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Acidity-Directed Synthesis of Substituted γ-Butyrolactones from Aliphatic Aldehydes

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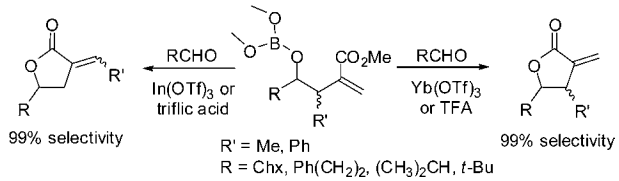
ABSTRACT



The strength of the Lewis or Brønsted acids controls the formation of either β,γ-disubstituted-α-methylene-γ-butyrolactones or γ-substituted-α-alkylidene-γ-butyrolactones via the lactonization or oxonia cope rearrangement–lactonization, respectively, of the borate intermediates resulting from the crotylboration of aliphatic aldehydes with ester-containing crotylboronates, such as (*E*)-methyl 2-boramethyl-2-butenoates.

α-Methylene-γ-butyrolactones have been shown to target the I$\kappa\beta$ kinase (IKK) and the transcription factor regulator nuclear factor-kappaB (NF-κB),[1] indicating their important role in inter- and intracellular signaling.[2] The binding of a series of suitably γ-substituted-α-alkylidene-γ-butyrolactones, analogues of diacylglycerol (DAG)-lactones, to protein kinase C (PK-C) revealed the enhanced affinity due to the α-alkylidine group.[3] Strategically substituted γ-butyrolactones, particularly α-alkylidene-γ-butyrolactones, are very important structural units in many natural products.[4] Their wide range of biological properties makes them popular synthetic targets.[5,6] Although several routes to their syntheses have been reported,[7] simple procedures are still being sought.

Preparation of diverse lactones by minor modifications in reaction conditions enhances the ability of synthetic chemists.[8] The following is the description of the first controlled one-pot synthesis of either β,γ-disubstituted-α-methylene- or γ-substituted-α-alkylidene-γ-butyrolactones from aliphatic aldehydes by an appropriate choice of Lewis or Bronsted acid-catalyzed crotylboration.[9]

In the presence of 10% $In(OTf)_3$, crotylboration of cyclohexanecarboxaldehyde (ChxCHO, **2a**) with (*E*)-methyl

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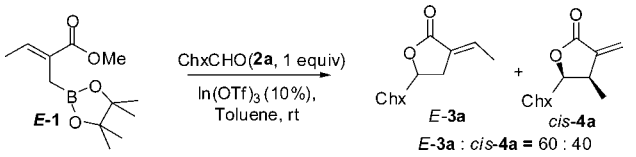
2-boramethyl-2-butenoate, *E*-**1**,[10,11] led to the formation of a mixture of α-*E*-ethylidene-γ-cyclohexyl-γ-butyrolactone (*E*-**3a**), along with the expected *cis*-α-methylene-β-methyl-γ-cyclohexyl-γ-butyrolactone (*cis*-**4a**) in a 3:2 ratio (Scheme 1). In contrast, a similar reaction of aromatic aldehydes, in

Scheme 1. $In(OTf)_3$-Catalyzed Crotylboration of **2a** with Crotylboronate *E*-**1**



the presence of Lewis or Bronsted acid, resulted in a general diastereoselective synthesis of either *cis*- or *trans*-β,γ-disubstituted-γ-butyrolactones.[8,12] Unlike the aromatics, the unexpected formation of *E*-**3a** for the aliphatic aldehydes led us to explore the reaction and determine the conditions for the exclusive preparation of either *E*-**3a** or *cis*-**4a**.

The presence of 20% $In(OTf)_3$ modestly increased the formation of the rearranged product *E*-**3a** from the crotylboration of 1 equiv of **2a** with *E*-**1**. While a similar result was also achieved by increasing the aldehyde equiv to 1.2, a combination of both variables provided a 3:1 ratio of *E*-**3a** and *cis*-**4a**. Further increasing the aldehyde to 1.5 equiv resulted in the formation of *E*-**3a** almost exclusively (Table 1, entry 5).

A mixture of *E*-**3a** and *cis*-**4a** in a 2:3 ratio was observed in the presence of 20% $In(OTf)_3$ when the aldehyde (**2a**) equivalent was decreased to 0.8. With 10% $In(OTf)_3$, a 1:3 mixture of lactones favoring *cis*-**4a** was obtained. Further decreasing the amount of aldehyde to 0.5 equiv provided *E*-**3a** and *cis*-**4a** in 15:85 ratio (Table 1, entry 9). Additional reduction of aldehyde renders this procedure impractical. The results are summarized in Table 1.

To achieve an exclusive synthesis of *cis*-**4a**, our next option was to examine the effect of Lewis acid strength[13] on the lactonization. While $Sn(OTf)_2$, $Cu(OTf)_2$, $Sc(OTf)_3$, and Bu_2BOTf-catalyzed reaction provided mixtures of lactones *E*-**3a** and *cis*-**4a**, the $Zn(OTf)_2$, $Yb(OTf)_3$-catalyzed

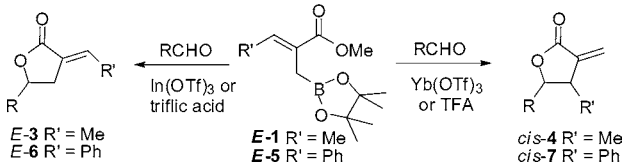
Table 1. Optimization of Reaction Conditions for the Selective Formation of *E*-**3a**/*cis*-**4a**[a]

entry	catalyst (mol %)	ChxCHO (equiv)	time (h)	yield[b] (%)	*E*-**3a**:*cis*-**4a**[c]
1	$In(OTf)_3$(10)	1.0	32	75	60:40
2	$In(OTf)_3$(20)	1.0	24	78	65:35
3	$In(OTf)_3$(10)	1.2	36	82	65:35
4	$In(OTf)_3$(20)	1.2	30	80	75:25
5	**$In(OTf)_3$(20)**	**1.5**	**30**	**90**	**99:1**
6	**CF_3SO_3H(20)**	**1.5**	**10**	**75**	**99:1**
7	$In(OTf)_3$(20)	0.8	24	80	40:60
8	$In(OTf)_3$(10)	0.8	36	75	25:75
9	$In(OTf)_3$(10)	0.5	24	75	15:85
10	$Sn(OTf)_2$(20)	1.1	30	80	70:30
11	$Cu(OTf)_2$(20)	1.1	24	76	66:34
12	$Sc(OTf)_3$(20)	1.1	24	85	58:42
13	Bu_2OTf(20)	1.1	18	70	58:42
14	$Zn(OTf)_2$(20)[d]	1.1	24	80	1:99
15	**$Yb(OTf)_3$(20)**[d]	**1.1**	**18**	**90**	**1:99**
16	**TFA(10)**	**1.1**	**24**	**80**	**1:99**

[a] Reaction conditions: *E*-**1**, **2a**, and catalyst in toluene at rt. [b] Isolated yield after chromatography. [c] Determined by ^1H NMR of the crude reaction mixture. [d] See ref 14.

reaction provided *cis*-**4a** essentially exclusively (Table 1, entries 14 and 15) (Scheme 2).[14]

Scheme 2. Selective Synthesis of γ-Substituted-α-*E*-alkylidene- or *cis*-β,γ-Disubstituted-α-methylene-γ-butyrolactones



On the basis of our earlier experience that the triflic acid-catalyzed reaction is faster than the Lewis acid-mediated reactions,[8] we also examined the effect of Brønsted acids, such as trifluoroacetic acid (TFA) and triflic acid, for the selective formation of either lactones. While a triflic acid-catalyzed reaction of *E*-**1** and **2a** provided *E*-**3a** in 99% selectivity (Table 1, entry 6), the weaker Brønsted acid, TFA-catalyzed crotylboration provided *cis*-**4a** in 99% selectivity (Table 1, entry 16).

To expand the versatility of this crotylboration−lactonization, we prepared the *Z*-crotylboronate[11] *Z*-**1** via the homologation[15] of the corresponding vinylaluminum[16] with

(9) For earlier reports on Lewis or Bronsted acid-catalyzed crotylboration, see: (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) Yu, S. H.; Ferguson, M. J.; McDonald, R.; Hall, D. G. *J. Am. Chem. Soc.* **2005**, *127*, 12808.

(10) Ramachandran, P. V.; Pratihar, D.; Biswas, D.; Reddy, M. V. R. *Org. Lett.* **2004**, *6*, 481.

(11) (a) Following the Cahn−Ingold−Prelog priority rules, the parent *Z*- and *E*-crotylboronates become *E*- and *Z*-, respectively (*E*-**1** and *E*-**5**, and *Z*-**1** and *Z*-**5**), when substituted with a COOMe group. Cahn, R. S.; Ingold, C.; Prelog. V. *Angew. Chem., Int. Ed. Engl.* **1966**, *5*, 385. (b) It should be remembered that the parent *Z*- and *E*-crotylboronates give *cis*- and *trans*-α-methyl homoallyl alcohols, respectively, via a six-membered Zimmerman−Traxler transition state. Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, *79*, 1920

(12) Elford, T. G.; Arimura, Y.; Yu, S. H.; Hall, D. G. *J. Org. Chem.* **2007**, *72*, 1276.

(13) For a review on the relative strengths of Lewis acids, see: Kobayashi, S.; Manabe, K. *Pure Appl. Chem.* **2000**, *72*, 1373.

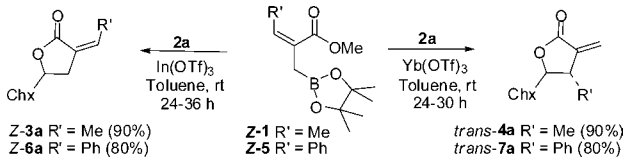
(14) It is noteworthy that we obtained the *cis*-lactone diastereoselectively with all of the catalysts, except in the case of $Zn(OTf)_2$ where a *cis*/*trans* ratio of 92:8 was obtained. The $Yb(OTf)_3$-catalyzed reaction provided a *cis*/*trans* lactone ratio of 99:1.

(15) Chataigner, I.; Lebreton, J.; Zammatio, F.; Villiéras, J. *Tetrahedron Lett.* **1997**, *38*, 3719.

(16) (a) Ramachandran, P. V.; Reddy, M. V. R.; Rudd, M. T. *Chem. Commun.* **1999**, 1979. (b) Ramachandran, P. V.; Rudd, M. T.; Burghardt, T. E.; Reddy, M. V. R. *J. Org. Chem.* **2003**, *68*, 9310.

iodomethylboronate.[17] The crotylboration of 1.5 equiv of **2a** with *Z*-**1**, in the presence of 20% $In(OTf)_3$, provided the corresponding α-*Z*-alkylidene lactone, *Z*-**3a**, almost exclusively (99:1) and the $Yb(OTf)_3$-catalyzed reaction provided *trans*-**4a** in 99% selectivity (Scheme 3).

Scheme 3. Selective Synthesis of γ-Substituted-α-*Z*-alkylidene- or *trans*-β,γ-Disubstituted-α-methylene-γ-butyrolactones



Having achieved the optimal conditions for the one-pot exclusive preparation of either α-*E*- or α-*Z*-alkylidene-γ-cyclohexyl-γ-butyrolactone (**3a**) or *cis*- or *trans*-α-methylene-β-alkyl-γ-cyclohexyl-γ-butyrolactone (**4a**) by changing the reagent (*E*- or *Z*-**1**) or the catalyst [$In(OTf)_3$ or $Yb(OTf)_3$], we further established the generality of the reaction with the crotylboration of a series of aliphatic aldehydes (**2b**−**d**) with **1** in the presence of either Lewis acid or Bronsted acid. In all of the cases the α-alkylidene lactone **3** or α-methylene lactone **4** was obtained almost exclusively (>99%) (Tables 2 and 3).

Table 2. Selective Synthesis of γ-Substituted-α-*E*/*Z*-alkylidene-γ-butyrolactones[a]

		RCHO			lactone		
entry	rgnt	no.	R	cat.[b]	no.	yield[c]	**3/6:4/7**[d]
1	*E*-**1**	**2a**	Chx	LA	*E*-**3a**	95	99:1
2	*E*-**1**	**2b**	$Ph(CH_2)_2$	LA	*E*-**3b**	85	99:1
3	*E*-**1**	**2c**	*i*-Pr	LA	*E*-**3c**	75	99:1
4	*E*-**1**	**2d**	*t*-Bu	LA	*E*-**3d**	80	99:1
5	*Z*-**1**	**2a**	Chx	LA	*Z*-**3a**	90	99:1
6	*E*-**5**	**2a**	Chx	LA	*E*-**6a**	85	98:2
7	*E*-**5**	**2b**	$Ph(CH_2)_2$	LA	*E*-**6b**	80	98:2
8	*E*-**5**	**2d**	*t*-Bu	LA	*E*-**6d**	70	98:2
9	*Z*-**5**	**2a**	Chx	LA	*Z*-**6a**	80	98:2
10	*E*-**1**	**2a**	Chx	BA	*E*-**3a**	75	99:1
11	*E*-**1**	**2b**	$Ph(CH_2)_2$	BA	*E*-**3b**	75	99:1

[a] Reaction conditions: aldehyde **2** (1.5−1.7 mmol) added to crotylboronate (1 mmol) and 20% LA or BA in toluene at rt for 12−48 h. [b] LA: $In(OTf)_3$. BA: CF_3SO_3H. [c] Percent isolated yield after chromatography. [d] Determined by ^1H NMR of the crude reaction mixture.

Crotylboration of these aldehydes with the phenyl-substituted "higher crotylboronate"[18] *E*-**5** was also examined. In these cases, the reaction rate was slower and 1.7 equiv of aldehyde was required to obtain the α-alkylidene lactone *E*-**6** with 98% selectivity. These results are also included in Tables 2 and 3.

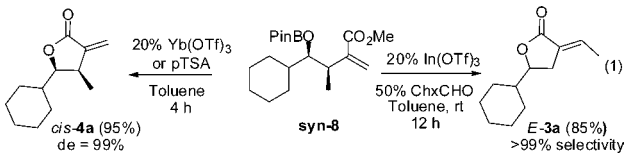
Table 3. Selective Synthesis of *cis*/*trans*-β,γ-Disubstituted-α-methylene-γ-butyrolactones[a]

		RCHO			lactone		
entry	rgnt	no.	R	cat.[b]	no.	yield[c]	**3/6:4/7**[d]
1	*E*-**1**	**2a**	Chx	LA	*cis*-**4a**	95	1:99
2	*E*-**1**	**2b**	$Ph(CH_2)_2$	LA	*cis*-**4b**	85	1:99
3	*E*-**1**	**2c**	*i*-Pr	LA	*cis*-**4c**	75	1:99
4	*E*-**1**	**2d**	*t*-Bu	LA	*cis*-**4d**	80	1:99
5	*Z*-**1**	**2a**	Chx	LA	*trans*-**4a**	90	1:99
6	*E*-**5**	**2a**	Chx	LA	*cis*-**7a**	85	1:99
7	*E*-**5**	**2b**	$Ph(CH_2)_2$	LA	*cis*-**7b**	80	1:99
8	*E*-**5**	**2d**	*t*-Bu	LA	*cis*-**7d**	70	1:99
9	*Z*-**5**	**2a**	Chx	LA	*trans*-**7a**	80	1:99
10	*E*-**1**	**2a**	Chx	BA	*cis*-**4a**	82	1:99
11	*E*-**1**	**2b**	$Ph(CH_2)_2$	BA	*cis*-**4b**	80	1:99
12	*E*-**1**	**2d**	*t*-Bu	BA	*cis*-**4d**	75	1:99

[a] Reaction conditions: aldehyde **2** (1.1 mmol) added to crotylboronate (1 mmol) and 20% LA or BA in toluene at rt for 18−36 h. [b] LA: $Yb(OTf)_3$. BA: TFA. [c] Percent isolated yield after chromatography. [d] Determined by ^1H NMR of the crude reaction mixture.

The formation of the unexpected α-*E*-alkylidene lactone was now analyzed. In the absence of a catalyst and under thermal condition, the crotylboration of aldehyde **2a** with *E*-**1** provides the intermediate *syn*-**8**.[11b] Exclusive formation of *cis*-**4a** in 99% de occurs upon lactonization with use of 20% pTSA, $In(OTF)_3$, or $Yb(OTf)_3$. However, the addition of 0.5 equiv of **2a** to *syn*-**8** in the presence of 20% $In(OTf)_3$ resulted in the exclusive formation of *E*-**3a**. A similar rearrangement did not occur in the presence of excess aldehyde and $Yb(OTf)_3$ (Scheme 4). This rearrangement is

Scheme 4. Lactonization or Rearrangement−Lactonization from Crotylboration Intermediate

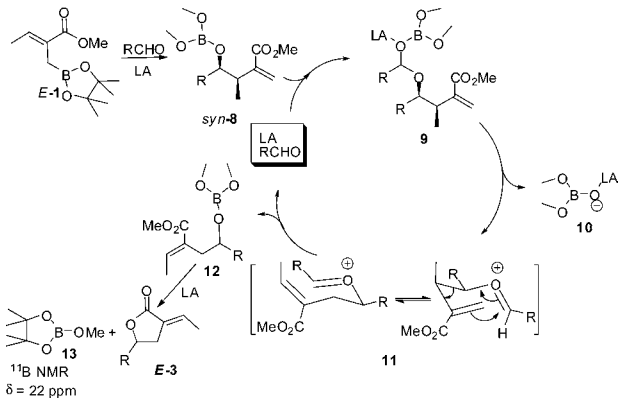


an irreversible process since the interconversion of *cis*-**4a** and *E*-**3a** was not possible in the presence of 20% $In(OTf)_3$ and excess aldehyde.

Thus, the formation of α-*E*-alkylidene-γ-alkyl-γ-butyrolactones can be rationalized as follows (Scheme 5).[19,20] The borate intermediate, *syn*-**8**, obtained from the initial crotylboration forms the acetal **9** in the presence of excess aldehyde.[21] The strong Lewis acid coordination to **9** results in an oxonium ion intermediate **11** via the elimination of **10**. This then undergoes an oxonia-Cope rearrangement and

(17) Wallace, R. H.; Zong. K. K. *Tetrahedron Lett.* **1992**, *33*, 6941.
(18) Reagents such as *E*- and *Z*-**5** have been termed "higher crotylboranes", see: Brown, H. C.; Narla, G. *Tetrahedron Lett.* **1997**, *38*, 219.
(19) For a discussion of a related one-pot synthesis of β- and δ-substituted homoallylic alcohols via crotylboration, see: Ramachandran, P. V.; Pratihar, D.; Biswas, D. *Chem. Commun.* **2005**, 1988.

Scheme 5. Catalytic Cycle for the Formation of α-Alkylidene Lactones



further addition of **10** providing the rearranged borate intermediate **12**. Lactonization and elimination of borate ester **13** provides the γ-substituted-α-alkylidene-γ-butyrolactones *E*-**3**.[22] A similar mechanism holds true for the formation of *Z*-**3** as well from *anti*-**8**.

In conclusion, we have developed an efficient process for the selective synthesis of *cis*- or *trans*-α-methylene-β,γ-disubstituted-γ-butyrolactones or *E*- or *Z*-α-alkylidine-γ-substituted-γ-butyrolactones via crotylboration with either the *E*- or *Z*-reagent, respectively, and the proper choice of either the Lewis or Bronsted acids. Further applications of this methodology for target synthesis are under way.

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

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(20) For the Lewis acid-catalyzed conversion of β- to δ-substituted homoallylic alcohols, see: (a) Nokami, J.; Yoshizane, K.; Matsuura, H.; Sumida, S. *J. Am. Chem. Soc.* **1998**, *120*, 6609. (b) Sumida, S. I.; Ohga, M.; Mitani, J.; Nokami, J. *J. Am. Chem. Soc.* **2000**, *122*, 1310. (c) Nokami, J.; Nomiyama, K.; Matsuda, S.; Imai, N.; Kataoka, H. *Angew. Chem., Int. Ed.* **2003**, *42*, 1273. (d) Loh, T. P.; Hu, Q. Y.; Ma, L. T. *J. Am. Chem. Soc.* **2001**, *123*, 2450. (e) Loh, T. P.; Tan, K. T.; Hu, Q. Y. *Angew. Chem., Int. Ed.* **2001**, *40*, 2921. (f) Cheng, H. S.; Loh, T. P. *J. Am. Chem. Soc.* **2003**, *125*, 2958.

(21) Addition of a different aldehyde (**2d**) to the intermediate *syn*-**8**, obtained from the allylboration of **2a** with *E*-**1** under refluxing conditions, provided a mixture of lactones *cis*-**4a** and *E*-**3d**.

(22) (a) The formation of *B*-methoxypinacolborane **13** was confirmed by ^{11}B NMR spectroscopy (δ 22 ppm, see the experimental details in the Supporting Information). (b) The PMR spectra of the progress of the reaction for the formation of the rearranged product *E*-**3a** is also provided in the Supporting Information.