Regiocontrolled Suzuki–Miyaura Couplings of 3,5-Dibromo-2-pyrone

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Abstract: In a similar way to its Stille coupling reactions, 3,5-dibromo-2-pyrone undergoes the Suzuki–Miyaura coupling reactions at either the C3- or the C5-position with high regioselectivity depending on the reaction conditions.

Key words: Suzuki–Miyaura, cross-coupling, boron, palladium catalyst, regioselectivity, copper

We have previously reported that 3,5-dibromo-2-pyrone undergoes Pd-catalyzed coupling reactions regioselectively at C3 over C5, providing various 3-alkynyl-, 3-alkenyl-, 3-aryl-, 3-amino-5-bromo-2-pyrones via the Sonogashira, Stille and Pd-catalyzed amination reactions, respectively.[1] The preferred coupling reactions at C3 would be due to the lower electron density at C3, accounting for the faster oxidative addition of Pd(0) at this position, as suggested by its ^{13}C NMR spectrum (Figure 1).

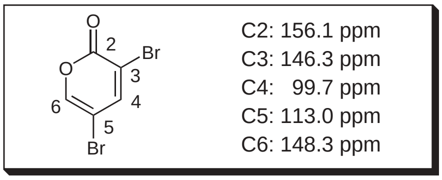
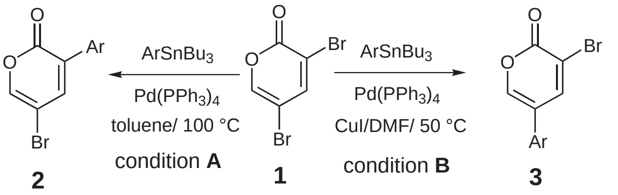


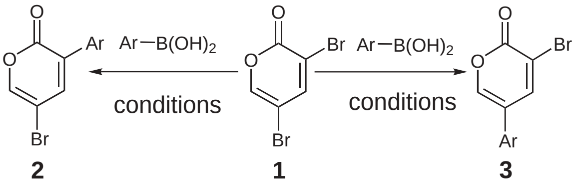
Figure 1 ^{13}C NMR spectrum of 3,5-dibromo-2-pyrone

More recently, we have demonstrated that the Stille coupling reactions of 1,3-dibromo-2-pyrone can be made at C5-position, rather than the usual C3-position, by changing the reaction conditions as described in Scheme 1.[2] The presence of Cu(I) reversed the regiochemical course of the reaction, when the reaction was carried out in a polar solvent.



Scheme 1 Regioselective Stille couplings of 3,5-(Br)$_2$-2-pyrone

The resulting regiochemical reversal has been attributed to the preferred formation of C5-Pd intermediate under condition B, together with its higher reactivity. While the underlying mechanistic fundamentals are still not clear, we have conducted Suzuki coupling reactions of **1**. As the Stille coupling reactions are quite susceptible toward steric hindrance, our previous couplings were not feasible with bulky aryl halides. Attempted couplings with 1-stannyl naphthalene provided the coupling product in less than 10% yield. The success of the Suzuki couplings would thus greatly expand the reaction scope, generating structurally more diverse synthetically useful 2-pyrone derivatives. Herein, we present our recent results on the couplings with aryl boronic acids,[3] which also proceeded in a highly regioselective fashion at either of the two C-Br, depending on the reaction conditions and the type of Pd-catalyst (Scheme 2).



Scheme 2 Regioselective Suzuki couplings of 3,5-(Br)$_2$-2-pyrone

A systematic study was conducted with Ph-B(OH)$_2$ as a model under the conditions varying solvent polarity, with and without Cu(I), using Pd(PPh$_3$)$_4$ as a catalyst, based on our previous success on the regiochemical control in the Stille coupling reactions.[2] As shown in Table 1 summarizing some of the notable cases, the solvent polarity and the presence of Cu(I) played a decisive role in determining the regiochemical outcomes.

Under the conditions in entry 4, the coupling reaction proceeded predominantly at C3, while the reaction took place at C5 under the conditions in entry 8. For the reasons that are not clear, we obtained better results with K$_2$CO$_3$, compared to other bases when the reaction was conducted in toluene. It is also worth noting that coupling reaction occurred at C3 under the conditions in entry 9 (the same conditions in entry 8 except temperature). In fact, we obtained the oxidative adduct **A** exclusively when an equimolar mixture of 3,5-dibromo-2-pyrone, Pd(PPh$_3$)$_4$ and CuI was stirred in DMF at room temperature (Scheme 3).

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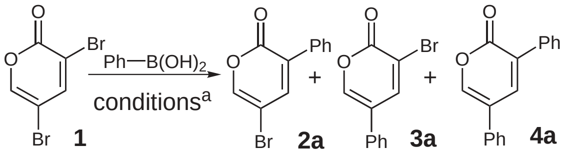
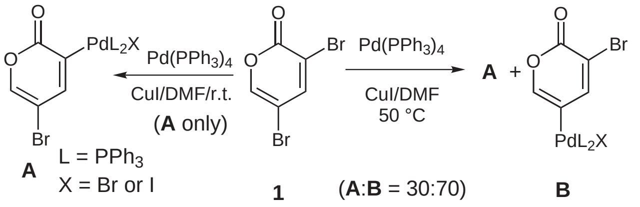
Table 1 Suzuki Couplings under Various Conditions



Entry	Conditions	Yield (%)[b] **2a**:**3a**:**4a**
1	Toluene, Cs_2CO_3, 100 °C, 20 min	64:trace:15
2	1,4-dioxane, Cs_2CO_3, 100 °C, 40 min	56:trace:14
3	Toluene, Na_2CO_3, 100 °C, 12 h	No reaction
4	Toluene, K_2CO_3, 100 °C, 4 h	81:trace:trace
5	Toluene, Cs_2CO_3, 100 °C, 1 h	57:trace:13
6	DMF, Cs_2CO_3, CuI (1 equiv), 50 °C, 30 min	trace:71:trace
7	DMF, K_2CO_3, CuI (1 equiv), 50 °C, 1 h	trace:71:trace
8	DMF, Na_2CO_3, CuI (1 equiv), 50 °C, 4 h	trace:89:trace
9	DMF, Na_2CO_3, CuI (1 equiv), r.t., 4 h	55:trace:trace
10	DMF, Na_2CO_3, 50 °C, 8 h	43:trace:5

[a] With 10 mol % $Pd(PPh_3)_4$.
[b] Isolated yields.



Scheme 3 Oxidative addition of 'Pd' onto 3,5-$(Br)_2$-2-pyrone

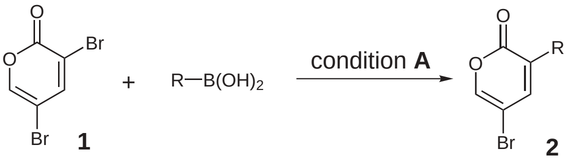
As reported earlier, the oxidative adducts **A** and **B** are sufficiently stable for silica gel column chromatography and spectroscopic characterizations. The bromide at Pd undergoes ligand exchange reaction with iodide.

The presence of Cu(I) in a polar solvent at elevated temperatures exerts a peculiar effect to enhance the formation of C5-Pd intermediate. Although the exact nature of the Cu(I) effect in the change of regiochemistry of the oxidative addition is not certain, it surely suppresses the formation of 3-pallado-2-pyrone (**A**). Remained to be answered is whether it exerts its effect through the prior coordination into the ester oxygen thus slowing down oxidative addition of 'PdL_2' at C3.

The Suzuki coupling reactions with various other aryl or vinyl boronic acids also proceeded regioselectively at C3 position under the conditions in entry 4 (condition **A**) to give a series of 3-substituted-5-bromo-2-pyrones in good yields (Table 2). In entries 5 and 6, no desired products were obtained under condition **A**. Running the reactions at lower temperature (80 °C) provided the coupling products, only in the range of 10–20% yield even after a prolonged heating. We have later found that the use of DAPCy [trans-$Pd(OAc)_2(Cy_2NH)_2$], prepared according to the literature method,[4] significantly increases the rate and chemical yields in these cases.

No detectable 3-substituted or 3,5-disubstituted 2-pyrones were observed in any cases. The electronic nature of the boronic acid does not appear to affect the reaction rate and product yield as both electron rich and poor aryl boronic acids were well coupled. The coupling reaction with sterically hindered 2-naphthyl boronic acid also proceeded smoothly to afford 3-(2-naphthyl)-5-bromo-2-pyrone (**2i**). There was no success with the analogous Stille coupling reaction using (2-naphthyl)tributyltin, because of the steric hindrance.

Table 2 Regioselective Suzuki Couplings with Various Aryl and Vinyl Boronic Acids under Condition **A**[a]



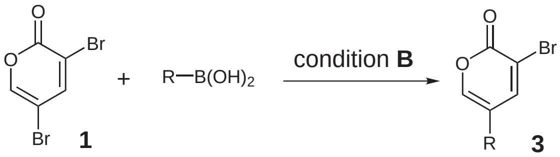
Entry	R	Time (h)	Product	Yield (%)[b]
1	4-$MeOC_6H_4$	2	**2b**	70
2	3,5-$Me_2C_6H_3$	4	**2c**	65
3	3,5-$F_2C_6H_3$	6	**2d**	74
4	Bu-CH=CH-	3	**2e**	55
5	Ph-CH=CH-	24	**2f**	40[c]
6	2-Benzofuranyl	2	**2g**	50[c]
7	2-Thiophenyl	6	**2h**	55
8	1-Naphthyl	3	**2i**	90

[a] Condition **A**: 10 mol % $Pd(PPh_3)_4$, toluene, K_2CO_3, 100 °C, 4 h.
[b] Isolated yield.
[c] Conditions: *trans*-$Pd(OAc)_2(Cy_2NH)_2$, toluene, K_2CO_3, 80 °C.

The couplings with the same boronic acids under the conditions in entry 8 (condition **B**) furnished 5-substituted-3-bromo-2-pyrones in good to excellent yields and selectivity (Table 3).[5] In entries 4, 6 and 7, we obtained small amounts of disubstituted 2-pyrones (15%, 14% and 11% isolated yield, respectively).

In summary, we have found that 3,5-dibromo-2-pyrone undergoes the Suzuki coupling reactions with various aryl- and vinyl boronic acids at either C3- or C5-position with high regioselectivity, depending on the reaction conditions. Similar to its Stille coupling reactions, Cu(I) and solvent polarity played a decisive role in the regiochemistry of the Suzuki coupling reactions. Further study is under way for the elucidation of their exact effects.

Table 3 Regioselective Suzuki Couplings with Various Aryl and Vinyl Boronic Acids under Condition **B**[a]



Entry	R	Time (h)	Product	Yield (%)[b]
1	4-MeOC$_6$H$_4$	4	**3b**	81
2	3,5-Me$_2$C$_6$H$_3$	3	**3c**	78
3	3,5-F$_2$C$_6$H$_3$	3	**3d**	72
4	Bu-CH=CH-	3	**3e**	86
5	Ph-CH=CH-	5	**3f**	91
6	2-Benzofuranyl	6	**3g**	83
7	2-Thiophenyl	6	**3h**	71
8	1-Naphthyl	3	**3i**	60

[a] Condition **B**: 10 mol % Pd(PPh$_3$)$_4$, DMF, Na$_2$CO$_3$, CuI (1 equiv), 50 °C, 4 h.

[b] Isolated yield.

Preparation of 2a (Condition A):
To a flask were charged **1** (30 mg, 0.12 mmol), phenylboronic acid (0.14 mmol), Pd(PPh$_3$)$_4$ (14 mg, 10 mol%), K$_2$CO$_3$ (33 mg, 0.28 mmol) and anhyd toluene (1.0 mL) at r.t. After 5 min, the reaction mixture was heated at 100 °C. After 4 h, the reaction mixture was cooled, concentrated and purified by silica gel column chromatography (hexanes–EtOAc = 50:1) to give **2a** (24 mg, 81% yield).

Preparation of 3a (Condition B):
To a flask were charged **1** (25 mg, 0.10 mmol), phenylboronic acid (0.10 mmol), CuI (19 mg, 0.01 mmol), Pd(PPh$_3$)$_4$ (11 mg, 10 mol%), Na$_2$CO$_3$ (20 mg, 0.02 mmol) and anhyd DMF (1.0 mL) at r.t. After 4 h at 50 °C, the reaction mixture was cooled, concentrated and purified by silica gel column chromatography (hexanes–EtOAc = 30:1) to give **3a** (22 mg, 89% yield).

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References

(1) (a) Lee, J.-H.; Cho, C.-G. *Tetrahedron Lett.* **2003**, *44*, 65. (b) Lee, J.-H.; Park, J.-S.; Cho, C.-G. *Org. Lett.* **2002**, *4*, 1171. (c) Lee, J.-H.; Kim, W.-S.; Lee, Y. Y.; Cho, C.-G. *Tetrahedron Lett.* **2002**, *43*, 5779. (d) Kim, W.-S.; Kim, H.-J.; Cho, C.-G. *Tetrahedron Lett.* **2002**, *43*, 9015.

(2) Kim, W.-S.; Kim, H.-J.; Cho, C.-G. *J. Am. Chem. Soc.* **2003**, *125*, 14288.

(3) (a) Suzuki, A. *J. Organomet. Chem.* **1999**, *57*, 147. (b) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.

(4) Tao, B.; Boykin, D. W. *Tetrahedron Lett.* **2003**, *44*, 7993.

(5) (a) Marrison, L. R.; Dickinson, J. M.; Fairlamb, I. J. S. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2667. (b) Marrison, L. R.; Dickinson, J. M.; Fairlamb, I. J. S. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3509. (c) Afarinkia, K.; Berna-Canovas, J. *Tetrahedron Lett.* **2000**, *41*, 4955. (d) Cerezo, S.; Moreno-Manas, M.; Pleixats, R. *Tetrahedron* **1998**, *54*, 7813.