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Heck versus Suzuki Palladium Catalysed Cross-Coupling of a Vinylboronate Ester with Aryl Halides.

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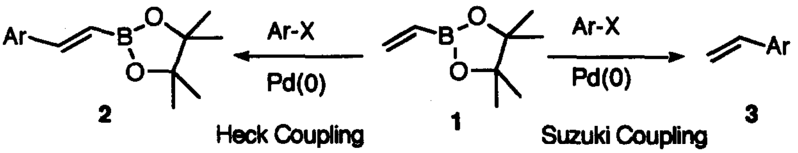
Abstract: Palladium(0) catalysed cross-coupling of a vinylboronate **1**, protected as its' pinacol ester, with aryl halides provides a mixture of the styryl boronates **2** and the styrenes **3** depending upon the reaction conditions.

Palladium catalysed cross-coupling reactions have become one of the most widely used procedures for synthesising new carbon-carbon bonds[1]. One reaction in particular, the palladium catalysed cross-coupling of organoboron derivatives has become extensively used for the synthesis of a wide range of carbon skeletons[2].

We were interested in examining the reaction of an alkenylboronate, such as **1**, which possessed a stable boronate ester and which could potentially react by either a Heck[3] or a Suzuki[4]-type process (**Scheme 1**). This would afford either arylvinylboronate **2** or styrene **3**, depending upon whether the palladium(0) adds across the alkene or inserts into the C-B bond of **1** (*vide infra*). If the Heck reaction product could be produced at the expense of the Suzuki product, the vinylboronate **1** could be considered as a vinyldianion equivalent, since the product from a Heck coupling would retain a boronate moiety for further reaction. In this communication we report upon our preliminary results on the coupling of vinylboronate ester **1** to aryl halides and the conditions which affect the observed products.

Scheme 1.



We examined the reaction of vinylboronate **1**[5] with a range of aryl halides, solvents, bases, palladium sources, palladium ligands and reaction temperatures to see if we could find optimum reaction conditions for the Heck reaction versus the Suzuki reaction. A brief summary of some of the reactions and the important findings from this investigation are shown in **Table 1**.

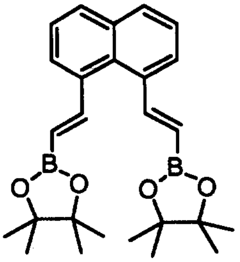
Several points are worth noting from the above results. Firstly, it was not possible to find a single set of conditions which worked best for all aryl halides. Instead, a few different conditions had to be examined for each halide to find the best conditions for obtaining the Heck versus Suzuki products. Secondly, reactions

Table 1.

Entry	Aryl halide	Method[a]	Temp (°C)	Time (h)	Conversion (%)[b]	Ratio (**2** :**3**)[c]	Yield (**2**)[d,e]
1	Iodobenzene	A	65	4	100	>95 : 5	66[f]
2	"	B	"	40	>90	87 : 13	32[g]
3	2-Bromoanisole	A	"	18	60	50 : 50	10[g]
4	2-Iodoanisole	C	45	6	31	33 : 66	10[h]
5	4-Bromoanisole	A	65	24	100	55 : 45	55[h]
6	"	B	"	"	>95	69 : 31	24[g] (6[i])
7	4-Iodoanisole	A	"	6	59	<10 : 90	n/a
8	"	A[j]	120	4.5	100	80 : 20	50[g]
9	4-Bromotoluene	A	"	24	32	20 : 80	7[h]
10	"	B	"	"	23	17 : 83	4[h]
11	4-Iodotoluene	A	"	6	49	43 : 57	21[h]
12	"	D	"	8	58	75 : 25	20[g]
13	"	D	45	6	40	100 : 0	40[h]
14	"	C	45-65	120	100	<10 : 90	n/a
15	Methyl 2-iodobenzoate	D	65	6	55	60 : 40	8[g]
16	"	C	45	6	100	0 : 100	0[h]
17	"	A[j]	120	18	100	87 : 13	58[g]
18	4-Bromobenzaldehyde	D	65	24	70	75 : 25	24[g]
19	4-Bromonitrobenzene	A	80	20	35	17 : 83	6[h]
20	1-Bromonaphthalene	A	"	24	100	62 : 38	57[g]
21	1,8-Diiodonaphthalene	A[j]	120	48	100	-	77[g]

a; See ref. 6 and 7. b; Conversion was estimated relative to consumed arylhalide by 200 MHz ^{1}H n.m.r. c; Ratio of products **2**:**3** was estimated from the crude 200 MHz ^{1}H n.m.r. spectrum. d; Yields are quoted relative to aryl halide used and are unoptimised. e; All compounds had satisfactory spectroscopic and analytical properties. f; Isolated yield after distillation. g; Isolated yield after silica gel chromatography. h; N.m.r. yield. i; Styrylboronate side-product. j; Method as A, but tributylamine and toluene used instead of triethylamine and acetonitrile, with 1 mol. % Pd catalyst..

conducted at lower temperatures (45 versus 65 °C) favour the Heck product **2** over the Suzuki product **3**, suggesting that the Heck product **2** may be the kinetically preferred (*vide infra*). Thirdly, the source of palladium(0) played only a minimal part in the reaction, i.e. palladium acetate gave similar results to tetrakistriphenylphosphenylpalladium(0), but use of phenanthroline[8] as ligand tended to give greater selectivity for the Heck product **2**. Tributylamine was slightly superior in most of the reactions when compared to triethylamine, i.e. conversions were very similar but the Heck products **2** were generally obtained with higher selectivity, especially if combined with toluene at 120 °C as in Entries 8, 17, and 21 (**Table 1**). Entry 21 is most noteworthy because the corresponding reactions with triethylamine gave a mixture of all the possible products and only 14 % of the double Heck product **4** was isolated after chromatography.



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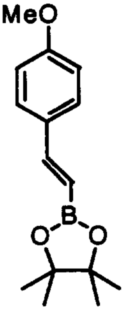

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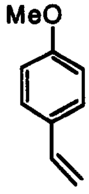

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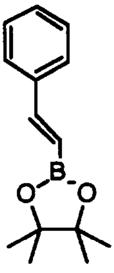

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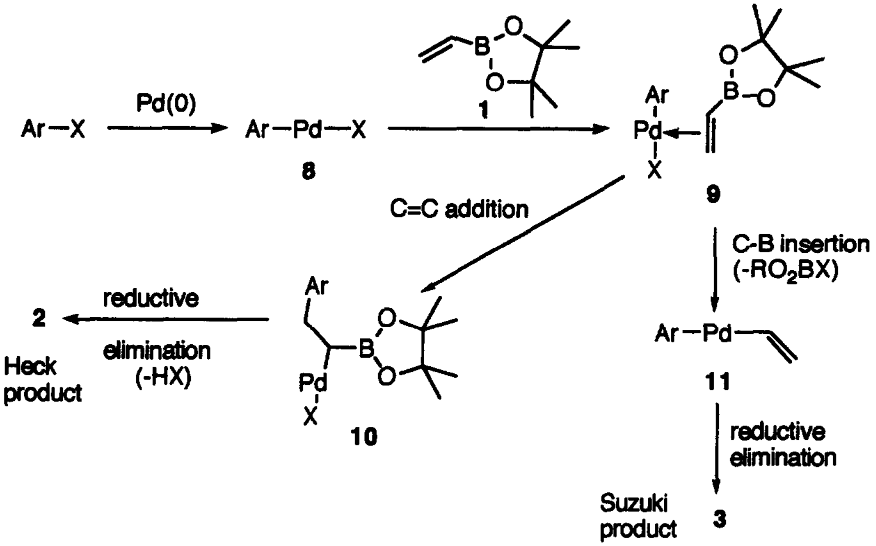
It is also interesting to note that we found in the case of 4-bromoanisole (Entry 6), evidence for exchange of the aryl groups on the phosphine ligands. Instead of simply isolating the Heck product (i.e. **5**) and Suzuki product (i.e. **6**), we found a Heck-derived product without the methoxy group, i.e. **7**. This type of exchange of less electron donating aryl groups on phosphorus for more electron donating groups in the presence of tetrakistriphenylphosphenylpalladium(0) has been reported[9].

Though not quoted in **Table 1**, we also tried many other reactions in which we used different solvents and/or additives. These reactions were either similar to, or worse than, acetonitrile, i.e. dimethylformamide usually gave very similar results, tetrahydrofuran favoured Suzuki products **3**, and toluene usually gave lower conversion unless combined with tributylamine at reflux (*vide supra*). Similarly, either using bases such as sodium acetate, proton sponge and pyridine and/or addition of sodium iodide and tetraethylammonium chloride also resulted in greater amounts of Suzuki products **3**. However, it was genarally possible to obtain the Heck products **2** as the major product in most cases with the correct choice of reaction conditions, though care had to be taken in separating the products by chromatography since prolonged exposure to silica gel had a deleterious effect on the strylboronates.

The origin of the balance between the two possible reaction products is probably decided by an intermediate palladium complex such as **9** (**Scheme 2**) resulting from coordination of the vinylboronate **1** to the oxidative addition product **8**. At this point, and perhaps depending upon the state of coordination of the palladium centre[10], the palladium complex **9** can either add across the C=C bond or insert into the weak, but hindered, C-B bond. Our results suggest that if the reaction is mediated by a palladium complex like **9** which is coordinatively unsaturated and sufficiently kinetically reactive, C=C addition predominates. Addition of increasing amounts of halide tends to favour formation of coordinatively more saturated palladium complexes which are likely to be thermodynamically more stable[10]. Hence addition of halide ion to our reactions (*vide supra*) results in greater selectivity for the Suzuki product **3** via a palladium complex which favours C-B insertion.

In summary, vinylboronates undergo both Suzuki and Heck cross-coupling, even if they possess reasonably hindered boronate esters. Reasonable to good selectivity for the Heck versus Suzuki products is generally possible, though the product distribution is strongly dependent upon the reaction conditions. Further investigations into these coupling reactions, particularly to optimise reaction conditions and product isolations, are in progress.

Scheme 2.



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5. Boronate **1** was prepared using a literature[a] procedure but replacing octanol with additon of 1 molar equivalent of pinacol, affording 55-85 % pure **1** after fractional distillation (b.p. 40-44 °C, @10mmHg); a) Hoffmann, R.W.; and Landmann, B.; *Chem. Ber.*, **1986**, *119*, 2013.
6. The conditions used in the general method[7] were as follows: A; $Pd(OAc)_2$ (2.5 mol%), PPh_3 (5 mol%), aryl halide (1 equiv.), vinylboronate **1** (1.2 equiv.), Et_3N (1.2 equiv.), MeCN, Ar, Δ. B; $Pd(PPh_3)_4$ (5 mol%), aryl halide (1 equiv.), vinylboronate **1** (1.2 equiv.), Et_3N (1.2 equiv.), MeCN, Ar, Δ. C; $Pd(OAc)_2$ (5 mol%), phenanthroline (5 mol%), aryl halide (1 equiv.), vinylboronate **1** (3 equiv.), ^{t}BuOK (3 equiv.), MeCN, Ar, Δ. D; $Pd(OAc)_2$ (5 mol%), phenanthroline (5 mol%), aryl halide (1 equiv.), vinylboronate **1** (1.2 equiv.), Et_3N (2 equiv.), MeCN, Ar, Δ.
7. General method, as used for Entry 14: 4-bromobenzaldehyde (0.50g, 2.71mmol), palladium acetate (0.033g, 5 mol%), and 1,10-phenanthroline monohydrate (0.027g, 5mol%) were dissolved in dry acetonitrile (5ml) under Ar. Triethylamine (0.75ml, 5.41mmol) and vinylboronate **1** (0.50ml, 3.25mmol) were added and the mixture was stirred at 65 °C for 24 h. The reaction mixture was then diluted with dichloromethane, washed with 10% HCl, water and satd. NaCl solution, dried ($MgSO_4$), filtered and evaporated to give a dark yellow oil. Purification by SiO_2 chromatography (hexane : diethyl ether, 95 : 5 as eluant) gave pure Heck product **2** (Ar = p-OHCPh) (0.17g, 24%).
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