4,4,6-Trimethyl-2-vinyl-1,3,2-dioxaborinane: An Efficient and Selective 2-Carbon Building Block for Vinylboronate Suzuki–Miyaura Coupling Reactions

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Abstract: An extremely simple and efficient palladium-catalyzed coupling procedure for the synthesis of functionalized styrenes and dienes is utilized to demonstrate how 4,4,6-trimethyl-2-vinyl-1,3,2-dioxaborinane can be employed to selectively undergo Suzuki–Miyaura coupling with a range of halide substrates.

Key words: Suzuki–Miyaura coupling, palladium(0), vinylboronate ester, chemoselectivity

An ongoing program has focused on the stereocontrolled synthesis of polyene natural products[1] which featured the total synthesis of the antibiotic and selective herbicide phthoxazolin A (**1**, Figure 1).[2] The strategy we have developed utilizes palladium(0)-catalyzed coupling of a two carbon building block **2**, the vinylboronate pinacol ester, which is a vinyl dianion equivalent, since it is able to react at either end following either a Heck or Suzuki–Miyaura reaction pathway. The scope of the Heck coupling of the vinylboronate **2** has been an ongoing investigation in our group;[3] formation of the Suzuki–Miyaura product has often been an undesirable result considering the synthetic targets examined to date. Consequently, its potential was never fully investigated and herein we report the efficient use of a vinylboronate ester to selectively derive Suzuki–Miyaura coupled products.

More recently, during studies towards the synthesis of the antibiotic and anticancer agent viridenomycin (**3**),[4] problems with the long term stability (slow polymerization occurs) of vinylboronate ester **2** led to the development of an alternative vinylboronate ester, 4,4,6-trimethyl-2-vinyl-1,3,2-dioxaborinane (**4**).[5] This has been shown to be free from the problems associated with polymerization upon storage, as encountered with ester **2** and it is also a superior reagent for Heck coupling reactions on the vinylboronate ester system.[5]

However, there have been recent reports which claim that vinylboronate esters are not suitable for the efficient and selective formation of terminal alkenes, particularly for functionalized styrenes, via the Suzuki–Miyaura coupling strategy.[6] Having previously only examined trying to optimize Heck couplings on vinylboronate esters, we therefore decided to examine the Suzuki–Miyaura coupling of ester **4** to find out if, indeed, these systems were unsatisfactory for these reactions as claimed.[6] In this communication we report that, in fact, Suzuki–Miyaura couplings of vinylboronate ester **4** is extremely efficient for the selective preparation of styrenes and dienes, through reaction with a range of aryl and alkenyl halide substrates using a simple and convenient experimental procedure.

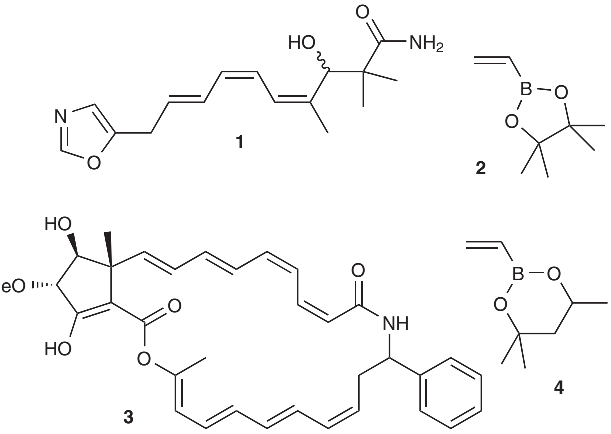

Figure 1 Synthetic targets and vinyl boronate esters

Classical Suzuki–Miyaura conditions were employed[7] for these coupling reactions, i.e. using tetrakistriphenylphosphinylpalladium(0) with either potassium *tert*-butoxide, potassium hydroxide or silver(I) oxide[8] as the bases, in refluxing THF, which allows a simple and robust set up with minimal required work up.[7] A range of aromatic, heteroaromatic and vinyl halide substrates were investigated, the results of which are summarized in Table 1.

The most significant point to report from the results shown in Table 1 is that the reaction shows complete chemoselectivity for the Suzuki–Miyaura pathway under conditions A to C (Table 1), i.e. there is no Heck-coupled products observed in any of the reactions performed despite the presence of a hindered boronate ester. This result compares favorably with the Heck coupling selectivity of boronate **4** which can give complete selectivity for the Heck pathway simply by changing the reaction conditions.[3,5] Heck-selective reaction conditions are characterized by the application of typically a trialkylamine (e.g.

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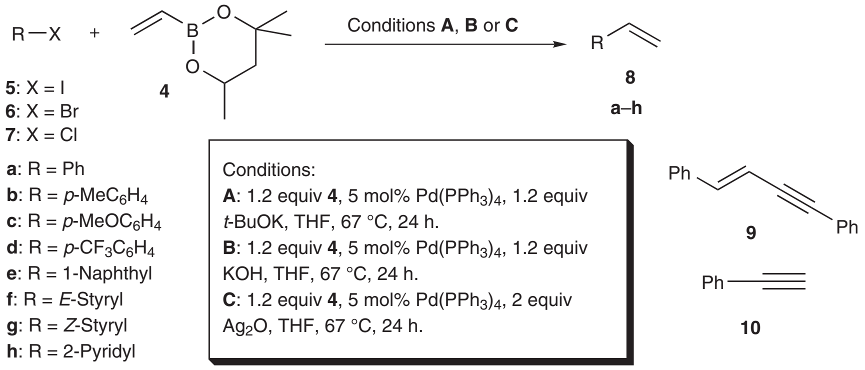
Table 1 Pd-Catalyzed Coupling of Vinylboronate **4** with a Range of Aryl and Alkenyl Halides



5: X = I
6: X = Br
7: X = Cl

a: R = Ph
b: R = *p*-MeC$_6$H$_4$
c: R = *p*-MeOC$_6$H$_4$
d: R = *p*-CF$_3$C$_6$H$_4$
e: R = 1-Naphthyl
f: R = *E*-Styryl
g: R = *Z*-Styryl
h: R = 2-Pyridyl

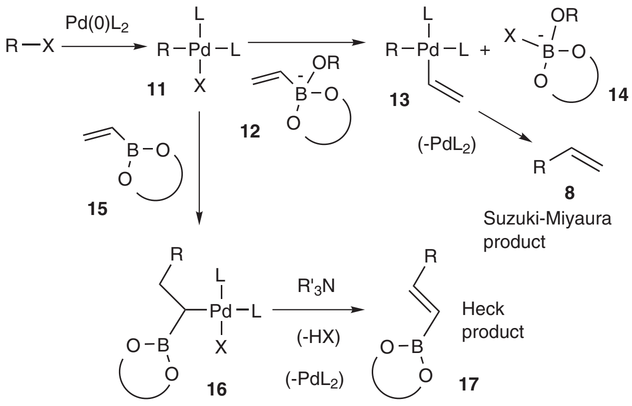
Conditions:
A: 1.2 equiv **4**, 5 mol% Pd(PPh$_3$)$_4$, 1.2 equiv *t*-BuOK, THF, 67 °C, 24 h.
B: 1.2 equiv **4**, 5 mol% Pd(PPh$_3$)$_4$, 1.2 equiv KOH, THF, 67 °C, 24 h.
C: 1.2 equiv **4**, 5 mol% Pd(PPh$_3$)$_4$, 2 equiv Ag$_2$O, THF, 67 °C, 24 h.

Entry	Substrate	Expected product[a]	Conditions and yields (%)		
			A – *t*-BuOK[b]	B – KOH[b]	C – Ag$_2$O[c]
1	**5a**	**8a**	62	73	51
2	**5b**	**8b**	75	68	83
3	**5c**	**8c**	95	66	90
4	**5d**	**8d**	87	75	76
5	**5e**	**8e**	65	74	96
6	**5f**	**8f**	26[c] (**9** 35%[e])	63[c]	51
7	**5g**	**8g**	0[e] (**10** 51%[a,d])	46[c] (**10** 24%[a,d])	56
8	**6a**	**8a**	56	36	0
9	**6b**	**8b**	52	35	0
10	**6c**	**8c**	65	28	0
11	**6d**	**8d**	71	50	11[d]
12	**6e**	**8e**	60	58	0
13	**6h**	**8h**	41	31	39[b]
14	**7a**	**8a**	0	0	0

[a] See ref.[9]
[b] GC yield determined through the use of undecane as the calibrated internal standard.
[c] Isolated yield is that after silica gel column chromatography.
[d] Determined by calculation from the ^{1}H NMR of the crude product.
[e] See ref.[10]

Bu$_3$N or Et$_3$N) or other non-nucleophilic bases (e.g. phenanthroline),[3] whereas the Suzuki–Miyaura reaction conditions are optimized by using nucleophilic oxygen bases. We believe that the major factor which decides the chemoselectivity of the coupling process is whether the vinylboronate is quarterernized as an 'ate'-complex (i.e. **12**, Scheme 1) causing the vinylboronate to undergo transmetallation with the intermediate palladium(II) complex **11** deriving Suzuki–Miyaura coupled products **8**,[11] or whether it is neutral (i.e. **15**) due to being hindered around boron. This forces the palladium(II) complex **11** to add across the double bond of **15** and derive Heck products **17** (see Scheme 1) due to the fact that trialkylamines or non-nucleophilic amines do not efficiently produce the vinylboronate 'ate'-complex in equilibrium. While the intermediacy of 'ate'-complexes of type **12** may be essential in determining which coupling process proceeds more efficiently, there may also be additional factors operating, such as changes in the palladium ligand coordination which also affect the selectivity.[11]

The yields in Table 1 obtained for each of the different halides used demonstrates the established reactivity trend of iodides (entries 1–7) being more reactive than bromides (entries 8–13), which in turn are much more reactive than the chlorides; these fail to react at all (entry 14) under the reactions conditions reported here. These results are indicative of a rate determining step which involves an oxidative addition of the halide to the active palladium(0) species in the catalytic cycle. This is further demonstrated when examining the syntheses of *para*-substituted styrenes (entries 1–4 and 8–11). In general, and best demonstrated under conditions B, the yields obtained increase with the electron-withdrawing nature of the substituent group.



Scheme 1 Mechanistic explanation for formation of the Heck vs. Suzuki–Miyaura coupled products

Of particular interest with respect to the synthesis of conjugated systems and polyenes are the reactions of the (*E*)- and (*Z*)-styryl iodides (entries 6, 7). The (*E*)-styryl iodide (**5f**) showed good coupling under conditions B and C, however, use of potassium *tert*-butoxide led to the formation of phenylacetylene **10**, which reacted further with (*E*)-styryl iodide (**5f**) to form the corresponding ene-yne **9**. For the (*Z*)-styryl iodide (**5g**), good coupling was again observed when using conditions B (some phenylacetylene produced) and C. When using potassium *tert*-butoxide, the major product was phenylacetylene, with only trace coupling to derive either the diene or ene-yne, which underlines the considerably increased susceptibility towards elimination of HI of the (*Z*)- vs. (*E*)-alkenyl iodides **5g** vs. **5f**, respectively. Hence, for sensitive substrates, the choice of base in such coupling reactions is vitally important.

When comparing the use of the different bases used for the coupling reactions (Table 1), for example with the iodides (with the exception of styryl systems), the order of reactivity generally followed the trend of *t*-BuOK > KOH, with the use of Ag_2O giving variable results depending on the nature of the halide substrate.

The results obtained (Table 1) demonstrate the potential use of the vinylboronate **4** in Suzuki–Miyaura coupling reactions for a range of substrates, which are generally much more convenient than using a strong alkylating agent such as 1,2-dibromoethane generating vinyl bromide in situ and coupling with different boronic acids.[6] Further studies on the optimization of these reactions is underway, particularly with respect to the bromides, and the factors which affect the chemoselectivity of the Suzuki–Miyaura vs. Heck coupling. These details and application of these reactions for use in natural product and polyene synthesis will be reported in due course.

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(7) **Typical Procedure, Conditions A.**
To an oven dried Schlenk-like tube under argon was added $Pd(PPh_3)_4$ (39 mg, 33.8 μmol) and *t*-BuOK (91 mg, 0.81 mmol), followed by THF (6 mL), substrate (0.675 mmol) and boronate **4** (0.125 g, 0.81 mmol). The tube was heated at 67 °C for 24 h before cooling, dilution with Et_2O (30 mL) and filtration through Celite. This solution was treated with undecane (50 μL, 37.5 mg) and a portion was analyzed by GC. ^1H NMR analysis to determine the Heck: Suzuki ratio, which was carried out after evaporation to give the crude product. Purification was carried out by silica gel column chromatography (hexane as eluant).

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