

A Palladium Catalyzed Cross-Coupling Between Furylborates (Generated *in situ*) and Organohalides

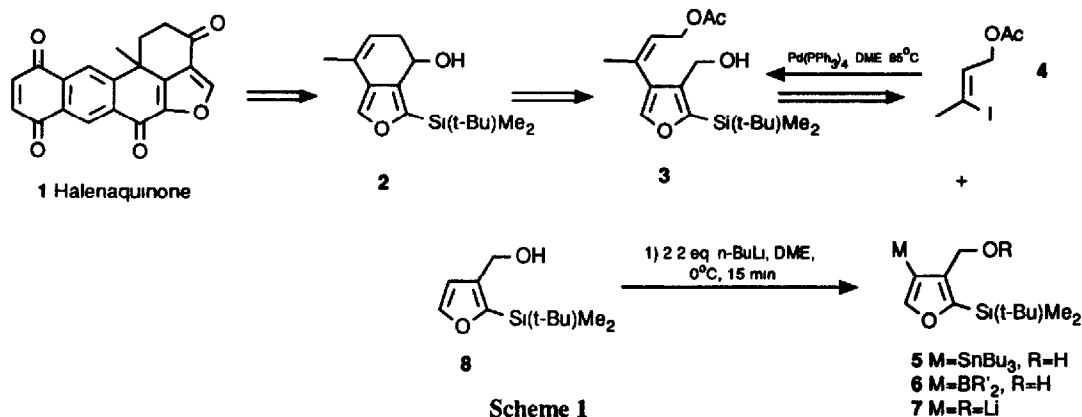
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Abstract: 4-Lithio-2-(*t*-butyldimethylsilyl)-3-(lithioxymethyl)furan, when treated with 2 equivalents of trimethyl borate, smoothly underwent palladium catalyzed cross-coupling reactions with a variety of organohalides to provide 2,3,4-trisubstituted furans in good to excellent yields

We recently required a synthesis of dihydroisobenzofuran **2** as an intermediate towards the synthesis of the antibiotic halenaquinone **1** (Scheme 1) ^{1,2} Retrosynthetic analysis of compound **2** lead to the acetate-alcohol **3**, which could presumably be prepared via a palladium catalyzed cross-coupling reaction



between vinyl iodide **4** and a 4-metallated-2-(*t*-butyldimethylsilyl)-3-(hydroxymethyl)furan (**5** or **6**) Previous work by our group³ has shown that the tri-*n*-butylstannylfuran **5** undergoes a somewhat sluggish palladium catalyzed cross-coupling reaction with arylbromides (50% yields), no reaction was observed with vinylhalides Therefore an alternative metal at the C-4 position of furan **5** was required. Since arylboronic acids⁴ have been used successfully in palladium catalyzed cross-coupling reactions, we investigated their use in the coupling reaction of furyl derivatives, such as **6**, with a variety of aryl- and vinyl-halides⁵ We herein report our findings

Previous cross-couplings involving arylboranes have involved the preparation and isolation of the corresponding arylboronic acid The boronic acids are usually prepared by either quenching a lithium anion

with trimethyl borate or an ipso-borodesilylation sequence, followed by an acidic workup⁴ Suzuki has reported that the palladium catalyzed cross-couplings of vinyl-⁶, alkyl-⁷ and aryl-⁴ boranes with alkyl halides requires the presence of bases, such as sodium hydroxide, ethoxide or carbonate for a successful reaction. It occurred to us that the direct trapping of an aryllithium anion with trimethyl borate should form a dimethyl arylborate with the liberation of an equivalent of lithium methoxide. The lithium methoxide, **generated *in situ***, should facilitate the coupling of an organohalide with the arylborate in the presence of palladium(0) **without the need of isolating the arylboronic acid**.

The above idea was realized when the dilithio furan **7**, generated by treating furan **8** with 2.2 equivalents of *n*-butyllithium⁸ (DME, 0°C, 15 min), was treated with 2 equivalents of trimethyl borate. Stirring the mixture for one hour (0°C) followed by the addition of the arylborate solution to a mixture of bromobenzene and Pd(PPh₃)₄ (in DME/H₂O (3/1)) and refluxing the solution (1 hour) provided, after a basic workup, coupled furan **9** in 68% yield (entry 1, Table 1).

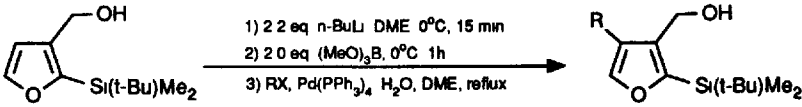


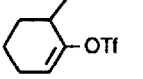
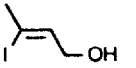
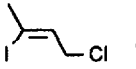
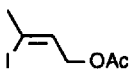
In general, the yields of the coupling reaction are good to excellent. The reaction was not limited to arylbromides since benzylbromide (entry 7), aryltriflate **22** (entry 9), vinyltriflate **23**⁹ (entry 10) and vinyliodides **24** and **4**¹⁰ (entries 11 and 13) coupled smoothly in yields ranging from 60-93%. The aryltriflate **21** (entry 8) provided the coupled product **16** in poor yield (14%), the low yield can be attributed to the presence of the electron releasing methoxy substituent (compare the result with entry 9).¹¹ The coupling reaction with (*Z*)-1-chloro-3-iodo-2-butene **25** provided a disappointing 20% yield of furan **20**. It was subsequently found that compound **25** is unstable above 25°C. Thus, refluxing the solution to effect the coupling reaction reduced the yield of compound **20** due to decomposition of compound **25**. The yield of acetate **3** was improved (from 50% to 80%) by employing Pd₂(dba)₃ (3 mol%) as the catalyst,¹² in addition the reaction time was reduced from 20 hours to 2 hours. The addition of water to the reaction mixture was not necessary to effect a complete reaction, however, the time to complete the coupling reaction with bromobenzene in the absence of water increased from 1 hour to 15 hours.¹³

A typical procedure is as follows. To a solution of furan **8** (200 mg) in DME (6 mL) under argon (at -78°C) was added *n*-butyllithium (2.2 eq). The solution was warmed to 0°C, stirred 15 minutes, and trimethyl borate (2 eq) added. The mixture was stirred for 1 hour (at 0°C) and then added to a preformed mixture of the organohalide (1.5 eq) and Pd(PPh₃)₄ (3 mol%) in DME/H₂O (3/1, 8 mL total). The mixture was refluxed (see Table 1 for the reflux time) under argon, cooled to room temperature and the solvent removed *in vacuo*. Sodium hydroxide (4 mL of 10%) was added and the mixture extracted with ether. Drying (Na₂SO₄) and removal of the solvent provided the product which was purified by column chromatography (silica gel) and/or distillation.¹⁴

We have therefore shown that 2,3,4-trisubstituted furans can be prepared via a modified Suzuki palladium catalyzed cross-coupling reaction in which the furylboronic acid is not isolated. Application of compound **3** towards the synthesis of halenaquinone **1** is currently in progress.

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Table 1: Palladium Catalyzed Cross-Couplings With Furylborates Generated *in situ*

			
Entry	RX	Reflux Time (h)	Product (% Yield) ^a
1	Bromobenzene	1	9 (68)
2	1-Bromonaphthalene	1	10 (64)
3	4-Bromotoluene	1	11 (75)
4	2-Bromo-1-nitrobenzene	1	12 (63)
5	2-Bromobenzaldehyde	1	13 (78)
6	2-Bromopyridine	15	14 (87)
7	Benzylbromide	15	15 (93)
8	 21	9	16 (14)
9	 22	1	17 (67)
10	 23	1	18 (70)
11	 24	1	19 (76)
12	 25	1	20 (20) ^b
13	 4	20 2 ^c	3 (50) + 19 (10) 3 (80)

a) isolated yields

b) the low yield is presumably due to the thermal instability of compound **23**c) using 3 mol% Pd₂(dba)₃ as the catalyst

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- 14 All compounds provided analytical and/or spectroscopic data consistent with their structures

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