Acidity Directed Synthesis of Substituted γ -Butyrolactones from Aliphatic Aldehydes

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General Informations: All operations were carried out under N₂ atmosphere in flame-dried glassware. Toluene and ether were purchased from Mallinckrodt chemicals. Other chemicals were used without further purification, unless otherwise noted. The ¹H, ¹¹B and ¹³C NMR spectra were recorded on a Varian Gemini-300 spectrometer with a Nalorac-Quad probe. Mass spectra were recorded using a Hewlett-Packard 5989B mass spectrometer/5890 series II gas chromatograph or a Finnigan mass spectrometer model 4000. CI gas used was isobutene. Flash chromatography was performed on 40-60 μm silica gel (230-400 mesh).

General Procedure for In(OTf)₃ or Triflic Acid-catalyzed Crotylboration of Aldehydes 2a-d with Crotylboronates E-1, Z-1, E-5, Z-5: To a solution of crotylboronate (1 mmol) and In(OTf)₃ or triflic acid (20 mol%) in toluene (2ml), aldehyde 2a-d (1.5 mmol in the case of crotylboronate E-1 and Z-1 and 1.7 mmol in the case of crotylboronate E-5 and Z-5) was added and the solution was stirred at rt. The reaction was followed by ¹¹B NMR spectroscopy. Upon completion of the reaction (change of δ from 32 ppm for crotylboronate to 22 ppm for methoxypinacolborane), the reaction mixture was washed with water and the product was extracted with diethyl ether (3X5ml). The combined organic layer was washed with brine, dried over anhydrous MgSO₄, and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, hexanes:ethyl acetate :: 95:5) to obtain E-3a-d, Z-3a, E-6a-c or Z-6a in 70-95% yield.

Table SI-1. Selective synthesis of γ-substituted-α-E-alkylidene-γ-butyrolactones 3 and 6.

entry	reagent	RCHO		catalyst ^a	time (h)	lactone		
		#	R			#	yield(%)	3/6:4/7
1	E-1	2a	Chx	LA	30	E-3a	95	99:1
2	E-1	2b	Ph(CH ₂) ₂	LA	24	E-3b	85	99:1
3	E-1	2c	<i>i</i> -Pr	LA	30	E-3c	75	99:1
4	E-1	2d	<i>t</i> -Bu	LA	36	E-3d	80	99:1
5	Z-1	2a	Chx	LA	30	Z-3a	90	99:1
6	E-5	2a	Chx	LA	30	E-6a	85	98:2
7	E-5	2b	Ph(CH ₂) ₂	LA	36	E-6b	80	98:2
8	E-5	2d	<i>t</i> -Bu	LA	48	E-6d	70	98:2
9	Z-5	2a	Chx	LA	30	Z-6a	80	98:2
10	E-1	2a	Chx	BA	10	E-3a	75	99:1
11	E-1	2b	Ph(CH ₂) ₂	BA	12	E-3b	75	99:1

^aLA: In(OTf)₃, BA: CF₃SO₃H

General Procedure for Yb(OTf)₃ or Trifluoroacetic Acid (TFA)-catalyzed Crotylboration of Aldehydes **2a-d with Crotylboronates **E-1**, **Z-1**, **E-5**, **Z-5**:** To a solution of crotylboronate (1 mmol) and Yb(OTf)₃ or TFA (20 mol%) in toluene (2ml), aldehyde **2a-d** (1.1 mmol) was added and the solution was stirred at rt. The reaction was followed by ¹¹B NMR spectroscopy. Upon completion of the reaction (change of δ from 32 ppm for crotylboronate to 22 ppm for methoxypinacolborane), the reaction mixture was washed with water and the product was extracted with diethyl ether (3X5ml). The combined organic layer was washed with brine, dried over anhydrous MgSO₄, and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, hexanes:ethyl acetate :: 95:5) to obtain *cis*-**4a-d**, *trans*-**4a**, *cis*-**7a-c** or *trans*-**7a** in 80-95% yield.

Table SI-2. Selective synthesis of *cis/trans*- β,γ -disubstituted- α -methylene- γ -butyrolactones **4 and **7**.**

entry	reagent	RCHO		catalyst ^a	time h	lactone		
		#	R			#	yield(%)	3/6:4/7
1	E-1	2a	Chx	LA	18	<i>cis</i> - 4a	95	1:99
2	E-1	2b	Ph(CH ₂) ₂	LA	24	<i>cis</i> - 4b	85	1:99
3	E-1	2c	<i>i</i> -Pr	LA	18	<i>cis</i> - 4c	75	1:99
4	E-1	2d	<i>t</i> -Bu	LA	24	<i>cis</i> - 4d	80	1:99
5	Z-1	2a	Chx	LA	20	<i>trans</i> - 4a	90	1:99
6	E-5	2a	Chx	LA	36	<i>cis</i> - 7a	85	1:99
7	E-5	2b	Ph(CH ₂) ₂	LA	30	<i>cis</i> - 7b	80	1:99
8	E-5	2d	<i>t</i> -Bu	LA	30	<i>cis</i> - 7d	70	1:99
9	Z-5	2a	Chx	LA	38	<i>trans</i> - 7a	80	1:99
10	E-1	2a	Chx	BA	24	<i>cis</i> - 4a	82	1:99
11	E-1	2b	Ph(CH ₂) ₂	BA	20	<i>cis</i> - 4b	80	1:99
12	E-1	2d	<i>t</i> -Bu	BA	30	<i>cis</i> - 4d	75	1:99

^aLA: Yb(OTf)₃, BA: CF₃CO₂H (TFA)

(E)-5-cyclohexyl-3-ethylenedihydrofuran-2(3H)-one E-3a: ¹H NMR (300 MHz, CDCl₃) δ (ppm): 6.74 (m, 1H), 4.24 (q, *J* = 7.05 Hz, *J* = 14.1, 1H), 2.85 (m, 1H), 2.52 (m, 1H), 1.83 (d, *J* = 6.9 Hz, 3H), 1.74 (m, 4H), 1.51 (m, 1H), 1.19 (m, 4H), 1.03 (m, 2H); ¹³C NMR (75 MHz, CDCl₃) δ (ppm): 170.9, 135.1, 127.7, 81.5, 43.2, 28.8, 28.2, 27.8, 26.3, 25.7, 25.6, 15.7; HRMS-EI *m/z* 194.1307 (calcd.), 194.1302 (actual). IR (cm⁻¹) 2927, 2854, 1750, 1681, 1210.

(Z)-5-cyclohexyl-3-ethylidenedihydrofuran-2(3H)-one Z-3a: ¹H NMR (300 MHz, CDCl₃) δ (ppm): 6.25 (m, 1H), 4.16 (q, *J* = 7.23 Hz, *J* = 10.86, 1H), 2.83 (m, 1H), 2.62 (m, 1H), 2.15 (d, *J* = 7.23 Hz, 3H), 1.92 (m, 1H), 1.69 (m, 4H), 1.49 (m, 1H), 1.21 (m, 4H), 0.99 (m, 1H); HRMS-EI *m/z* 194.1307 (calcd.), 194.1301 (actual). IR (cm⁻¹) 2927, 2854, 1750, 1681, 1210.

(E)-3-ethylidene-5-phenethyldihydrofuran-2(3H)-one E-3b: ¹H NMR (300 MHz, CDCl₃) δ (ppm): 6.80 (m, 1H), 4.50 (m, 1H), 2.9 (m, 1H), 2.79 (m, 2H), 2.48 (m, 1H), 1.98 (m, 2H), 1.83 (d, *J* = 7.08, 3H); ¹³C NMR (75 MHz, CDCl₃) δ (ppm): 170.5, 140.8, 135.7, 128.6, 128.5, 126.3, 126.2, 76.6, 38.4, 31.4, 31.1, 15.7; HRMS-EI *m/z* 216.1150 (calcd.), 216.1156 (actual). IR (cm⁻¹) 3027, 2932, 2861, 1755, 1681, 1603, 1496, 1454, 1217.

(E)-3-ethylidene-5-isopropyldihydrofuran-2(3H)-one E-3c: ¹H NMR (300 MHz, CDCl₃) δ (ppm): 6.79 (m, 1H), 4.25 (m, 1H), 2.81 (m, 1H), 2.52 (m, 1H), 1.80 (d, *J* = 7.03 Hz, 2H), 1.12 (m, 6H); HRMS-EI *m/z* 154.0993 (calcd.), 154.0988 (actual). IR (cm⁻¹) 2964, 2873, 1760, 1682, 1481, 1209.

(E)-5-*t*-butyl-3-ethylidenedihydrofuran-2(3H)-one E-3d: ¹H NMR (300 MHz, CDCl₃) δ (ppm): 6.72 (m, 1H), 4.19 (dd, *J* = 8.04 Hz, *J* = 1.38 Hz, 1H), 2.72 (m, 1H), 2.56 (m, 1H), 1.81 (d, *J* = 7.02 Hz, 2H), 0.91 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ (ppm): 171.0, 135.1, 128.0, 84.8, 34.3, 26.4, 24.6, 15.7; HRMS-EI *m/z* 168.1150 (calcd.), 168.1151 (actual). IR (cm⁻¹) 2964, 2874, 1760, 1683, 1480, 1369, 1209.

(E)-3-benzylidene-5-cyclohexyldihydrofuran-2(3H)-one E-6a: ¹H NMR (300 MHz, CDCl₃) δ (ppm): 7.51 (m, 5H), 4.35 (q, *J* = 13.64 Hz, *J* = 6.70 Hz, 1H), 3.25 (m, 1H), 2.92 (m, 1H), 1.90 (m, 1H), 1.76 (m, 5H), 1.24 (m, 5H); ¹³C NMR (75 MHz, CDCl₃) δ (ppm): 171.1, 136.1, 130.0, 129.7, 128.9, 124.9, 81.6, 43.3, 31.4, 28.0, 27.8, 26.3, 25.7, 25.6, 24.7; HRMS-EI *m/z* 256.1463 (calcd.), 256.1466 (actual). IR (cm⁻¹) 2927, 2853, 1750, 1654, 1449, 1227.

(E)-3-Benzylidene-5-*tert*-butyldihydrofuran-2(3H)-one E-6d: NMR (300 MHz, CDCl₃) δ (ppm): 0.98 (s, 9H), 2.93 (m, 1H), 3.12 (m, 1H), 4.31 (m, 1H), 7.53 (m, 6H); NMR (75 MHz, CDCl₃) δ (ppm): 172.4, 136.2, 134.8, 130.1, 129.8, 129.0, 125.3, 84.9, 34.4, 29.1, 24.7; HRMS-EI *m/z* 230.1307 (calcd.), 230.1310 (actual). IR (cm⁻¹) 2961, 2925, 2870, 1733, 1645, 1449, 1261.

cis-5-cyclohexyl-4-methyl-3-methylenedihydrofuran-2(3H)-one cis-4a: ^1H NMR (300 MHz, CDCl_3) δ 6.10 (d, $J = 1.8$ Hz, 1H), 5.48 (d, $J = 1.50$ Hz, 1H), 4.1 (t, $J = 7.05$ Hz, 1H), 3.10 (m, 1H), 1.70 (m, 6H), 1.20 (m, 8H).; HRMS-EI m/z 194.1307 (calcd.), 194.1301 (actual). IR (cm^{-1}) 2930, 2854, 1764, 1269.

trans-5-cyclohexyl-4-methyl-3-methylenedihydrofuran-2(3H)-one trans-4a: ^1H NMR (300 MHz, CDCl_3) δ 6.22 (d, $J = 2.97$ Hz, 1H), 5.54 (d, $J = 2.52$ Hz, 1H), 3.81 (t, $J = 5.91$ Hz, 1H), 2.84 (m, 1H), 1.75 (m, 5H), 1.24 (d, $J = 6.84$ Hz, 3H), 1.20 (m, 5H).; HRMS-EI m/z 194.1307 (calcd.), 194.1302 (actual). IR (cm^{-1}) 2930, 2853, 1765, 1269.

cis-4-methyl-3-methylene-5-phenethyldihydrofuran-2(3H)-one cis-4b: ^1H NMR (300 MHz, CDCl_3) δ 7.23 (m, 5H), 6.23 (d, $J = 2.67$ Hz, 1H), 5.54 (d, $J = 2.37$ Hz, 1H), 4.51 (m, 1H), 3.16 (m, 1H), 2.91 (m, 1H), 2.71 (m, 1H), 1.81 (m, 2H), 1.15 (d, $J = 7.14$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ (ppm) 169.7, 140.9, 140.7, 128.6, 126.2, 121.0, 120.9, 80.1, 37.4, 32.7, 31.8, 13.9.; HRMS-EI m/z 216.1150 (calcd.), 216.1155 (actual). IR (cm^{-1}) 2928, 1760, 1602, 1497, 1454, 1262.

cis-5-isopropyl-4-methyl-3-methylenedihydrofuran-2(3H)-one cis-4c: ^1H NMR (300 MHz, CDCl_3) δ (ppm) 6.20 (d, $J = 1.8$ Hz, 1H), 5.50 (d, $J = 1.50$ Hz, 1H), 4.1 (t, $J = 7.05$ Hz, 1H), 3.10 (m, 1H), 1.91 (m, 1H), 1.12 (d, $J = 7.10$ Hz, 3H), 0.91 (m, 6H); ^{13}C NMR (75 MHz, CDCl_3) δ (ppm) 170.4, 142.1, 119.9, 85.9, 37.4, 28.5, 18.9, 18.9, 14.4.; HRMS-EI m/z 154.0994 (calcd.), 154.0991 (actual). IR (cm^{-1}) 2931, 2853, 1761, 1269.

cis-5-cyclohexyl-3-methylene-4-phenyldihydrofuran-2(3H)-one cis-7a: ^1H NMR (300 MHz, CDCl_3) δ (ppm): 7.35 (m, 5H), 6.32 (d, $J = 1.8$ Hz, 1H), 5.56 (d, $J = 1.53$ Hz, 1H), 4.31 (m, 1H), 4.22 (m, 1H), 1.96 (m, 1H), 1.68 (m, 1H), 1.53 (m, 2H), 1.35 (m, 2H), 1.06 (m, 4H), 0.86 (m, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ (ppm): 170.2, 140.5, 138.7, 129.4, 128.7, 128.6, 127.5, 123.1, 85.9, 49.2, 37.9, 29.1, 28.4, 26.1, 25.2, 24.7. HRMS-EI m/z 256.1463 (calcd.), 256.1461 (actual). IR (cm^{-1}) 2930, 2853, 1756, 1716, 1662, 1496, 1453, 1270.

cis-3-methylene-5-phenethyl-4-phenyldihydrofuran-2(3H)-one cis-7b: ^1H NMR (300 MHz, CDCl_3) δ (ppm): 7.15 (m, 10H), 6.47 (d, $J = 2.61$ Hz, 1H), 5.62 (d, $J = 2.3$ Hz, 1H), 4.70 (m, 1H), 4.35 (m, 1H), 2.75 (m, 1H), 2.58 (m, 1H), 1.66 (m, 1H), 1.43 (m, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ (ppm): 170.0, 140.7, 139.0, 137.5, 129.1, 128.8, 128.6, 128.4, 127.8, 126.1, 124.5, 80.5, 49.3, 34.3, 31.8.; HRMS-EI m/z 274.0994 (calcd.), 278.1307 (calcd.), 278.1311. IR (cm^{-1}) 2928, 1760, 1602, 1496, 1454, 1262.

cis-5-isopropyl-3-methylene-4-phenyldihydrofuran-2(3H)-one cis-7c: ^1H NMR (300 MHz, CDCl_3) δ (ppm): 7.40 (m, 5H), 6.39 (d, $J = 2.5$ Hz, 1H), 5.64 (d, $J = 2.2$ Hz, 1H), 4.32 (m, 2H), 1.07 (d, $J = 6.6$ Hz, 3H), 0.75 (d, $J = 6.9$ Hz, 1H).; HRMS-EI m/z 216.1150 (calcd.), 216.1151. IR (cm^{-1}) 2931, 2853, 1761, 1495, 1451, 1269.

300 MHz ^1H NMR of compound *E*-3a in CDCl_3

75.5 MHz ^{13}C NMR of compound *E*-3a in CDCl_3

300 MHz ^1H NMR of compound **E-3b** in CDCl_3

75.5 MHz ¹³C NMR of compound *E-3b* in CDCl₃

300 MHz ^1H NMR of compound *E*-3c in CDCl_3

300 MHz ^1H NMR of compound **E-3d** in CDCl_3

75.5 MHz ^{13}C NMR of compound *E*-**3d** in CDCl_3

300 MHz ^1H NMR of compound Z-3a in CDCl_3

300 MHz ^1H NMR of compound *E*-6a in CDCl_3

75.5 MHz ¹³C NMR of compound *E*-6a in CDCl₃

300 MHz ^1H NMR of compound **E-6d** in CDCl_3

75.5 MHz ^{13}C NMR of compound *E*-6d in CDCl_3

300 MHz ^1H NMR of compound *cis*-4a in CDCl_3

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300 MHz ^1H NMR of compound *cis*-4b in CDCl_3

75.5 MHz ¹³C NMR of compound *cis*-4b in CDCl₃

300 MHz ¹H NMR of compound *cis*-4c in CDCl₃

75.5 MHz ^{13}C NMR of compound *cis*-**4c** in CDCl_3

300 MHz ^1H NMR of compound *trans*-**4a** in CDCl_3

300 MHz ^1H NMR of compound *cis*-7a in CDCl_3

75.5 MHz ^{13}C NMR of compound *cis*-**7a** in CDCl_3

300 MHz ^1H NMR of compound *cis*-7b in CDCl_3

75.5 MHz ^{13}C NMR of compound *cis*-**7b** in CDCl_3

300 MHz ^1H NMR of compound *cis*-7c in CDCl_3

The ^1H NMR spectra of the progress of the reaction for the formation of the rearranged product *E*-3a in $\text{In}(\text{OTf})_3$ -catalyzed crotylboration of **2a** with *E*-1