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Initial investigation into the Suzuki–Miyaura vinylation of hindered aryl bromides utilizing potassium vinyltrifluoroborate

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Abstract—An initial study of the Suzuki–Miyaura cross-coupling of potassium vinyltrifluoroborate (**2**) and hindered aryl bromides is presented. Coupling of benzyl 3,5-bis(benzyloxy)-4-bromobenzoate (**1**) leads to a mixture of the desired styrene derivative, and the reduced product.

Substituted styrenes are synthetically useful as intermediates and in the formation of new polymeric material. It has been shown that mild vinylation can be accomplished utilizing vinylmagnesium bromide,[1] vinyltrimethylsilane,[2] and vinylpolysiloxanes[3] as starting materials to couple with aryl iodides. It has also been shown that trivinylcyclotriboroxane[4] and vinylpolysiloxanes[5] can be coupled with aryl bromides to give newly formed styrenes.

Molander has shown that potassium vinyltrifluoroborate is a stable reagent that works as a great partner in the Suzuki–Miyaura cross-coupling reaction with aryl halides to yield styrene derivatives.[6] Because this reagent is stable and easy to store, it overcomes the limitations associated with vinylboronic acid, which is known to polymerize.[7,8] It also overcomes the typical expenses associated with formation of the more stable vinylboronic esters.[9] To our knowledge, there are not any examples of a Suzuki–Miyaura vinylation of a hindered aryl bromide with the *ortho*, *ortho'*-substitution pattern with potassium vinyltrifluoroborate (and there are only a few examples using the other vinyl reagents previously mentioned).[5] The vinylation of hindered aryl bromides with *ortho*, *ortho'*-substitution is of particular interest to our research group for the continued synthesis and development of new analogs of the antibiotic cytosporone E[10] as illustrated in Figure 1.

The use of potassium vinyltrifluoroborate (**2**) in the Suzuki–Miyaura cross-coupling reaction with benzyl 3,5-bis(benzyloxy)-4-bromobenzoate (**1**) under typical conditions as described by Molander and co-workers for vinylation[6] (Table 1, entries 1 and 3) and alkenylation[11] (Table 1, entry 2) did not give the vinylated product, **3**. Changing the solvent from *n*-propanol with or without water to THF, H_2O (10:1) and changing the base to Cs_2CO_3, the Suzuki–Miyaura coupling did

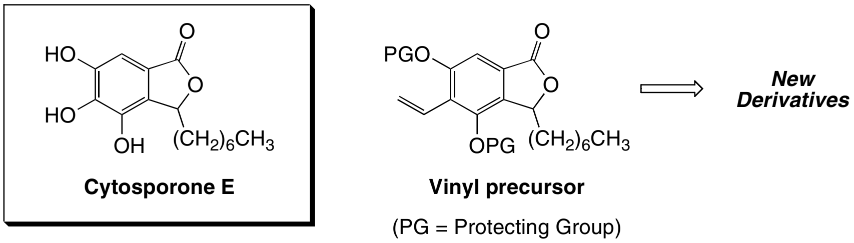

Figure 1.

Keywords: Suzuki–Miyaura; Potassium vinyltrifluoroborate; Styrenes; Palladium catalysis; Hindered aryl bromides.

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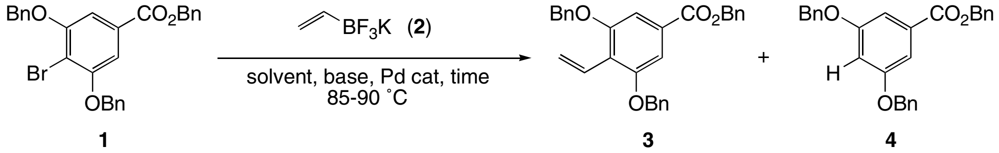
Table 1. Optimizing the cross-coupling reaction of potassium vinyltrifluoroborate (**2**) and benzyl 3,5-bis(benzyloxy)-4-bromobenzoate[12] (**1**)



Entry	Catalyst	Catalyst mol %	Equiv of **2**	Solvent	Base	Time	pdt ratio[a] (**3**:**4**)	% Yield[b] (**3**)
1[c]	$PdCl_2(dppf)·CH_2Cl_2$	2	2.0	*i*-PrOH–H_2O	Et_3N	4 d	nd[c]	nd
2	$PdCl_2(dppf)·CH_2Cl_2$	2	1.0	*i*-PrOH–H_2O	*t*-BuNH$_2$	4 d	nd[c]	nd
3	$PdCl_2(dppf)·CH_2Cl_2$	2	1.2	*n*-PrOH	Et_3N	23 h	nd[c]	nd
4	$PdCl_2(dppf)·CH_2Cl_2$	9	1.0	THF, H_2O	Cs_2CO_3	48 h	13.5:1	15
5	$PdCl_2(dppf)·CH_2Cl_2$	9	1.0	THF, H_2O	Cs_2CO_3	6 d	3.3:1	19
6	$PdCl_2(dppf)·CH_2Cl_2$	9 × 2[e]	2.5	THF, H_2O	Cs_2CO_3	9 d	1.5:1	13
7	$PdCl_2(dppf)·CH_2Cl_2$	9 × 2[e]	5.0	THF, H_2O	Cs_2CO_3	3 d	1:0	73[f]
8	$PdCl_2(dppf)·CH_2Cl_2$	9 × 2[e]	10.0	THF, H_2O	Cs_2CO_3	4 d	1:0	87[f]
9	$Pd(OAc)_2/Ph_3P$	5 × 2[g]	1.1	THF, H_2O	Cs_2CO_3	3 d	1.4:1	30
10	$Pd(OAc)_2/Ph_3P$	5 × 2[g]	5.0	THF, H_2O	Cs_2CO_3	3 d	10:1	52

[a] Ratios were determined by ^1H NMR or by GC analysis of the crude mixture. Products are defined in parentheses.

[b] Average of at least two runs.

[c] After day three the reaction had stopped progressing, so another 2 mol % of catalyst, 2 equiv of **2**, and 3 equiv of base were added.

[d] Ratio and yields not determined due to hydrolysis during the reaction.

[e] A total of 18 mol % of the catalyst was added in two equal portions, one at the beginning of the reaction and the other after 24 h.

[f] Isolated yield.

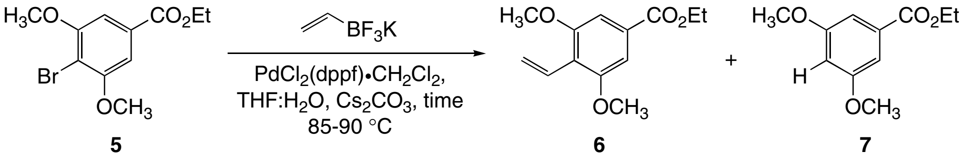
[g] A total of 10 mol % of the catalyst was added in two equal portions, one at the beginning of the reaction and the other after 24 h.

proceed to give the coupled product, **3** (Table 1, entries 4 and 5). However, the reaction did not reach completion. To complicate the issue the reduced product, **4**, was formed and it could not be readily separated from the desired product. In an attempt to eliminate the formation of the reduced product, the amount of potassium vinyltrifluoroborate was increased from 1 equiv to 2.5 equiv (Table 1, entry 6). However, this did not correct the situation and the reduced product still appeared.

The conditions that gave the best results were to use 5 equiv of potassium vinyltrifluoroborate (**2**) in a 10:1 solvent mixture of THF, H_2O at 0.2 M, 3 equiv of Cs_2CO_3 as the base and a total of 18 mol % of the Pd(II) catalyst, $PdCl_2(dppf)·CH_2Cl_2$.[13] Under these conditions, the coupling reactions were typically complete in 3–4 d based on TLC. Using less than 5 equiv of borate **2** would result in the formation of the reduced product. Entry 8 shows that 10 equiv of borate **2** increases the yield at the cost of losing more borate. If the optimized reaction conditions described above are used with the exception that the total catalyst loading is only 9 mol %, the reaction does not continue past 40–50% conversion based on GC analysis.[14] If the entire 18 mol % of catalyst is used all at once, the result would be the same. The reaction worked best if the catalyst is added in two equal portions of 9 mol %. The first at the beginning of the reaction and the second after 24 or 48 h, either way the results were the same.

Table 2 illustrates that the coupling conditions optimized for aryl bromide **1** also worked for compound **5** to give no reduced product as determined by GC. The yield of Suzuki–Miyaura product in entry 1 was 11% based on GC analysis (compounds **5** and **6** could not be readily separated) after two days. If the reaction was allowed to progress longer, for seven days, then the yield of the coupled product increases to 53% based on GC analysis. However, the conversion of the reaction is rather slow; after two days the percent conversion is 10% and after seven days it is 58%. It is striking to note that the reaction progresses cleanly to yield the Suzuki–Miyaura product without reduction of the aryl bromide, even if at a slow rate.

Table 2. Vinylation of ethyl 4-bromo-3,5-dimethoxybenzoate[15] (**5**) using the optimized conditions for aryl bromide **1** from Table 1

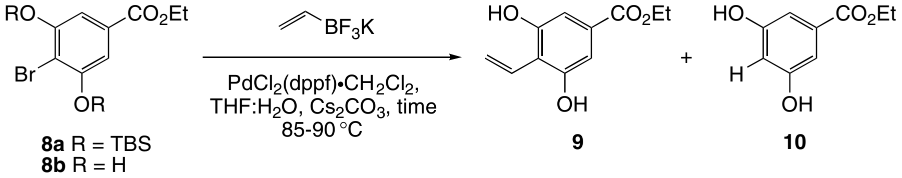


Entry	Time (d)	pdt ratio[a] (**6**:**7**:**5**)	% Yield[b] (**6**)
1	2	1:0:9	11
2	7	1.4:0:1	53

[a] Product ratios and yields determined by GCMS analysis. Products are defined in parentheses.

[b] Average of at least two runs.

Table 3. Vinylation of ethyl 4-bromo-3,5-bis(*t*-butyldimethylsilyloxy)benzoate (**8a**) and ethyl 4-bromo-3,5-dihydroxybenzoate (**8b**) using the optimized conditions for aryl bromide **1** from Table 1



R	Time (d)	pdt[a] (**9**:**10**:**8b**)	% Yield[b] (**9**)
TBS	2	1:0:5	18
H	2	5:1:15	24

[a] Product ratios and yields determined by GCMS analysis. Products are defined in parentheses.

[b] Average of two runs.

Applying the same reaction conditions to ethyl 4-bromo-3,5-bis(*t*-butyldimethylsilyloxy)benzoate (**8a**) in Table 3 gave two inseparable products (**9** and **8b**) after two days of reaction. The first product being the desired coupled product, **9**, in 18% yield with no starting material present and no sign of the reduced product. The major product for this reaction was the removal of the silyl groups to yield ethyl 4-bromo-3,5-dihydroxybenzoate (**8b**) in an average yield of 82%. (Again the products were purified as an inseparable mixture.) This was not a surprising result based on the fact that it has been shown that phenolic silyl groups have been removed in the presence of Cs_2CO_3[16] and in the presence of a Pd(II) catalyst.[17]

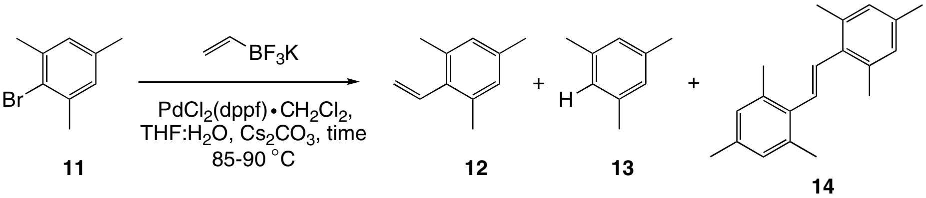
Based on the results with TBS protected aryl bromide **8a**, with the major product being the deprotected diol, **8b**, we wanted to see what would happen if we took diol **8b** and applied the coupling directions directly. Table 3 shows that under the reaction conditions the major product after two days was the desired coupled product, **9**, obtained with low conversion and in the presence of the reduced product, **10**.

Suzuki–Miyaura vinylation of bromomesitylene (**11**) using potassium vinyltrifluoroborate was accomplished. Entries 1 and 2 in Table 4 show that there was no desired coupling product formed, whereas entries 3–5 show the formation of the desired styrene derivative, **12**. In all the entries, there was no evidence of the reduced product, **13**. Entries 1 and 2 gave only the stilbene product 1,2-dimesitylethene (**14**),[18] which comes from the Suzuki–Miyaura coupling followed by a Heck reaction.[19] Entry 1 gave the stilbene product in 76% yield under the normal reaction conditions using the 18 mol % of catalyst. Entry 2 gave the stilbene product in 98% yield, which came after a third addition of 5 mol % after 72 h of reflux.

Entries 3–5 did afford the desired Suzuki–Miyaura coupling product, **12**, in 20–32% yield but as an inseparable mixture with the starting material, **10**, and the stilbene product, **14**. The difference between these sets of experiments (entries 1 and 2 vs 3–5) was the heating process. In the first two entries (1 and 2), the biphasic reactions were thoroughly stirred and completely submerged in the oil bath during reflux leading to sole formation of the stilbene product, **14**. During the second set of reactions (entries 3–5), the reactions were not stirred and only the aqueous layer of the biphasic solution was submerged in the oil bath during reflux.

In summary, these initial results indicate that the Suzuki–Miyaura vinylation of hindered aryl bromides with the *ortho*, *ortho'*-substitution pattern using potassium vinyltrifluoroborate can be achieved in good yields

Table 4. Vinylation of bromomesitylene (**11**) using the optimized conditions for aryl bromide **1** from Table 1



Entry	Time (d)	pdt ratio[a] (**12**:**13**:**14**:**11**)	% Yield (**12**)
1	4	0:0:1:0	0
2	4	0:0:1:0	0
3[b]	3	2.5:0:trace:1	22
4[b]	3	1.9:0:1:6.4	20
5[b]	4	3.3:0:1:5.8	32

[a] Product ratios and yields determined by GCMS analysis. Products are defined in parentheses.

[b] Reactions were not stirred during reflux as they were in entries 1 and 2.

without the formation of side products (Table 1, entries 7 and 8). The major side product in the coupling is typically the reduced product, which in the case of aryl bromides **1** and **5** could be eliminated under the conditions described in this report. Further investigations into these coupling reactions are in progress.

Acknowledgements

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13. *Typical Suzuki–Miyaura coupling conditions*: Potassium vinyltrifluoroborate (**2**) (258 mg, 1.92 mmol), cesium carbonate (378 mg, 1.16 mmol), $PdCl_2(dppf)\cdot CH_2Cl_2$ (25.6 mg, 0.0349 mmol) and benzyl 4-bromo-3,5-bis(benzyloxy)benzoate (**1**) (200 mg, 0.386 mmol) were suspended in degassed THF (6.9 mL) and degassed deionized H_2O (0.69 mL) in a 25 mL round bottom flask equipped with a reflux condenser. The rust-red solution was completely submerged in an oil bath and stirred at a temperature between 85 and 90 °C (reflux). After 24 h, another 9 mol % of $PdCl_2(dppf)\cdot CH_2Cl_2$ (25.6 mg, 0.0341 mmol) was added. The reaction was considered complete after about 72 h, as determined by TLC. The resulting brown solution was quenched with 10 mL of H_2O and extracted with Et_2O (20 mL × 3). The combined organic layers were washed with 1 M HCl (20 mL) and brine (20 mL). The clear, yellow solution was dried over $MgSO_4$, and filtered. The solvent was removed under reduced pressure using a rotary evaporator. The red–brown residue was purified using flash chromatography (3% EtOAc/2% $CHCl_3$/Hexanes) to yield **3** as a white solid in 73% yield (132 mg, 0.294 mmol). Mp = 102–103 °C. ^1H NMR ($CDCl_3$): δ 7.44–7.28 (m, 15H), 7.08 (dd, $J = 18.1$ and 12.2 Hz, 1H), 6.25 (dd, $J = 18.0$ and 2.5 Hz, 1H), 5.52 (dd, $J = 12.2$ and 2.6 Hz, 1H), 5.34 (s, 2H), 5.12 (s, 4H). ^{13}C NMR ($CDCl_3$): δ 166.2, 157.6, 136.8, 136.2, 129.5, 128.8, 128.7, 128.4, 128.3, 128.2, 127.7, 127.0, 121.6, 120.4, 106.9, 71.0, 67.0. IR (solid) 3063, 3026, 1708, 1623, 1567, 1120, 1114 cm^{-1}. Anal. Calcd for $C_{30}H_{26}O_4\cdot 1/4\ H_2O$: C, 79.19; H, 5.87. Found: C, 79.51; H, 6.01.
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