Pergamon

Tetrahedron Letters 44 (2003) 7645–7648

TETRAHEDRON
LETTERS

4,4,6-Trimethyl-2-vinyl-1,3,2-dioxaborinane: a superior 2-carbon building block for vinylboronate Heck couplings

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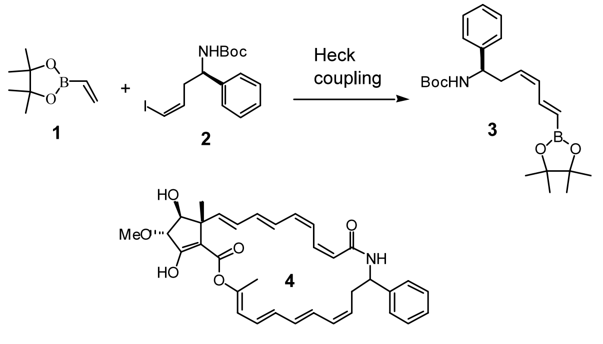
Received 26 June 2003; revised 28 July 2003; accepted 8 August 2003

Abstract—4,4,6-Trimethyl-2-vinyl-1,3,2-dioxaborinane is a superior reagent in terms of stability and reactivity in comparison to the vinylboronate pinacol ester, giving improved selectivity for Heck versus Suzuki coupling with both aryl iodides and bromides, and being easier to prepare and store.

As part of an ongoing program concerned with the total synthesis of polyene natural products[1] using palladium coupling methodology and the vinylboronate-derived vinyl-dianion equivalent **1**,[2] we have been employing vinylboronate pinacol ester **1** for the stereoselective construction of polyene systems, resulting in the synthesis of phthoxazolin A.[3] More recently, we turned our attention to viridenomycin **4**[4] (note: the stereochemistry at the benzylic centre is not known) using this approach for the two polyene sections, and therefore needed to perform a Heck coupling between vinylboronate **1** and the (*S*)-phenylglycine-derived (*Z*)-alkenyl iodide **2** [note: (*S*)-absolute stereochemistry assumed at the benzylic centre] in order to prepare dienyl boronate **3**, a key intermediate en route to the southern hemisphere of viridenomycin **4** (Eq. (1)). However, we encountered problems with the stability of ester **1** as a pure, neat liquid, when stored over several months. We therefore undertook to identify a more stable analogue, which we hoped would perform similarly, or perhaps more selectively in palladium-catalysed coupling reactions. In this communication, we report such an improved vinylboronate ester for Heck coupling processes.



(1)

Vinylboronate **1** is readily prepared on a multigram scale from commercial reagents by an adapted literature method[5] and is isolated as a colourless liquid after distillation. However, pinacol ester **1** readily azeotropes with both diethyl ether and tetrahydrofuran, which means that careful fractional distillation is required to obtain the ester in its pure form. Although one can readily obtain boronate **1** as a constant boiling mixture of THF and **1** in reasonable yields (60–85%), obtaining pure ester **1**, results in a yield reduction of up to 30%. In addition, we have noted that pure batches of ester **1** slowly transform into a thixotropic material upon storage in the fridge, even over periods as short as 2 weeks, which can set almost solid. The resulting polymerised material is virtually insoluble in all organic solvents. A second issue with respect to boronate **1** concerns its volatility, which not only impacts upon its ease of purification by distillation, but it was noted that when degassing Heck reactions by sparging with argon, it was possible to almost evaporate ester **1** out of the reaction mixture (bp 115–120°C at 760 mmHg). Hence, a less volatile, more stable analogue to ester **1** was required.

In seeking an alternative to pinacol ester **1**, vinylboronates **5** and **6** derived from benzopinacol and 2-methyl-2,4-pentanediol (hexylene glycol), respectively, were prepared as indicated in Eq. (2). Both esters

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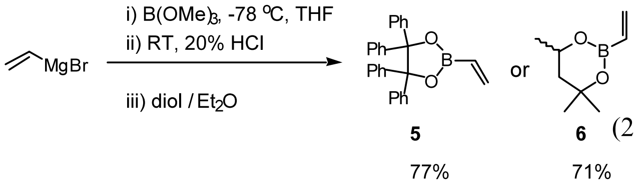
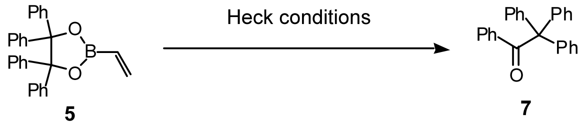
doi:10.1016/j.tetlet.2003.08.032

showed immediate advantage over ester **1**, in terms of increased yields and ease of purification; vinylboronate **5** is a light grey solid and is thus easily obtained and purified by recrystallisation. In contrast, vinylboronate **6** is a liquid, but fortunately one that can be readily obtained from a THF solution as a pure compound by distillation due to its higher boiling point (50–55°C at 0.46 mmHg) than ester **1**.



(2)

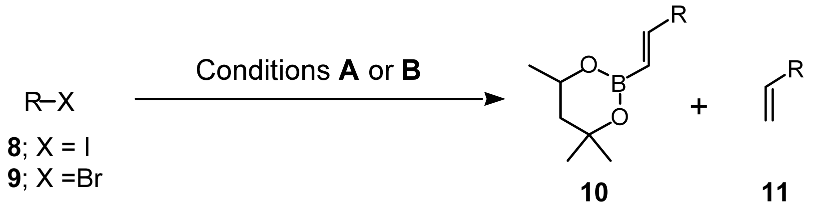
Having obtained these new vinylboronates **5** and **6**, trial Heck couplings were attempted under classical Heck conditions, i.e. aryl iodides, with tri-*n*-butylamine, palladium(II) acetate and triphenylphosphine as the catalyst. By way of a comparison, a number of couplings were also undertaken with aryl bromides, since previous work had shown these to be more reluctant partners in Heck couplings with vinylboronate **1**.[6] The results of these reactions are summarised in Eqs. (3) and (4) and Table 1.



(3)

Under Heck conditions, vinylboronate **5** gives only the pinacol rearrangement product, i.e. ketone **7**, perhaps not unexpectedly, given the sensitivity of tetraphenylethane diol towards this rearrangement.[6]

Inspection of the results in Table 1 reveals a series of mostly Heck-selective reactions with vinylboronate **6** for all the phenyl and electron rich aryl systems (entries 1–9, Table 1), with the order of reactivity between iodides **8** and bromide **9** roughly in accord with that normally observed and indicative of a mechanism involving a rate-determining oxidative addition of Pd(0) to R-X.[7]



8; X = I
9; X =Br

8, **9**, **10**, **11**
a; R = Ph
b; R= *p*-MeC_6H_4
c; R= *p*-$MeOC_6H_4$
d; R= *o*-$NH_2C_6H_4$
e; R = 1-Naphthyl
f; R =*p*-$O_2NC_6H_4$
g; R = 2-Thiophenyl
h; R = 3-Furyl
I; r =2-Pyridyl
j; R = 3-Pyridyl

Conditions
A: 1.2 eq. **6**, 5 mol % $Pd(OAc)_2$, 12 mol % PPh_3, 1.2 eq. *n*-Bu_3N, PhMe, reflux, 8 h;
B: 1.2 eq. **6**, 10 mol % $Pd(OAc)_2$, 22 mol % PPh_3, 2.0 eq. *n*-Bu_3N, PhMe, reflux, 96 h.

(4)

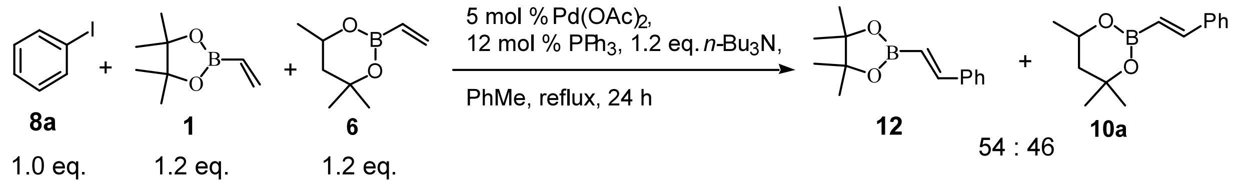
Table 1.

Entry	Halide	Conditions	Conversion%[a,b,c]	**10**:**11** ratio[c,d]	Yield of **10** (%)[c,e]
1	**8a**	A	100 (100)	100:0 (100:0)	97 (100)
2	**8b**	A	100 (100)	100:0 (100:0)	77 (69)
3	**8c**	A	100 (100)	80:20 (80:20)	48 (50)
4	**9b**	B	>95 (64)	80:20 (80:20)	77 (51)
5	**9c**	B	95 (>95)	82:18 (69:31)	40 (24)
6	**9d**	B	40 (NA[f])	95:5 (NA[f])	33 (NA[f])
7	**9e**	B	100 (100)	65:35 (62:38)	50 (57)
8	**9f**	B	>90 (>90)	85:15 (87:13)	51 (48)
9	**9g**	B	100 (0)	100:0 (–)	77 (–)
10	**9h**	B	78 (0)	100:0 (–)	28 (–)
11	**9i**	B	0 (0)	NA[g] (–)	NA[h] (–)
12	**9j**	B	0 (NA[f])	NA[g] (NA[f])	NA[h] (NA[f])

[a] Reactions were performed in sealed tubes, using conditions A for iodides and B for bromides.
[b] Conversion was calculated by the ratio of product to starting halide, determined by ^{1}H NMR of the crude product.
[c] The figures in parentheses are the corresponding results obtained using vinylboronate pinacol ester **1** (see Refs. 2a,b).
[d] The ratio was determined by ^{1}H NMR of the crude product.
[e] Yields are isolated yields after either chromatography or distillation. See Ref. 8.
[f] NA denotes no data has been reported for comparison.
[g] Only styrene **10a** was observed.
[h] NA denotes product was not isolated.

The data in Table 1 also suggest that boronate **6** is an improvement over pinacol ester **1**, although the reaction conditions previously employed[2] are slightly different to the ones shown above. Most striking are entries 9 and 10 (Table 1), involving the coupling of 2-bromothiophene and 3-bromofuran, respectively. Previously, it had been found that 2-iodothiophene afforded the Heck product in 46% yield (92:8 Heck/Suzuki) only if silver(I) acetate was added and 3-bromofuran failed to react at all. Using ester **6**, both 2-bromothiophene and 3-bromofuran are selectively converted to the corresponding Heck products. However, coupling with pyridine halides is still not possible (entries 11 and 12, Table 1), although there is evidence of slow reaction; only styrene is produced due a low level of aryl-exchange with the phosphine ligand.[2b,9]

In order to obtain a direct comparison between the esters **1** and **6**, a competition experiment was run using iodobenzene, as outlined in Eq. (5). After complete consumption of the iodobenzene, styrylboronates **12** and **10a** were formed in a 54:46 ratio by ^{1}H NMR of the crude product, which clearly shows that ester **6** is similar in reactivity, behaving as though it is slightly more hindered that the corresponding pinacol ester. This result probably explains why generally ester **6** is a more selective reagent in these Heck reactions and may well also explain its greater stability upon storage.



(5)

Further applications of ester **6** for the synthesis of polyene systems will be reported in due course.

Acknowledgements

We are grateful to the EPSRC for a CASE studentships (GR/99315155) to C.T. and for a DTA award to S.J.R.T., and to Pfizer Global Research and Development and GlaxoSmithKline Pharmaceuticals for additional funding.

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5. Boronate **6** was prepared via a modification of the procedure described by Hoffmann, R. W.; Landmann, B.; *Chem. Ber.* **1986**, *119*, 2013–2024, substituting *rac*-2-methyl-2,4-pentanediol for *n*-octanol.
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8. All new compounds had satisfactory analytical and spectroscopic properties. Selected data: **10a**) δ_H (300 MHz) 1.22 (3H, s, **CH$_3$**), 1.27 (6H, s, 2×**CH$_3$**), 1.38–1.44 (1H, m, **CH**), 1.68–1.70 (1H, m, **CH**), 4.10–4.17 (1H, m, **CH**), 6.09 (1H, d, *J* 18.1 Hz, **CHB**), 7.11–7.18 (4H, m, Ar**H**), 7.22 (1H, dd, *J* 6.9, 1.2 Hz, Ar**H**), 7.57 (1H, d, *J* 18.1 Hz, **CH**); **10b**) δ_H (400 MHz) 1.20 (3H, s, **CH$_3$**), 1.24 (6H, s, 2×**CH$_3$**), 1.39–1.47 (1H, m, **CH**), 1.63–1.67 (1H, m, **CH**), 4.14–4.18 (1H, m, **CH**), 2.24 (3H, s, **CH$_3$**), 5.98 (1H, d, *J* 18.5 Hz, **CHB**), 7.19 (2H, d, *J* 8.1 Hz, Ar**H**), 7.36 (1H, d, *J* 18.5 Hz, **CH**), 7.39 (2H, d, *J* 8.1 Hz, Ar**H**); **10c**) δ_H (400 MHz) 1.21 (3H, s, **CH$_3$**), 1.23 (3H, s, **CH$_3$**), 1.25 (3H, s, **CH$_3$**), 1.41–1.46 (1H, m, **CH**), 1.68 (1H, dd, *J* 11.1, 2.6 Hz, **CH**), 3.68 (3H, s, O**CH$_3$**), 4.18–4.22 (1H, m, **CH**), 5.87 (1H, d, *J* 18.2 Hz, **CHB**), 6.98 (2H, dd, *J* 6.8, 2.1 Hz, Ar**H**), 7.33 (1H, d, 18.2 Hz, **CH**), 7.46 (2H, dd, *J* 6.8, 2.1 Hz, Ar**H**); **10d**) δ_H (300 MHz) 1.22 (3H, s, **CH$_3$**), 1.26 (3H, s, **CH$_3$**), 1.32 (3H, s, **CH$_3$**), 1.37–1.43 (1H, m, **CH**), 1.59 (1H, dd, *J* 11.1, 3.0 Hz, **CH**), 3.58 (2H, bs, **NH$_2$**), 4.11–4.17 (1H, m, **CH**), 6.22 (1H, d, *J* 18.2 Hz, **CHB**), 6.77 (1H, dd, *J* 7.9, 1.6 Hz, Ar**H**), 7.08 (dd, *J* 7.9, 1.6 Hz, Ar**H**), 7.26 (1H, t, *J* 7.9 Hz, Ar**H**), 7.35 (1H, t, *J* 7.9 Hz, Ar**H**), 7.47 (1H, d, *J* 18.2 Hz, **CH**); **10e**) δ_H (400 MHz) 1.23 (3H, s, **CH$_3$**), 1.27 (3H, s, **CH$_3$**), 1.30 (3H, s, **CH$_3$**), 1.40–1.46 (1H, m, **CH**), 1.60–1.64 (1H, m, **CH**), 4.08–4.13 (1H, m, **CH**), 6.21 (1H, d, *J* 18.3

Hz, C**HB**), 7.41–7.55 (3H, m, Ar**H**), 7.79–7.91 (3H, m, Ar**H**), 8.25 (1H, d, *J* 18.3 Hz, C**H**), 8.29 (1H, d, *J* 8.0 Hz, Ar**H**); **10f**) δ_H (300 MHz) 1.21 (3H, s, C**H**$_3$), 1.26 (3H, s, C**H**$_3$), 1.31 (3H, s, C**H**$_3$), 1.39–45 (1H, m, C**H**), 1.64–1.69 (1H, m, C**H**), 4.09–4.17 (1H, m, C**H**), 6.35 (1H, d, *J* 18.5 Hz, C**HB**), 7.47 (1H, d, *J* 18.5 Hz, C**H**), 7.67 (2H, d, *J* 8.5 Hz, Ar**H**), 8.22 (2H, d, *J* 8.5 Hz, Ar**H**); **10g**) δ_H (400 MHz) 1.22 (3H, s, C**H**$_3$), 1.25 (3H, s, C**H**$_3$), 1.29 (3H, s, C**H**$_3$), 1.39–1.45 (1H, m, C**H**), 1.64–1.67 (1H, m, C**H**), 4.15–4.23 (1H, m, C**H**), 5.80 (1H, d, *J* 18.1 Hz, C**HB**), 6.89 (1H, dd, *J* 5.1, 3.4 Hz, Ar**H**), 7.09 (1H, d, *J* 3.4 Hz, Ar**H**), 7.34 (1H, d, *J* 5.1 Hz, Ar**H**), 7.59 (1H, d, *J* 18.1 Hz, C**H**); **10h** δ_H (400 MHz) 1.23–1.33 (9H, m, 3×C**H**$_3$), 1.54–1.57 (1H, m, C**H**), 1.81 (1H, dd, *J* 14, 2.4 Hz, C**H**), 4.22–4.28 (1H, m, C**H**), 5.77 (1H, d, *J* 18.0 Hz, C**HB**), 6.59 (1H, s, Ar**H**), 7.18 (1H, d, *J* 18.0 Hz, C**H**), 7.34 (1H, s, Ar**H**), 7.47 (1H, s, Ar**H**).

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