

# Control of Stereochemistry: A General Synthesis of *cis*- or *trans*- $\beta,\gamma$ -Disubstituted- $\gamma$ -butyrolactones Following *Z*-Crotylboration

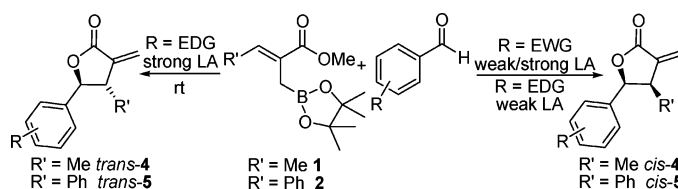
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Received June 26, 2006 (Revised Manuscript Received July 17, 2006)

## ABSTRACT



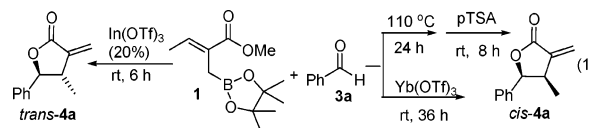
A general and practical procedure for the highly diastereoselective preparation of either the *cis*- or *trans*- $\beta,\gamma$ -disubstituted- $\gamma$ -butyrolactones by appropriate choice of Lewis or Bronsted acid catalysts during crotylboration or lactonization is reported. The *cis*-stereochemistry of the *Z*-crotylboration product can be inverted with strong acids during lactonization. A carbocation mechanism and catalytic cycle has been proposed.

Control of diastereoselectivity is crucial for the efficient synthesis of complex molecules and continues to be a challenge.<sup>1</sup> Crotylboration of aldehydes which typically provides syn-homoallylic alcohols from *Z*- and anti-products from *E*-crotylboranes, is a stereoselective C–C bond forming reaction.<sup>2</sup> Stereospecific  $\gamma$ -butyrolactones are building blocks of several natural products and their stereoselective synthesis is significant.<sup>3</sup>

The crotylboration of benzaldehyde (**3a**) under thermal condition with functionalized *Z*-crotylboronates **1** and **2**, followed by lactonization is a general route to *cis*- $\gamma$ -butyrolactones (eq 1).<sup>4,5</sup> The reactivity of similar crotylbo-

ronates has been improved with Lewis acid catalysis.<sup>6</sup> We have now observed a significant influence of the catalysts on the stereo-outcome of the lactones.

The crotylboration of **3a** with **1**, in the presence of catalytic  $\text{In}(\text{OTf})_3$ , continued until lactonization and provided *trans*-**4a** (dr = 98:2) (eq 1) almost exclusively! However,  $\text{Yb}(\text{OTf})_3$ -catalyzed reaction of **3a** with **1** proceeded in the anticipated manner and furnished *cis*-**4a** (dr = 92:8) (eq 1). We examined the crotylboration–lactonization of aldehydes with **1** and **2** to understand the complementary nature of the Lewis acids. Herein we report the first general diastereoselective synthesis of *cis*- or *trans*- $\beta,\gamma$ -disubstituted- $\gamma$ -butyrolactones using *Z*-crotylboronates by the selection of appropriate catalysts for lactonization.



Our initial focus on the Lewis acid strength<sup>7</sup> (Table 1) confirmed that the presence of stronger Lewis acids pro-

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(2) (a) Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 293. (b) Roush, W. R.; Halterman, R. L. *J. Am. Chem. Soc.* **1986**, *108*, 294.

(3) Hoffmann, H. M. R.; Rabe, J. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 110.

(4) (a) Ramachandran, P. V.; Pratihari, D.; Biswas, D.; Srivastava, A.; Reddy, M. V. R.; *Org. Lett.* **2004**, *6*, 481. (b) Kennedy, J. W. J.; Hall, D. G. *J. Am. Chem. Soc.* **2002**, *124*, 898.

(5) (a) Although reagents **1** and **2** are *E*- according to Cahn–Ingold–Prelog rules, on the basis of analogy with *Z*-crotylboranes (ref 2), we use *Z*-crotylboration for convenience throughout this manuscript. (b) Reagents such as **2** have been termed “higher crotylboranes”, see the following example: Brown, H. C.; Narla, G. *Tetrahedron Lett.* **1997**, *38*, 219.

**Table 1.** Effect of Lewis Acids on Crotylboration of Benzaldehyde<sup>a</sup>

entry	boronate	Lewis acid	reacn		yield <sup>b</sup> (%)	dr <sup>c</sup> cis:trans
			time (h)	lactone		
1	1	Sc(OTf) <sub>3</sub>	8	4a	85	3:97
2	1	In(OTf) <sub>3</sub>	6	4a	85	2:98
3	1	Bu <sub>3</sub> BOTf	20	4a	90	7:93
4	1	ZnCl <sub>2</sub>	36	4a	94	90:10
5	1	Yb(OTf) <sub>3</sub>	36	4a	80	92:8
6	1	Et <sub>3</sub> B	48	4a	88	93:7
7	1	TiCl <sub>4</sub>	36	4a	80	90:10
8	2	Sc(OTf) <sub>3</sub>	14	5a	82	2:98
9	2	In(OTf) <sub>3</sub>	10	5a	91	2:98
10	2	Bu <sub>3</sub> BOTf	36	5a	80	2:98
11	2	Et <sub>3</sub> B	48	5a	85	95:5
12	2	Yb(OTf) <sub>3</sub>	30	5a	83	95:5

<sup>a</sup> Reaction conditions: crotylboronate **1** or **2** (1 mmol), benzaldehyde **3a** (1.5 mmol), and 20% catalyst in toluene at room temperature. Entries 3, 5, 6, 10, 11, and 12 are with 40% catalyst. Entries 3 and 4 are in diethyl ether and 5 and 12 are in THF. <sup>b</sup> Isolated yield after chromatography. <sup>c</sup> Determined by <sup>1</sup>H NMR of the crude reaction mixture.

vided the lactone with the reversed stereochemistry, whereas weaker Lewis acids showed no influence on the stereo-outcome (eq 2). Crotylboration of **3a** with **1**, in the presence of strong Lewis acids, such as In(OTf)<sub>3</sub> and Sc(OTf)<sub>3</sub>, was completed within 6–8 h at room temperature (rt), as compared to 7 d for the uncatalyzed reaction, and provided *trans*-**4a** with very high diastereoselectivity (Table 1, entries 1 and 2). On the other hand, Lewis acids with moderate activity, such as ZnCl<sub>2</sub>, Yb(OTf)<sub>3</sub>, Et<sub>3</sub>B, and TiCl<sub>4</sub> provided *cis*-**4a** in 90–93% diastereoselectivity. Similar diastereomeric ratios were observed in the case of **2** as well.

We then selected In(OTf)<sub>3</sub> for the crotylboration of a series of substituted benzaldehydes and noticed that the reversal in stereochemistry of the lactone is dependent on the electronic environment of the aldehydes as well! While an electron-donating substituent on the benzene ring inverted the stereochemistry, an electron-withdrawing group provided the *cis*-lactone (Table 2). A correlation was also observed for the rate of the reaction: benzaldehydes with electron-donating groups reacted faster than those with electron-withdrawing groups. Thus, the crotylboration of anisaldehydes (**3b–d**) and *p*-tolualdehyde (**3e**) with **1**, in the presence of catalytic In(OTf)<sub>3</sub>, provided the corresponding *trans*-lactones, *trans*-**4b–e** (entries 1–4) and the reaction of *p*- and *m*-nitro-, *p*-cyano-, *p*-trifluoromethyl- and pentafluorobenzaldehydes (**3j–n**) with **1** provided the corresponding *cis*-lactones, *cis*-**4j–n**, respectively, with very

(6) (a) Kennedy, J. W. J.; Hall, D. G. *J. Am. Chem. Soc.* **2002**, *124*, 11586. (b) Ishiyama, T.; Ahiko, T.-a.; Miyaoura, N. *J. Am. Chem. Soc.* **2002**, *124*, 12414. (c) Kennedy, J. W. J.; Hall, D. G. *J. Org. Chem.* **2004**, *69*, 4412.

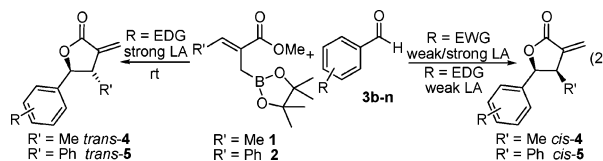
(7) For a review on the relative strength of Lewis acids, see the following: (a) Marshman, R. W. *Aldrichim. Acta.* **1995**, *28*, 77. (b) Kobayashi, S.; Manabe, K. *Pure Appl. Chem.* **2000**, *72*, 1373.

**Table 2.** Influence of Electronic Nature of Substituents of Benzaldehyde on Crotylboration with **1** and **2**<sup>a</sup>

entry	reagent	aldehyde		reacn time (h)	lactone		
		#	R		#	yield <sup>b</sup> (%)	dr <sup>c</sup> cis:trans
1	1	3b	4-MeO	12	4b	85	5:95
2	1	3c	3-MeO	8	4c	90	10:90
3	1	3d	2-MeO	7	4d	88	10:90
4	1	3e	4-Me	10	4e	95	3:97
5	1	3f	4-Cl	7	4f	90	33:67
6	1	3g	4-Br	8	4g	80	40:60
7	1	3h	3-Cl	8	4h	85	55:45
8	1	3i	2-Cl	8	4i	95	75:25
9	1	3j	4-NO <sub>2</sub>	18	4j	95	99:1
10	1	3k	3-NO <sub>2</sub>	14	4k	96	92:8
11	1	3l	4-CN	16	4l	89	97:3
12	1	3m	4-CF <sub>3</sub>	16	4m	95	98:2
13	1	3n	F <sub>5</sub>	18	4n	90	95:5
14	2	3b	4-MeO	10	5b	80	2:98
15	2	3e	4-Me	10	5e	98	2:98
16	2	3f	4-Cl	10	5f	80	31:69
17	2	3g	4-Br	10	5g	83	30:70
18	2	3j	4-NO <sub>2</sub>	16	5j	96	90:10
19	2	3l	4-CN	16	5l	95	98:2
20	2	3m	4-CF <sub>3</sub>	14	5m	87	95:5
21	2	3n	F <sub>5</sub>	18	5n	95	98:2

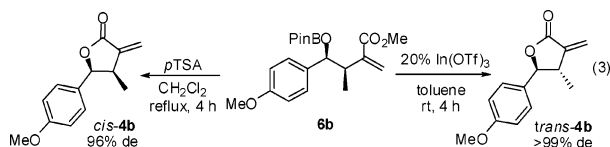
<sup>a</sup> Reaction condition: **1** or **2** (1 mmol), 20% In(OTf)<sub>3</sub>, and aldehyde **3b–n** (1.5 mmol) in toluene at room temperature. <sup>b</sup> Isolated yield after chromatography. <sup>c</sup> Determined by <sup>1</sup>H NMR of the crude reaction mixture.

high selectivity, (entry 9–12). Parallel observations were made with **2** as well.



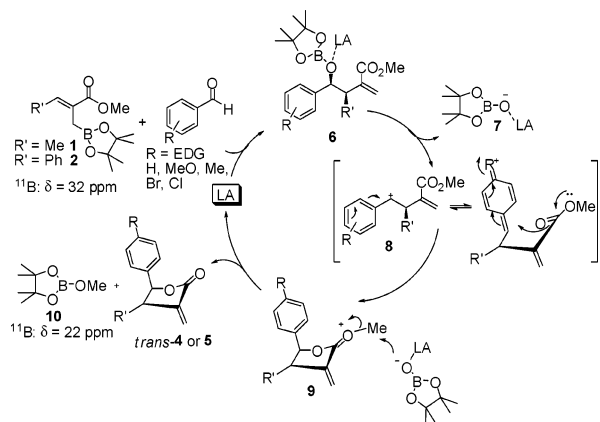
Halogen substituents provide a mixture of lactones. In line with the decreased resonance contribution, 4-bromobenzaldehyde (**3g**) provided increased ratio (40%) of *cis*-**4g** (entry 6) as compared to 4-chlorobenzaldehyde (**3f**), which gave 33% of *cis*-**4f** (entry 5). As expected, with an increased polar effect, 2-chlorobenzaldehyde (**3i**) provided 75% of *cis*-**4i** (entry 8).

After establishing a trend for the inversion of the lactone stereochemistry, we set out to trace the occurrence of the reversal. The crotylboration of **3b** with **1** under thermal condition, in the absence of a catalyst, provided the intermediate **6b**, which upon lactonization using *p*TSA, provided *cis*-**4b** in 96% de. However, lactonization using 20% In(OTf)<sub>3</sub> resulted in the exclusive formation of *trans*-**4b**, revealing that the reversal occurred during crotylboration following crotylboration.



A catalytic cycle for the formation of the *trans*-lactone is postulated in Scheme 1. The strong Lewis acid coordination

**Scheme 1.** Postulated Catalytic Cycle for *trans*-Lactone Formation



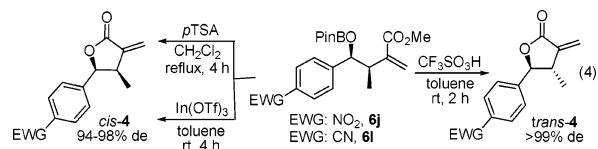
to the borate intermediate **6** provides the benzylic carbocation intermediate **8** via the elimination of **7**.<sup>8</sup> The lactonization is shown by curved arrows. The formation of *B*-methoxypinacolborane **10** was confirmed by <sup>11</sup>B NMR spectroscopy ( $\delta$ : 22 ppm, see experimental in Supporting Information). The role of the substituents and the rates of the reaction support the carbocation mechanism.

To achieve a truly general procedure, we proceeded to prepare the *trans*-lactones from benzaldehydes bearing

(8) Ramachandran, P. V.; Pratihari, D.; Biswas, D. *Chem. Commun.* **2005**, 1988.

electron-withdrawing groups also. On the basis of the mechanism, we envisaged the use of strong acids during the allylboration or lactonization. Following a literature report, we carried out the reaction of **3j** with **1** in the presence of 20% triflic acid, which resulted in *cis*-**4j** only.<sup>9</sup> Increasing the amount of the catalyst to 50% gave a 7:3 mixture and 1 equiv of the catalyst gave a 9:1 mixture favoring *trans*-**4j**. However, in the latter two cases, the yield of the product was considerably reduced, presumably because of the acidification of the reagent to the boronic acid.

We then treated the intermediate **6j**, prepared from **3j** and **1**, under thermal condition, with triflic acid (1 equiv) and obtained *trans*-**4j** exclusively in 80% yields! The generality of this reaction was demonstrated with **6l**, prepared from **3l** (eq 4).



In summary, we have presented a general and practical procedure for the highly diastereoselective preparation of either the *cis*- or *trans*- $\beta,\gamma$ -disubstituted- $\gamma$ -butyrolactones by appropriate choice of Lewis or Bronsted acid catalysts. A chiral version of this reaction is being pursued.

**Acknowledgment.** Financial support from the Herbert C. Brown Center for Borane Research is gratefully acknowledged.

**Supporting Information Available:** Experimental details and spectral data of compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(9) A *trans*-lactone was reported for the lone example of electron-rich benzaldehyde. Yu, S. H.; Ferguson, M. J.; McDonald, R.; Hall, D. G. *J. Am. Chem. Soc.* **2005**, *127*, 12808.