Dramatic Rate Enhancement with Preservation of Stereospecificity

in the

First Metal-Catalyzed Additions of Allylboronates

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General Information

Boronates **1** were prepared according to our previously published procedure.¹ Boronate **4** was prepared according to the procedure of Hoffmann and Schlapbach.² Toluene and CH₂Cl₂ were distilled over CaH₂, and all aldehydes were purified by Kugelrohr distillation before use. All other chemicals, including the Lewis Acids, were purchased from either the Aldrich Chemical Company or Caledon Chemicals and used as received. Thin layer chromatography data was performed on Merck Silica Gel 60 F254 plates and were visualized with UV light and 1% KMnO_{4(aq)}. R_f values are approximate. NMR spectra were recorded on Bruker AM 300, Bruker AM 200, Varian INOVA-300, INOVA-400 or INOVA-500 instruments. The residual solvent protons (¹H) or the solvent carbons (¹³C) were used as internal standards. Boron NMR spectra are referenced to external BF₃·OEt₂; ¹⁹F spectra are referenced to external CFC₃ and were run by Glen Bigam of the University of Alberta Spectral Services. ¹H NMR data are presented as follows: chemical shift in ppm downfield from tetramethylsilane (multiplicity, coupling constant, integration). The following abbreviations are used in reporting NMR data: s, singlet; br s, broad singlet; d, doublet; t, triplet; q, quartet; qt, quartet of triplets; dd, doublet of doublets; dt, doublet of triplets; AB, AB quartet; m, multiplet. High resolution mass spectra were recorded by the University of Alberta Mass Spectrometry Services Laboratory using either electron impact (EI) or electrospray (ES) ionization techniques. Infrared spectra were recorded by University of Alberta Spectral Services and combustion analyses were performed by the University of Alberta Micro-Analytical Lab.

General Procedure for NMR Catalyst Search

The reaction with scandium triflate is representative. An NMR tube was charged with Sc(OTf)₃ (9 mg, 0.02 mmol) and dried overnight under vacuum at 130 °C. Benzaldehyde (5 µL, 0.05 mmol) was then added, followed by a 0.07 M solution of boronate **1a** in CD₂Cl₂ (0.75 mL, 0.053 mmol). ¹H and ¹¹B

¹ Kennedy, J. W. J.; Hall, D. G. *J. Am. Chem. Soc.* **2002**, *124*, 898-899.

² Hoffmann, R. W.; Schlapbach, A. *Tetrahedron* **1992**, *48*, 1959-1968.

NMR spectra were recorded daily for 7 days. The quartet at 4.14 (O-CH₂-Me for boronate **1a**) and the singlet at 6.32 (olefin proton for lactone **2a**) as reference peaks in the proton spectra; the boron spectra only showed two peaks. Some ¹H spectra were complicated by the paramagnetic nature of some of the catalysts.³ To remove any adventitious triflic acid, one NMR reaction was run using Sc(OTf)₃, boronate **1a** (12.8 mg in 0.75 mL of CD₂Cl₂), benzaldehyde (4.5 μL, 0.044 mmol), and diisopropylamine (4.2 μL, 0.024 mmol).

Figure 1: Comparison of Sc(OTf)₃, Cu(OTf)₂, and Yb(OTf)₃ in CD₂Cl₂, Toluene-*d*₈, and THF-*d*₆

Studies with boronate **4** were performed in an analogous manner, except that the spectra were recorded every hour for 7 hours, reflecting the increased reactivity of these boronates.

³ This method was inspired by that of Brown and co-workers: Brown, H. C.; Racherla, U. S.; Pellechia, P. J. *J. Org. Chem.* **1990**, 55, 1868-1874.

Figure 2: Reaction rates with Boronate 4

Figure 3: Representative ^1H NMR Spectrum for 1a/2a (CD_2Cl_2 , 500 MHz)

Figure 4: Representative ^{11}B NMR Spectrum for 1a/2a (CD_2Cl_2 , 64 MHz)

Estimation of half-life reaction times for 1a and 4 (footnote 10)

The half-life reaction time between $\text{Sc}(\text{OTf})_3$ -catalyzed and uncatalyzed runs in the case of control allylboronate **4** was taken directly from the graph found in the S.I section. In the case of allylboronate **1a**, the data for the background uncatalyzed run were extrapolated from an expanded version of Figure 1, and assumed plot linearity. This analysis constitutes an underestimation given the expected exponential shape of the plot. These data were collected under the NMR screening conditions described previously of 50 mol% $\text{Sc}(\text{OTf})_3$.

NMR studies on mixtures of 1a and $\text{Sc}(\text{OTf})_3$

Due to the high concentrations of allylboronate and metal needed in these experiments, it was necessary to carry out these experiments in acetonitrile in order to obtain a completely homogeneous solution. Experiments in CD_2Cl_2 also revealed the presence of a defined complex although in much smaller proportion due to the limited solubility of $\text{Sc}(\text{OTf})_3$ in that solvent. In CD_3CN , the proportion of the complex vs free allylboronate **1a** was high and it was found to increase with the increasing amount

of $\text{Sc}(\text{OTf})_3$. With 50 mol% $\text{Sc}(\text{OTf})_3$ the complex/free **1a** ratio is 1:2, and with 100 mol% $\text{Sc}(\text{OTf})_3$ the complex/free **1a** ratio is 1:1. The latter conditions are those used for the spectrum shown below.

Proton NMR chemical shift analysis:

A: Free 1a			B: 1a - $\text{Sc}(\text{OTf})_3$			
Position	Signal	δ (ppm)	Position	Signal	δ (ppm)	Difference
1	CH_3	1.22	1'	CH_3	1.43	+ 0.21
2	CH_2	4.10	2'	CH_2	4.62	+ 0.52
3	C	-	3'	C	-	-
4	C	-	4'	C	-	-
5	C	-	5'	C	-	-
6	CH_2	2.35	6'	CH_2	2.60	+ 0.25
7	CH_3	1.00	7'	CH_3	1.08	+ 0.08
8	CH_3	1.74	8'	CH_3	1.99	+ 0.21
9	CH_2	1.75	9'	CH_2	1.55	- 0.20
10	pinacol C	-	10'	pinacol C	-	-
11	pinacol CH_3	1.18	11'	pinacol CH_3	1.38	+ 0.20

Generally, all signals in **1a** experienced slight broadening with a significant downfield chemical shift upon formation of a complex with $\text{Sc}(\text{OTf})_3$. Remarkably, a +0.2 ppm shift was observed for the pinacol methyl protons, similar to the +0.21 ppm shift for the methyl protons on the ethoxycarbonyl group. This result constitutes reasonable evidence for the formation of a chelate of type **3** (see paper Figure 3), implicating coordination of scandium to both the carboxyester and the boronate groups. It is very unlikely that such a large downfield shift in the pinacol methyl resonance could arise in a single point complex between $\text{Sc}(\text{III})$ and the carboxyester (to be true, this would require the inductive effect to be felt through as many as 8 atoms away). In the absence of crystallographic data, however, it does not seem possible to assess whether one or two boronate oxygens are coordinated to scandium. Methylene number 9 is the only signal experiencing an upfield shift. It is plausible, due to a significant increase of the electrophilicity of the boronate upon formation of the scandium complex, that it may exist as a tetrahedral adduct with the solvent (acetonitrile) or adventitious water molecules. Boron NMR shift data (CD_3CN , 64 MHz, 33.8 ppm for **1a**, 12.8 ppm for **1a**- $\text{Sc}(\text{OTf})_3$) is also consistent with a tetrahedral boronate.

Figure 5: ^1H NMR of Boronate 1a in CD_3CN (400 MHz)

Figure 6: ^1H NMR of Boronate 1a with 1 equiv. $\text{Sc}(\text{OTf})_3$ in CD_3CN (400 MHz) with Expansion

Reaction of Aldehydes with a Tetrasubstituted Allylsilane

The corresponding trimethylallylsilane of allylboronate **1a** was synthesized in a manner similar to that described previously.¹ Commercial iodomethyltrimethylsilane (Aldrich, distilled) was used as the electrophile to trap the vinylcopper intermediate. The resulting allylsilane was obtained as a pure isomer and purified by flash-chromatography (EtOAc/Hexanes). It was reacted with benzaldehyde with a variety of Lewis acids under different stoichiometries at room temperature in methylene chloride.

Summary of results

Sc(OTf)₃ and Cu(OTf)₂ (10-20 mol%, 6-10 days): No reaction

TiCl₄ (20% up to 100 mol%, 14 days): only a 21% yield of lactone **2a** in a 3:1 isomer ratio favouring the same one obtained in the allylboration.

Experimental Procedures for Lactones 2⁴

(4*R**, 5*R**)-3-Methylidene-2-oxo-4-ethyl-4-methyl-5-phenyltetrahydrofuran **2a**

A slurry of boronate **1a** (140 mg, 0.495 mmol), benzaldehyde (55 mg, 0.52 mmol) and Sc(OTf)₃ (25 mg, 0.052 mmol) were stirred in toluene (0.5 mL) at RT under Argon for 24 h. The mixture was then diluted with NH₄Cl/NH₄OH (9:1, v/v, 5 mL) and extracted with Et₂O (3 x 5 mL). The combined extractions were washed with brine (5 mL), dried (Na₂SO₄) and evaporated to give the product (99 mg, 0.46 mmol, 93%). ¹H NMR (CDCl₃, 500 MHz) was identical to that previously reported.¹ Similarly, reactions using Cu(OTf)₂ and Yb(OTf)₃ gave the product in yields of 67% and 91% respectively after flash chromatography.

(4*R**, 5*S**)-3-Methylidene-2-oxo-4-methyl-4-butyl-5-(2-iodophenyl)tetrahydrofuran **2b**

A solution of boronate **1b** (124 mg, 0.401 mmol) and *m*-iodobenzaldehyde (142 mg, 0.614 mmol) in toluene (0.4 mL) was treated with Sc(OTf)₃ (20 mg, 0.041 mmol). The resulting slurry was

⁴ Although ¹H NMR studies showed that these reactions were generally complete within 6 h, they were allowed to run 16-24 hours for practical considerations.

stirred at RT under Ar for 24 h. Reaction was then diluted with water (5 mL) and extracted with Et₂O (3 x 5 mL). The combined extracts were washed with brine (5 mL), dried (Na₂SO₄) and evaporated to give the crude product (280 mg). Flash chromatography (1% EtOAc/Toluene, 30 g SiO₂) gave the pure product (82 mg, 0.22 mmol, 55%).

TLC (1% EtOAc/Toluene, KMnO₄): 0.42;

¹H NMR (400 MHz, CDCl₃): δ 7.76 (m, 2H), 7.27 (m, 1H), 7.11 (apparent t, *J* = 7.8 Hz, 1H) 6.32 (s, 1H), 5.50 (s, 1H), 5.06 (s, 1H), 1.32 (s, 3H), 1.15-0.90 (m, 5H), 0.78 (m, 1H), 0.73 (t, *J* = 7.0 Hz, 3H);

¹³C NMR (100 MHz, CDCl₃): δ 169.9, 143.3, 137.4, 137.2, 134.9, 130.0, 125.3, 121.4, 94.1, 87.3, 46.9, 34.3, 25.0, 22.8, 21.6, 13.8;

IR (CH₂Cl₂ cast, cm⁻¹): 2957, 1770, 1660, 1592, 1119;

HRMS (EI, *m/z*) Calcd for C₁₆H₁₉O₂I: 370.04297. Found: 370.04344.

(4R*, 5S*)-3-Methylidene-2-oxo-4-methyl-4-butyl-5-(pentafluorophenyl)tetrahydrofuran 2c

As per lactone **2b**, with boronate **1b** (132 mg, 0.424 mmol) and pentafluorobenzaldehyde (132 mg, 0.674 mmol) in toluene (0.4 mL) was treated with Sc(OTf)₃ (21 mg, 0.043 mmol) and stirred at RT under Ar for 24 h. Work up gave the product as a crude oil (212 mg). Flash chromatography (1% EtOAc/Toluene, 22 g SiO₂) gave the pure product (75 mg, 0.22 mmol, 53%).

TLC (1% EtOAc/Toluene, KMnO₄): 0.42;

¹H NMR (400 MHz, CDCl₃): δ 6.34 (s, 1H), 5.57 (s, 1H), 5.48 (s, 1H), 1.55 (dt, *J* = 13.3 Hz, 4.2 Hz, 1H), 1.35 (s, 3H), 1.35-0.90 (m, 5H), 0.75 (t, *J* = 7.2 Hz, 3H);

¹³C NMR (100 MHz, CDCl₃): δ 169.3, 146.3 and 143.8,⁵ 142.7, 142.6 and 140.1,⁵ 139.0 and 136.5,⁵ 121.6, 110.3,⁵ 80.6, 46.2, 34.5, 25.5, 24.6, 22.9, 13.7;

¹⁹F NMR (376 MHz, CDCl₃): δ -139.6 (br s, 2F), -152.3 (tt, *J* = 20.9 Hz, 2.6 Hz, 1F), -161.1 (dt, *J* = 22.1 Hz, 8.0 Hz, 2F);

IR (CH₂Cl₂ cast, cm⁻¹): 2960, 1781, 1655, 1130;

HRMS (ES, *m/z*) Calcd for C₁₆H₁₅F₅O₂Na: 357.088991. Found: 357.088836;

Anal. Calcd for C₁₆H₁₅F₅O₂: C, 57.48; H, 4.53. Found: C, 57.40; H, 4.42.

(4*R, 5*S**)-3-Methylidene-2-oxo-4-ethyl-4-methyl-5-(2-phenylethyl)tetrahydrofuran 2d**

A solution of boronate **1a** (103 mg, 0.365 mmol) and hydrocinnamaldehyde (74 mg, 0.55 mmol) in toluene (0.6 mL) was treated with Sc(OTf)₃ (20 mg, 0.041 mmol) and stirred at RT under Ar for 24 h. Reaction was then diluted with water (5 mL) and extracted with Et₂O (3 x 5 mL). The combined extracts were washed with brine (5 mL), dried (Na₂SO₄) and evaporated to give the crude product (145 mg). Flash chromatography (10% Et₂O/Hexanes, 7 g SiO₂) gave the pure product (57 mg, 0.23 mmol, 64%). Similarly, using Yb(OTf)₃ instead of scandium afforded the product in 66% yield.

TLC (1% EtOAc/Toluene, KMnO₄): 0.26;

¹H NMR (500 MHz, CDCl₃): δ 7.28 (m, 2H), 7.18 (m, 3H), 6.23 (s, 1H), 5.41 (s, 1H), 4.17 (dd, *J* = 10.8 Hz, 2.9 Hz), 2.94 (m, 1H), 2.68 (m, 1H), 1.78 (m, 2H), 1.52 (m, 2H), 1.08 (s, 3H), 0.80 (t, *J* = 7.4 Hz, 3H);

¹³C NMR (125 MHz, CDCl₃): δ 170.4, 144.0, 141.0, 128.5, 126.1, 120.6, 84.4, 45.0, 33.6, 32.8, 32.3, 20.2, 8.3;

IR (CH₂Cl₂ cast, cm⁻¹): 3061, 2967, 1762, 1659, 1602, 1113, 751, 700;

HRMS (EI, *m/z*) Calcd for C₁₆H₂₂O₂: 244.14633. Found: 244.14648;

Anal. Calcd for C₁₆H₂₂O₂: C, 78.64; H, 8.27. Found: C, 78.28; H, 8.38.

(4*R, 5*R**)-3-Methylidene-2-oxo-4-methyl-4,5-dibutyltetrahydrofuran 2e**

A solution of boronate **1b** (126 mg, 0.406 mmol) and valeraldehyde (53 mg, 0.61 mmol) in toluene (0.8 mL) was treated with Sc(OTf)₃ (17 mg, 0.034 mmol) and stirred at RT under Ar for 24 h. Reaction was diluted with water (5 mL) and extracted with Et₂O (3 x 5 mL). The combined extracts were washed with brine (5 mL), dried (Na₂SO₄) and evaporated to give the crude product (160 mg). Flash chromatography (10% EtOAc/Hexanes, 10 g SiO₂) gave the pure product (47 mg, 0.21 mmol, 51%). A further 10 mg of product was obtained which was contaminated with trace amounts of valeraldehyde pinacol acetal. Overall yield: 57 mg, 0.25 mmol, 62%.

TLC (10% EtOAc/Hexanes, KMnO₄): 0.38;

⁵ These signals are complex, broad patterns due to ¹³C-¹⁹F splitting. They are well resolved singlets at 145.1, 141.4, 137.7 and 110.2 ppm respectively in ¹⁹F decoupled spectra.

^1H NMR (500 MHz, CDCl_3): δ 6.18 (s, 1H), 5.38 (s, 1H), 3.98 (dd, $J = 10.6$ Hz, 2.9 Hz, 1H), 1.56 (m, 3H), 1.35 (m, 5H), 1.24 (m, 2H), 1.16 (m, 2H), 1.14 (s, 3H), 0.90 (t, $J = 7.0$ Hz, 3H), 0.85 (t, $J = 7.0$ Hz, 3H);

^{13}C NMR (125 MHz, CDCl_3): δ 170.7, 144.5, 120.0, 88.1, 45.2, 33.6, 28.8, 28.4, 25.6, 23.1, 22.5, 21.5, 13.9, 13.8;

IR (CH_2Cl_2 cast, cm^{-1}): 3093, 2957, 1770, 1660, 1106;

HRMS (EI, m/z) Calcd for $\text{C}_{14}\text{H}_{24}\text{O}_2$: 224.17763. Found: 224.17647;

Anal. Calcd for $\text{C}_{14}\text{H}_{24}\text{O}_2$: C, 74.94; H, 10.80. Found: C, 74.45; H, 10.87.

(4*R, 5*R**)-3-Methylidene-2-oxo-4-methyl-4-butyl-5-(2-methylpropyl)tetrahydrofuran 2f**

A solution of boronate **1b** (126 mg, 0.405 mmol) and isovaleraldehyde (54 mg, 0.62 mmol) in toluene (0.8 mL) was treated with $\text{Sc}(\text{OTf})_3$ (22 mg, 0.045 mmol) and stirred at RT under Ar for 24 h. Reaction was diluted with water (5 mL) and extracted with Et_2O (3 x 5 mL). The combined extracts were washed with brine (5 mL), dried (Na_2SO_4) and evaporated to give the crude product (88 mg). Flash chromatography (5% Et_2O /Hexanes, 10 g SiO_2) gave the pure product (48 mg, 0.21 mmol, 53%).

TLC (1% EtOAc /Toluene, KMnO_4): 0.20;

^1H NMR (500 MHz, CDCl_3): δ 6.18 (s, 1H), 5.38 (s, 1H), 4.06 (dd, $J = 9.9$ Hz, 1.2 Hz, 1H), 1.86 (m, 1H), 1.59 (m, 1H), 1.4-1.0 (m, 7H), 1.13 (s, 3H), 0.97 (d, $J = 6.7$ Hz, 3H), 0.92 (d, $J = 6.6$ Hz, 3H), 0.86 (t, $J = 7.1$ Hz, 3H);

^{13}C NMR (100 MHz, CDCl_3): δ 170.8, 144.3, 120.0, 86.0, 45.2, 37.3, 33.4, 25.6, 25.2, 23.5, 23.1, 21.6, 21.1, 13.9;

IR (CH_2Cl_2 cast, cm^{-1}): 2957, 1769, 1661, 1111;

HRMS (EI, m/z) Calcd for $\text{C}_{14}\text{H}_{24}\text{O}_2$: 224.17763. Found: 224.17738.

(4*R, 5*R**)-3-Methylidene-2-oxo-4-methyl-4-ethyl-5-(cyclohexyl)tetrahydrofuran 2g**

A solution of boronate **1a** (126 mg, 0.405 mmol, 10:1 *Z*/*E* mixture) and cyclohexanecarboxaldehyde (111 mg, 0.394 mmol) in toluene (0.75 mL) was treated with $\text{Cu}(\text{OTf})_2$ (15 mg, 0.043 mmol) and stirred at 60 °C under Ar for 16 h. Reaction was then diluted with water (5 mL) and extracted with Et_2O (3 x 5 mL). The combined extracts were washed with brine (5 mL), dried

(Na₂SO₄) and evaporated to give the crude product (164 mg). Flash chromatography (1% EtOAc/Toluene, 10 g SiO₂) gave the pure product (47 mg, 0.21 mmol, 54%) as an inseparable 10:1 mixture of diastereomers.

TLC (1% EtOAc/Toluene, KMnO₄): 0.20;

¹H NMR (500 MHz, CDCl₃): δ 6.16 (s, 1H), 5.33 (s, 1H), 3.97 (d, *J* = 4.2 Hz, 1H), 1.80-1.45 (m, 8H), 1.4-1.0 (m, 5H), 1.17 (s, 3H), 0.82 (t, *J* = 7.4 Hz, 3H);

¹³C NMR (125 MHz, CDCl₃): δ 170.7, 144.1, 118.9, 89.1, 45.2, 40.0, 34.4, 30.9, 27.4, 26.4, 26.1, 25.7, 19.9, 8.2;

IR (CH₂Cl₂ cast, cm⁻¹): 3093, 2928, 1765, 1655, 1111;

HRMS (EI, *m/z*) Calcd for C₁₄H₂₂O₂: 222.16199. Found: 222.16219.

^1H and ^{13}C NMR Spectra

Lactone **2b**

^1H (400 MHz) and ^{13}C (100 MHz) NMR in CDCl_3

Lactone **2c**

^1H (400 MHz) and ^{13}C (100 MHz) NMR in CDCl_3

Lactone **2d**

^1H (500 MHz) and ^{13}C (125 MHz) NMR in CDCl_3

Lactone **2e**

^1H (500 MHz) and ^{13}C (125 MHz) NMR in CDCl_3

Lactone **2f**

^1H (500 MHz) and ^{13}C (100 MHz) NMR in CDCl_3

Lactone **2g**

^1H (500 MHz) and ^{13}C (125 MHz) NMR in CDCl_3