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Control of Stereochemistry: A General Synthesis of *cis*- or *trans*-β,γ-Disubstituted-γ-butyrolactones Following *Z*-Crotylboration

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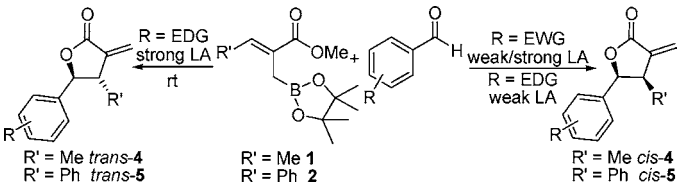
ABSTRACT

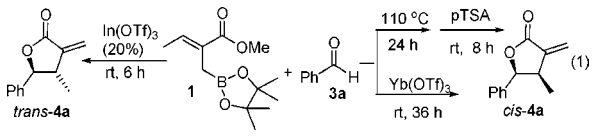


A general and practical procedure for the highly diastereoselective preparation of either the *cis*- or *trans*-β,γ-disubstituted-γ-butyrolactones by appropriate choice of Lewis or Bronsted acid catalysts during crotylboration or lactonization is reported. The cis-stereochemistry of the *Z*-crotylboration 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.[1] 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.[2] Stereospecific γ-butyrolactones are building blocks of several natural products and their stereoselective synthesis is significant.[3]

The crotylboration of benzaldehyde (**3a**) under thermal condition with functionalized *Z*-crotylboronates **1** and **2**, followed by lactonization is a general route to *cis*-γ-butyrolactones (eq 1).[4,5] The reactivity of similar crotylboronates has been improved with Lewis acid catalysis.[6] 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 $In(OTf)_3$, continued until lactonization and provided *trans*-**4a** (dr = 98:2) (eq 1) almost exclusively! However, $Yb(OTf)_3$-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*-β,γ-disubstituted-γ-butyrolactones using *Z*-crotylboronates by the selection of appropriate catalysts for lactonization.



Our initial focus on the Lewis acid strength[7] (Table 1) confirmed that the presence of stronger Lewis acids pro-

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

(4) (a) Ramachandran, P. V.; Pratihar, 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.

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Table 1. Effect of Lewis Acids on Crotylboration of Benzaldehyde[a]

entry	boronate	Lewis acid	reacn time (h)	lactone	yield[b] (%)	dr[c] cis:trans
1	**1**	$Sc(OTf)_3$	8	**4a**	85	3:97
2	**1**	$In(OTf)_3$	6	**4a**	85	2:98
3	**1**	Bu_2BOTf	20	**4a**	90	7:93
4	**1**	$ZnCl_2$	36	**4a**	94	90:10
5	**1**	$Yb(OTf)_3$	36	**4a**	80	92:8
6	**1**	Et_3B	48	**4a**	88	93:7
7	**1**	$TiCl_4$	36	**4a**	80	90:10
8	**2**	$Sc(OTf)_3$	14	**5a**	82	2:98
9	**2**	$In(OTf)_3$	10	**5a**	91	2:98
10	**2**	Bu_2BOTf	36	**5a**	80	2:98
11	**2**	Et_3B	48	**5a**	85	95:5
12	**2**	$Yb(OTf)_3$	30	**5a**	83	95:5

[a] 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. [b] Isolated yield after chromatography. [c] Determined by ^1H NMR of the crude reaction mixture.

vided the lactone with the reversed stereochemistry, whereas weaker Lewis acids showed no influence on the stereooutcome (eq 2). Crotylboration of **3a** with **1**, in the presence of strong Lewis acids, such as $In(OTf)_3$ and $Sc(OTf)_3$, 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 $ZnCl_2$, $Yb(OTf)_3$, Et_3B, and $TiCl_4$ provided *cis*-**4a** in 90−93% diastereoselectivity. Similar diastereomeric ratios were observed in the case of **2** as well.

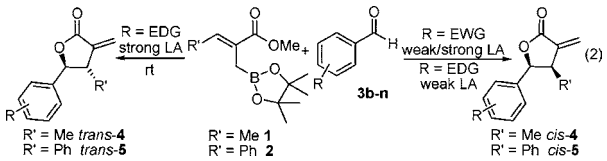
We then selected $In(OTf)_3$ for the crotylboration of a series of substituted benzaldehydes and noticed that the reversal in stereochemistry of the lactone is dependent on the electronic environment of the aldehydes as well! While an electron-donating substituent on the benzene ring inverted the stereochemistry, 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 $In(OTf)_3$, 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

Table 2. Influence of Electronic Nature of Substituents of Benzaldehyde on Crotylboration with **1** and **2**[a]

		aldehyde		reacn time	lactone		
entry	reagent	#	R	(h)	#	yld[b] (%)	dr[c] *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_2	18	**4j**	95	99:1
10	**1**	**3k**	3-NO_2	14	**4k**	96	92:8
11	**1**	**3l**	4-CN	16	**4l**	89	97:3
12	**1**	**3m**	4-CF_3	16	**4m**	95	98:2
13	**1**	**3n**	F_5	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_2	16	**5j**	96	90:10
19	**2**	**3l**	4-CN	16	**5l**	95	98:2
20	**2**	**3m**	4-CF_3	14	**5m**	87	95:5
21	**2**	**3n**	F_5	18	**5n**	95	98:2

[a] Reaction condition: **1** or **2** (1 mmol), 20% $In(OTf)_3$, and aldehyde **3b**−**n** (1.5 mmol) in toluene at room temperature. [b] Isolated yield after chromatography. [c] Determined by ^1H NMR of the crude reaction mixture.

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

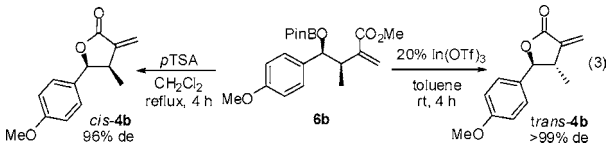


Halogen substituents provide a mixture of lactones. In line with the decreased resonance contribution, 4-bromobenzaldehyde (**3g**) provided increased ratio (40%) of *cis*-**4g** (entry 6) as compared to 4-chlorobenzaldehyde (**3f**), which gave 33% of *cis*-**4f** (entry 5). As expected, with an increased 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% $In(OTf)_3$ resulted in the exclusive formation of *trans*-**4b**, revealing that the reversal occurred during lactonization following crotylboration.

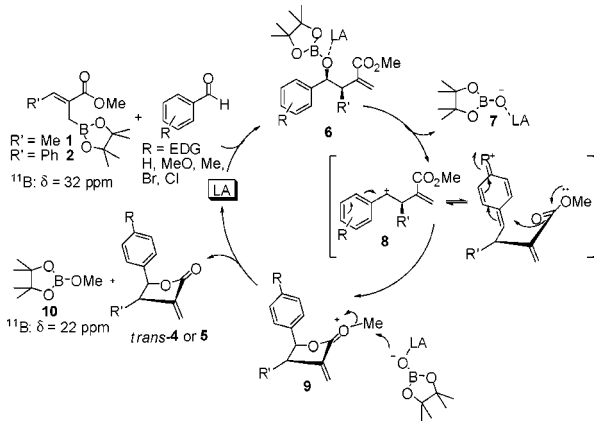
(6) (a) Kennedy, J. W. J.; Hall, D. G. *J. Am. Chem. Soc.* **2002**, *124*, 11586. (b) Ishiyama, T.; Ahiko, T.-a.; Miyaura, N. *J. Am. Chem. Soc.* **2002**, *124*, 12414. (c) Kennedy, J. W. J.; Hall, D. G. *J. Org. Chem.* **2004**, *69*, 4412.

(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.



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

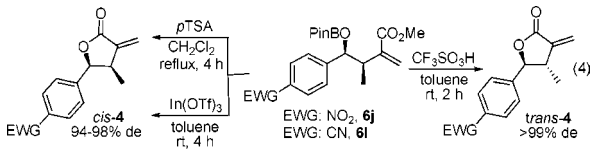
Scheme 1. Postulated Catalytic Cycle for *trans*-Lactone Formation



to the borate intermediate **6** provides the benzylic carbocation intermediate **8** via the elimination of **7**.[8] The lactonization is shown by curved arrows. The formation of *B*-methoxypinacolborane **10** was confirmed by ^{11}B NMR spectroscopy (δ: 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 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.[9] 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*- β,γ-disubstituted-γ-butyrolactones by appropriate choice of Lewis or Bronsted acid catalysts. A chiral version of this reaction is being pursued.

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

(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.