closed six-membered transition state. When the three aldehydes were each reacted with *Z*-**1**, only the 4-nitrobenzaldehyde

(16) Ramachandran, P. V.; Pratihar, D.; Biswas, D. *Org. Lett.* **2006**, *8*, 3877−3879.
(17) Baraniak, J.; Wojciech, J. S. *J. Chem. Soc., Perkin Trans. 1* **1987**, *8*, 1645−1656.

TABLE 5. Lactonization of Acyclic Methyl Esters under Triflic Acid Conditions



Entry	methyl ester	product	ratio of products[a]
1	**20a** R = NO_2	**10a/10b**	90:1
2	**21a** R = Br	**11a/11b**	66:1
3	**22a** R = OMe	**12a/12b**	16:84
4	**20b** R = NO_2	**10a/10b**	0:100

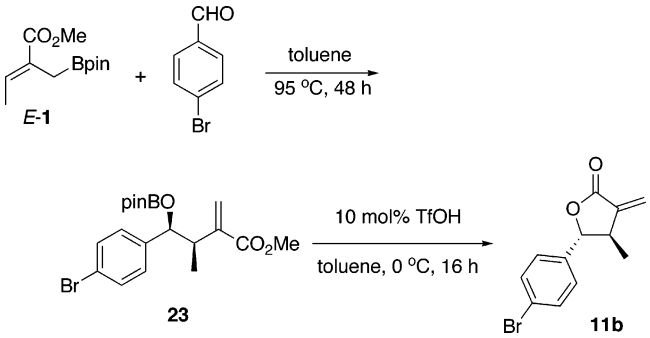
[a] Ratio determined by ^{1}H NMR analysis of crude reaction mixture.

resulted in any acyclic methyl ester product being isolated. For the other two cases, only the corresponding lactones were isolated after workup. Interestingly, after **20b** was left on the benchtop for 2 weeks, an ^{1}H NMR experiment was re-run, and considerable conversion of **20b** to lactone **10b** was observed. Therefore, it was assumed that **21b** and **22b** were not isolable due to the fact that they were probably cyclizing spontaneously under the reaction conditions or at room temperature to their corresponding lactones. The isolated acyclic methyl esters were subjected to triflic acid catalysis at 0 °C for 16 h (standard catalyzed conditions). All underwent lactonization to their corresponding lactones, and these results are summarized in Table 5.

As can be seen from these results, **20a** cyclizes to give mainly the *cis*-lactone, and **20b** cyclizes to give the *trans*-lactone, which is in agreement with our previous results (entry 1, Tables 2 and 3). Furthermore, **22a** cyclizes to give mainly the *trans*-lactone (entry 3, Table 5), which is also in agreement with our previous result (entry 5, Table 2). Specifically, if a carbocation can be stabilized, it will give the *trans*-lactone as the major product. If no appreciable stabilization is possible, then the *cis*-lactone will be observed as the major product (entry 1, Table 5). Whereas these first two results were quite reassuring, we noted that the result in entry 2, however, was completely opposite to what was expected. The *p*-bromophenyl group can stabilize a carbocation through resonance, so the *trans*-lactone was expected as the major product based on our previous result using allylboronate *E*-**1** and *p*-bromobenzaldehyde under triflic acid catalysis (entry 3, Table 2). Instead, the cis isomer was observed as the major product from **21a**. It should be realized, however, that the free alcohols that we isolated and then subjected to the catalyzed allylboration conditions are not the true intermediates that would be present in the typical allylboration/lactonization reactions. The free alcohols may form in a serendipitous manner depending on the reaction conditions, but the anticipated intermediate would contain a pinacol borate unit at the benzylic position, not a free hydroxyl group. These borate intermediates may be more prone to acid-catalyzed isomerization. At this point, we went back and made the borate analogue of **21a, 23,** via a standard thermal allylboration procedure (Scheme 1).

An ^{1}H NMR analysis was performed on the crude reaction mixture before any workup was done to confirm the presence of the borate group on the molecule. Once this had been confirmed, the borate intermediate **23** was subjected to the triflic acid-catalyzed conditions. To our satisfaction, ^{1}H NMR analysis of the crude product after workup showed the presence of the

SCHEME 1. Synthesis of Borate Intermediate and Lactonization under TfOH Conditions



trans-lactone as the major product with only a trace amount of the *cis*-lactone present.

As a side note, this surprising observation that the free alcohol intermediate **21a** leads to one isomer while the corresponding borate intermediate **23** leads to the other isomer brings to light a selectivity issue with triflic acid activation. As discussed earlier, in the triflic acid-catalyzed allylboration reaction, the triflic acid activates the borate and causes carbocation formation, which then allows for intramolecular trapping via the ester either before any bond rotation can occur (A, Figure 2, leading to the expected *cis*-lactones) or after bond rotation (B, Figure 2, leading to the observed reversal of stereochemical outcome in the form of the *trans*-lactone). However, if the borate intermediate is trapped and hydrolyzed to the corresponding alcohol, and then subjected to the triflic acid conditions, a different stereochemical outcome is observed. To explain this dichotomy, a mechanism that does not include carbocation formation must be considered to explain the lactonization that provides retention of stereochemistry. In these instances, the triflic acid must be preferentially activating the carboxyester in the presence of the free alcohol (Figure 4). The activated ester is then attacked intramo-

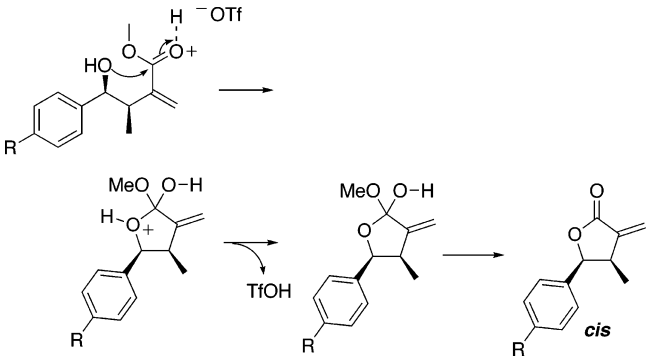


FIGURE 4. Cyclization of open methyl ester intermediates containing a free alcohol.

lecularly by the nearby alcohol, which leads to the eventual elimination of a molecule of methanol. This substitution-type mechanism would explain the retention of stereochemistry with certain aldehyde substrates. Another alternative, which is more consistent with the absence of O^{18} labeling when using *p*-nitrobenzaldehyde (vide supra), supports the notion that a carbocation is also formed in these cases but that its extreme reactivity precludes a bond rotation prior to attack by the ester.

3.4. Proposal of a Full Mechanistic Cycle and Issue of Triflic Acid Turnover. With all of this information now in hand, the reaction stereochemistry has been clarified. The reversal of

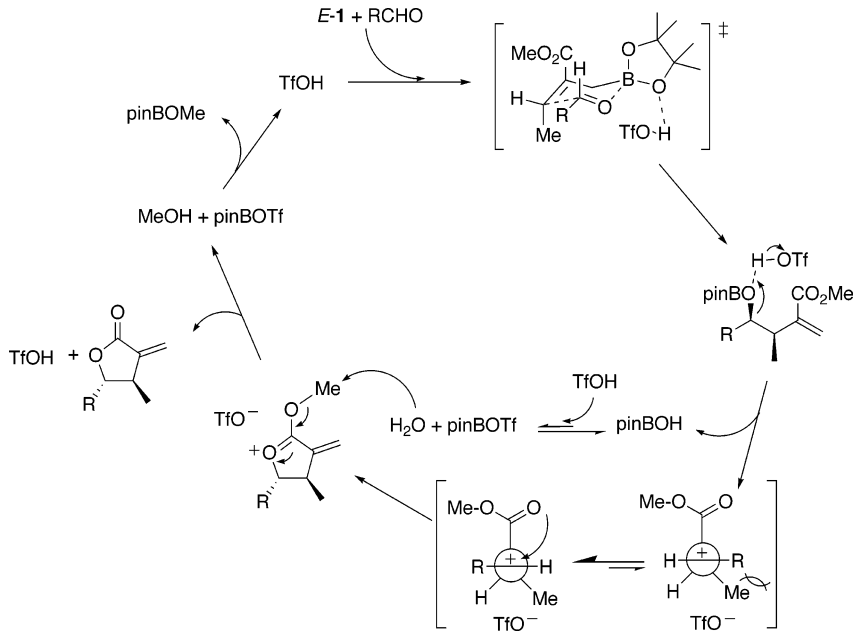


FIGURE 5. Triflic acid-catalyzed allylboration/lactonization mechanism.

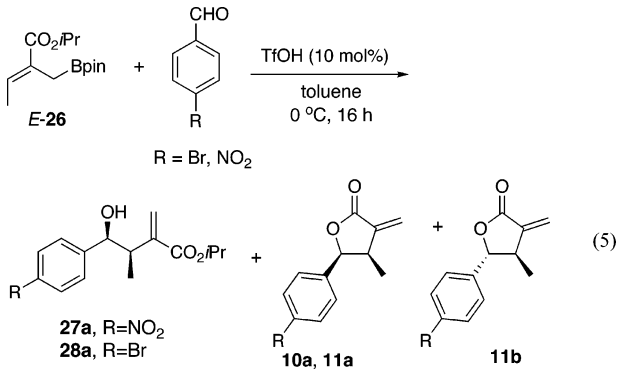
observed stereochemistry originates from the formation of a carbocation from the borate intermediate, which is followed by bond rotation to a more favorable conformer and subsequent trapping by the nearby ester group to give the *trans*-lactone (Figure 5). For aldehydes that do not stabilize a carbocation, this catalytic cycle is still valid. The difference for these aldehydes is that once the intermediate carbocation forms, it would be attacked immediately by the nearby ester to form the lactone before any bond rotation can occur. As protonation/ionization could require a conformation where both the borate and the carboxyester are held in close proximity to allow an effective proton transfer, the carbocation would be generated in the unfavorable arrangement (with syn R and Me groups) that leads to the *cis*-lactone instead of the *trans*-lactone as shown in Figure 5.

Triflic acid plays numerous functions in the postulated multistep mechanism of Figure 5. First, it is expected to catalyze the allylboration reaction by the same electrophilic boronate activation mechanism demonstrated before for the Lewis acid-catalyzed variant.[18] As seen from this mechanistic cycle, the possible catalyst turnover requires the formation of one molecule of water from pinBOH and another equivalent of triflic acid. This water molecule would then act as a nucleophile on the methoxy moiety of the alkoxyoxonium intermediate, leading to the lactone product and a molecule of methanol. One full equivalent of the triflic acid is also regenerated at this point via elimination of pinBOMe, making the entire cycle catalytic in TfOH. The overall reaction for the byproducts is shown in eq 4. As already mentioned, the molecule of water produced is

$$\text{pinBOH} + \text{MeOH} \xrightarrow{\text{TfOH}} \text{pinBOMe} + \text{H}_2\text{O} \qquad (4)$$

consumed in the reaction, and the only byproduct of the reaction would be pinBOMe. It should be noted that the attack of water on the oxonium carbon (as opposed to the methoxy carbon) would lead to the same outcome, but it is not consistent with the absence of oxygen-18 labeling in the experiments described in section 3.2.

It is important to note that the issue of catalyst turnover remains uncertain and that there are other options for this catalytic cycle. Instead of a molecule of water, it could be the triflate anion itself that attacks the oxonium's methoxy group to form the final lactone products. This mechanism would lead to the formation of MeOTf, which would be a dead-end as it would cause irreversible consumption of the triflic acid. The initial catalyst, triflic acid, would not be regenerated, and the reaction would require another species to perpetuate the cycle. In this regard, it is possible that pinBOTf could take over in the catalytic cycle and act as a Lewis acid to promote further allylboration/lactonization reactions to occur. At this point, it is not immediately evident which catalytic cycle is occurring. The triflate anion is a very poor nucleophile but still might be capable of undergoing attack on the oxonium's alkoxy group. A borate can be observed in the crude ^{11}B NMR at ~22 ppm, but this could correspond to either pinBOTf or pinBOMe. To gain more information about this proposed catalytic cycle, we went one step further and synthesized the isopropyl allylboronate *E*-**26** analogue of *E*-**1** and subjected it to the triflic acid allylboration conditions with two different aldehydes (eq 5).



(18) Rauniyar, V.; Hall, D. G. *J. Am. Chem. Soc.* **2004**, *126*, 4518−4519.

Quite surprisingly, both aldehydes reacted with *E*-**26** to give the expected corresponding lactones **10a** and **11b** as products.

As can be seen, however, there were considerable amounts of the open allylboration products that had failed to undergo lactonization. For the reaction between *E*-**26** and *p*-bromobenzaldehyde, **28a**, **11a**, and **11b** were obtained in a ratio of 1.3:1:2.8. The *trans*-lactone **11b** was still the major product, and the presence of **28a** can be rationalized by the intermediate borate being much slower to undergo lactonization as compared to the methyl ester analogue (Figure 2). The presence of **11a** could be due to direct attack of the hydroxyborate intermediate on the ester. This process would be slow but would explain how some of the *cis*-lactone **11a** is formed. For the reaction between *E*-**26** and *p*-nitrobenzaldehyde, **27a** and **10a** were obtained in a ratio of 3.2:1. This result was surprising, but if one considers the electronic nature of the aldehyde (electron poor), carbocation formation is less favorable and slower. Thus, most of the borate intermediate would not undergo carbocation formation and subsequent lactonization, and would be quenched as the *cis*-alcohol during workup. Regardless of the obtained mixtures, the presence of **11b** provides some interesting insight into the process of lactonization. Attack of a nucleophile (either H_2O or TfO^-) on the isopropoxy group is much slower as compared to the methoxy group, and this would allow for the previously slower process of hydroxyborate attack on the ester to become much more important and lead to the presence of the *cis*-lactone **11a**. The same rational holds true for the *p*-nitrobenzaldehyde example; however, it is inconsequential since the cis product is the expected one regardless of which process is faster. In both cases, lactonization is slower, which is in agreement with a mechanism involving nucleophilic attack on the oxonium's alkoxy substituent by either water or the triflate anion. Overall, although triflic acid is essential to initiate this allylboration/lactonization process, the issue of detailed catalyst turnover remains speculative.

Conclusion

In summary, we have described a study of the substrate scope for the triflic acid-catalyzed allylboration/lactonization reaction and identified the presence of a unique reversal in observed stereochemistry in many of the α-*exo*-methylene-γ-lactone products. The nature of the aldehyde substrate is determinant for the stereochemistry of the lactone products. We went on to investigate the mechanism of this reaction process and confirmed our previous suspicions that the lactonization was proceeding via a carbocation-promoted mechanism. We showed that lactone epimerization can occur in most cases, however, not in substantially large enough amounts to account for the observed diastereomeric ratios in the triflic acid-catalyzed allylboration reaction. Furthermore, oxygen-18 labeling was used to track the aldehyde oxygen throughout the reaction sequence and indicated that none of the aldehyde oxygen was present in the final lactone products. The main mechanism of this triflic acid-catalyzed allylboration reaction involves the formation of a carbocation intermediate from the initially formed open borate product. This event is followed by trapping of the carbocation by the neighboring ester, either before or after bond rotation occurs, which leads to the observed diastereoselectivities in the lactone products. Mechanistic possibilities to explain catalyst turnover were discussed, and control experiments support a cycle involving a nucleophilic attack on the ester's alkoxy substituent.

Experimental Procedures

Allylboronates *E*-**1**, *Z*-**1**, and *E*-**26** were synthesized according to previous literature procedures.[2]

General Procedure for the Synthesis of Lactones under TfOH-Catalyzed Conditions using *E*-1 or *Z*-1 (10−19). A solution of *E*- or *Z*-allylboronate **1** (100 mg, 0.42 mmol) and aldehyde (0.83 mmol) in toluene (1 mL) at 0 °C was treated with TfOH (4 μL, 0.04 mmol) and stirred at 0 °C under an Ar atmosphere for 16 h. The mixture was then diluted with NH_4Cl(aq)/NH_4OH (9:1 v/v, 10 mL) and extracted with Et_2O (3 × 20 mL). The combined extracts were washed with brine (2 × 20 mL), dried with anhydrous Na_2SO_4, filtered, and concentrated. Crude products were then purified by flash chromatography to yield the corresponding lactone.

***cis*-4-Methyl-3-methylene-5-(4-nitrophenyl)-dihydro-furan-2-one (10a).** Flash chromatography (20% EtOAc/hexanes) yielded the product as a yellow solid in 53% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.27−8.25 (m, 2H), 7.41−7.38 (m, 2H), 6.38 (d, 1H, J = 2.5 Hz), 5.70 (d, 1H, J = 8.1 Hz), 5.66 (d, 1H, J = 2.4 Hz), 3.57−3.47 (m, 1H), 0.80 (d, 3H, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.7, 147.9, 143.6, 135.2, 126.9, 123.8, 122.9, 80.7, 38.7, 15.8; IR (CH_2Cl_2 cast film, cm^{-1}): 3082, 2973, 2933, 1770, 1521, 1349; HRMS (EI, *m*/*z*) Calcd for $C_{12}H_{11}NO_4$: 233.06880. Found: 233.06846. Elem. Anal. (%) Calcd for $C_{12}H_{11}NO_4$: C, 61.80; H, 4.75; N, 6.01. Found: C, 61.99; H, 4.97; N, 5.74.

***trans*-4-Methyl-3-methylene-5-(4-nitrophenyl)-dihydro-furan-2-one (10b).** Flash chromatography (20% EtOAc/hexanes) yielded the product as a pale yellow solid in 52% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.30−8.26 (m, 2H), 7.57−7.52 (m, 2H), 6.38 (d, 1H, J = 3.3 Hz), 5.65 (d, 1H, J = 2.7 Hz), 5.02 (d, 1H, J = 7.6), 2.96−2.86 (m, 1H), 1.40 (d, 3H, J = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.3, 145.7, 139.3, 126.5, 124.2, 122.2, 94.4, 84.3, 43.5, 16.2; IR (microscope, cm^{-1}): 3510, 3114, 2974, 2936, 1773, 1519, 1352, 1266, 1145; HRMS (EI, *m*/*z*) Calcd for $C_{12}H_{11}NO_4$: 233.06880. Found: 233.06893. Elem. Anal. (%) Calcd for $C_{12}H_{11}NO_4$: C, 61.84; H, 4.76; N, 6.01. Found: C, 61.91; H, 4.83; N, 5.99.

General Procedure for the Synthesis of Lactones under Thermal Conditions Followed by *p*-Toluenesulfonic Acid Monohydrate using *E*-1 or *Z*-1 (10−19). A solution of *E*- or *Z*-allylboronate **1** (100 mg, 0.42 mmol) and aldehyde (0.46 mmol) in toluene (0.5 mL) was heated to 110 °C in a high-pressure vessel under an Ar atmosphere for 72 h. *p*-TSA•H_2O (230 mg, 1.2 mmol) was then added, and the mixture was stirred overnight at room temperature. The reaction was quenched with $NaHCO_3$ (aq) (20 mL) and extracted with Et_2O (3 × 20 mL). The combined extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated. Flash chromatography gave the corresponding lactone.

General Procedure for the Synthesis of Butyric Acid Methyl Esters (20−22). A solution of the corresponding *E*- or *Z*-allylboronate (100 mg, 0.42 mmol) and aldehyde (0.46 mmol) in toluene (0.5 mL) was heated at 95 °C under an Ar atmosphere for 42 h. The reaction was allowed to cool to room temperature, and the solvent was removed. Flash chromatography gave the corresponding methyl ester.

***cis*-4-Hydroxy-3-methyl-2-methylene-4-(4-nitrophenyl)-butyric Acid Methyl Ester (20a).** Flash chromatography (20% EtOAc/hexanes) yielded the product as a yellow oil in 69% yield. (Note: the corresponding *trans*-lactone was isolated in 6% yield.) ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.21−8.16 (m, 2H), 7.56−7.51 (m, 2H), 6.31 (d, 1H, J = 0.8 Hz), 5.59 (t, 1H, J = 0.9 Hz), 5.00 (t, 1H, J = 3.4 Hz), 3.80 (s, 3H), 3.13 (ddddd, 1H, J = 7.1, 7.1, 7.1, 3.4, 1.0 Hz), 2.75, (d, 1H, J = 1.0 Hz), 0.98 (d, 3H, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.1, 150.1, 147.2, 141.8, 127.1, 127.0, 123.3, 74.6, 52.3, 42.9, 12.0; IR (cast film microscope, cm^{-1}): 3508, 2952, 1712, 1520, 1348; HRMS (EI, *m*/*z*) Calcd for $C_{12}H_{12}NO_4$ $[M - OCH_3]^+$: 234.07663. Found: 234.07614.

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Supporting Information Available: Full experimental details, spectral data, and copies of ^{1}H and ^{13}C NMR for all new compounds **10**−**12**, **14**, **16**−**22**, and **26**. This material is available free of charge via the Internet at http://pubs.acs.org.

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