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Regioselective double Suzuki couplings of 4,5-dibromothiophene-2-carboxaldehyde

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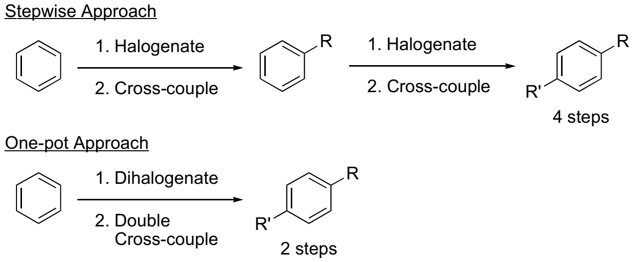
Abstract—Conditions have been identified that enable the one-pot double Suzuki coupling of 4,5-dibromothiophene-2-carboxaldehyde to proceed in good yield. The key to success in these reactions is the use of minimal amounts of water to avoid significant amounts of dehalogenation during the first coupling.

Cross-coupling reactions are a well established family of reactions that find great use in the preparation of substituted aromatic compounds.[1] Through these reactions, C–C, C–N, C–O, and even C–S bonds can be formed with a high degree of control and functional group tolerance. As a result, it is hardly surprising that cross-coupling chemistry is one of the main methods employed in the synthesis of substituted aromatics.

At the same time, the use of cross-coupling chemistry to introduce more than one substituent is inherently less than ideal. For each substituent to be installed, a halogenation and a coupling reaction are required. Thus, a minimum of two steps are needed to introduce each new group. If multiple groups are to be installed, this results in a very linear sequence (Scheme 1).

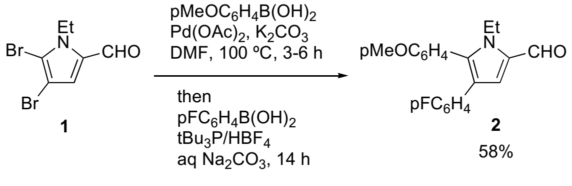
In an effort to render the use of cross-coupling reactions to introduce multiple substituents more efficient, we have been interested in developing the regioselective, one-pot polycoupling reaction of polyhaloaromatics.[2,3] In this case, multiple halogens are introduced in one step and then, in the second step, different substituents are introduced via sequential cross-coupling reactions. The regiocontrol in these cross-coupling reactions is determined by the electronic differences between the different halogenated sites and is highly predictable.[4]



Scheme 1. Stepwise vs one-pot cross-coupling methods.

Our earliest efforts developing the polycoupling route to polysubstituted aromatics focussed on the pyrrole nucleus.[2a,b] Particularly successful results were obtained with dibromopyrrole aldehyde **1**.[2a] (Scheme 2) Thus, the use of palladium acetate as the catalyst provided excellent selectivity for coupling at C5, with no competing coupling at C4. By simple addition of a phosphine ligand with the second boronic acid, though, coupling at C4 occurred to afford the dicoupled material in good overall yield.

In light of this success, an obvious extension to consider was related heteroaromatic aldehydes. One such system



Scheme 2. Pyrrole aldehyde **1** double couplings.

Keywords: Regioselective; Suzuki coupling; Thiophenes; One-pot; Dehalogenation.

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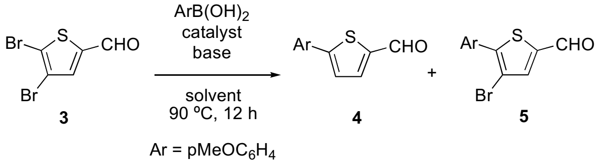
Table 1. Catalyst studies



Entry	Catalyst	Base	Solvent	Product
1	$Pd(OAc)_2$	aq K_2CO_3	DMF	**4** (75%)
2	$Pd(OAc)_2$	aq Na_2CO_3	EtOH/toluene (1:3 v/v)	Complex mixture
3	$Pd(OAc)_2$	K_2CO_3	DMF	No rxn
4	$Pd(OAc)_2$, $t$$Bu_3P/HBF_4$	aq Na_2CO_3	EtOH/toluene (1:3 v/v)	**4** (82%)
5	$Pd(OAc)_2$, $t$$Bu_3P/HBF_4$	Cs_2CO_3	EtOH/toluene (1:3 v/v)	**5** (42%)
6	$Pd(OAc)_2$, $t$$Bu_3P/HBF_4$	aq Cs_2CO_3	DMF	**5** (58%) **4** (38%)
7	$Pd(OAc)_2$, $t$$Bu_3P/HBF_4$	Cs_2CO_3	Dioxane	No rxn

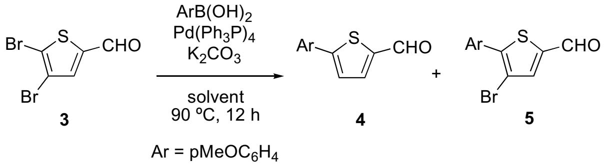
is thiophene aldehyde **3**.[5] Despite the apparent similarities, application of the conditions used for regioselective couplings of pyrrole aldehyde **1** to aldehyde **3** failed to afford any significant quantities to the desired double coupling product.

In an effort to determine the source of this failure, investigation of just the first coupling at C5 was undertaken. One complication that was quickly noted was the appearance of a significant by-product **4** in many of the reactions. This apparent product of coupling followed by dehalogenation was difficult to separate from the mono-coupled product **5**.[6,7] As can be seen, variation in solvent when using palladium acetate as the catalyst did not avoid this dehalogenation (Table 1, entries 1 and 4). Curiously, attempts to use anhydrous reaction conditions did shut down the dehalogenation, but resulted in no reaction (Table 1, entry 3).

Next, more active palladium catalysts were examined, but even bis(tri-*tert*-butylphosphine)palladium(II) acetate failed to improve the coupling results.[8] Choice of base or solvent made little difference, although again attempts to use anhydrous conditions failed to afford any coupling or dehalogenation (Table 1, entry 7).

From these results, it appeared that the presence of water was both crucial for the coupling but also involved in the dehalogenation. Indeed, using tetrakis(triphenylphosphine) palladium(0) as the catalyst with potassium carbonate as the base in a mixture of dioxane and water supported this hypothesis (Table 2). Thus, in a 4:1 solvent mixture, dehalogenation was the major product, while in an 8:1 mixture the reaction failed to proceed to completion within 24 h. Selecting a value between these two (6:1) was a good compromise, affording complete conversion within 5 h, but minimizing the amount of dehalogenation (<10% as determined by ^{1}H NMR).

Table 2. Dioxane/water studies



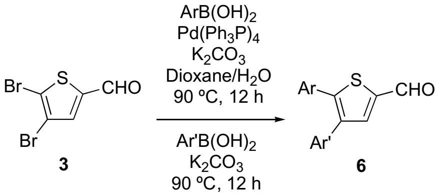
Entry	Ratio (H_2O/dioxane)	% Yield of **5**	% Yield of **4**
1	1:4	35	55
2	1:6	95	3
3	1:8	35[a]	0

[a] Remainder was covered starting material.

Fortunately, the second coupling also proceeded under these same conditions, enabling a simple one-pot double coupling method using tetrakis(triphenylphosphine) palladium(0) and potassium carbonate. The catalyst remained active for the second coupling, so only additional base and the second boronic acid needed to be added. Interestingly, no particular care needed to be taken to exclude oxygen and these reactions were performed under a simple atmosphere of air rather than nitrogen or argon.

With reaction conditions in hand, the application to a variety of boronic acids was explored.[9,10] (Table 3) Not unexpectedly, the reaction worked best with electron-rich boronic acids. Still, electron-deficient and even alkenyl boronic acids worked at modestly reduced yields (Table 3, entries 2, 3, and 6). Finally, steric hindrance

Table 3. Double coupling results



Entry	Ar	Ar′	% Yield
1	p-$MeOC_6H_4$	Ph	97
2	p-FC_6H_4	Ph	82
3	Ph	p-FC_6H_4	56
4	Ph	3,4-$DiMeOC_6H_4$	80
5	o-$MeOC_6H_4$	Ph	25
6	*trans*-Heptenyl	p-$MeOC_6H_5$	41

also decreased the efficiency, but an ortho substituted boronic acid did afford the coupled product (Table 3, entry 5).

In short, we have identified conditions that are effective for the regioselective double Suzuki coupling of thiophene aldehyde **3**. This sequential, one-pot reaction affords the double-coupled products in generally good yield and is expected to be of great utility in the preparation of substituted thiophenes for a variety of applications. Efforts are currently underway to extend these dicoupling conditions to furfural and other thiophenes.

Acknowledgments

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References and notes

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5. No previous efforts have been reported on the regioselective coupling of thiophene aldehyde **3**, although one report has investigated 3,5-dibromothiophene-2-carboxaldehyde Kodani, T.; Matsude, K.; Yamada, T.; Kobatake, S.; Irie, M. *J. Am. Chem. Soc.* **2000**, *122*, 9631–9637.
6. Interestingly, the formation of **4** does not appear to be the result of dehalogenation of **5**, since resubjection of **5** to the reaction conditions, but in the absence of a boronic acid, does not result in the formation of **4** and resubjection of **5** to the reaction conditions in the presence of a boronic acid only affords the product of a second Suzuki coupling.
7. The identity of compound **4** was confirmed by comparison to the spectral data for this compound reported in the literature Alson, D. A.; Najera, C.; Pacheco, M. C. *J. Org. Chem.* **2002**, *67*, 5588–5594, Hydrogenolysis of **5** also affords compound **4**, thereby confirming the regioselectivity of the first coupling.
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9. *Representative procedure*: To a solution of dibromothiophene aldehyde **3** (0.3 mmol) in 4 mL of dioxane/water (6:1 v/v) was added boronic acid (0.33 mmol), potassium carbonate (0.6 mmol), and tetrakis(triphenylphosphine) palladium(0) (0.015 mmol). The reaction mixture was heated to 90 °C overnight (12 h) and shaken on an orbital shaker. At this point, the second boronic acid (0.45 mmol) and more potassium carbonate (0.66 mmol) were added and the reaction was shaken and heated for an additional 12 h. The reaction was then cooled to room temperature and partitioned between ether and water. The organic layer was dried with magnesium sulfate, filtered, and concentrated in vacuo. The crude residue was purified by column chromatography using 20% ether/hexanes as the eluent to afford the double-coupled product.
10. All new compounds exhibited spectral properties consistent with the assigned structures. *5-(4′-Methoxyphenyl)-4-phenylthiophene-2-carboxaldehyde*: Brown oil. IR (cm^{-1}, neat) 2860, 2820, 1665, 1435 1252, 1176, 1043, 831; ^{1}H NMR (360 MHz, CDCl$_3$) 9.89 (s, 1H), 7.77 (s, 1H), 7.34–7.24 (m, 7H), 6.82 (d, $J = 6.8$ Hz, 2H), 3.81 (s, 3H); ^{13}C NMR (90 MHz, CDCl$_3$) 183.0, 160.2, 149.2, 140.7, 139.6, 138.9, 135.5, 130.6, 129.1, 128.8, 127.7, 125.5, 114.3, 55.4. HRMS (EI) Calcd for $C_{18}H_{14}O_2S$ 402.0784; found, 402.0785. *5-(4′-Fluorophenyl)-4-phenylthiophene-2-carboxaldehyde*: Tan solid. Mp 78–79 °C. IR (cm^{-1}, neat) 2860, 2820, 1645, 1375, 1236, 1159, 1038, 835; ^{1}H NMR (360 MHz, CDCl$_3$) 9.92 (s, 1H), 7.79 (s, 1H), 7.59 (d, $J = 6.8$ Hz, 2H), 7.44 (t, $J = 6.8$ Hz, 2H), 7.34–7.24 (m, 3H), 7.00 (t, $J = 8.6$ Hz, 2H); ^{13}C NMR (90 MHz, CDCl$_3$) 182.9, 166.3, 147.5, 141.5, 139.8, 139.2, 135.0, 131.1 (d, $J = 34$ Hz), 130.7, 129.1 (d, $J = 60$ Hz), 128.9, 127.9, 116.0 (d, $J = 54$ Hz). HRMS (EI) Calcd for $C_{17}H_{11}OS$ 390.0515; found, 390.0515. *4-(4′-Fluorophenyl)-5-phenylthiophene-2-carboxaldehyde*: Brown oil. IR (cm^{-1}, neat) 2860, 2820, 1650, 1480, 1232, 1162, 1041, 829; ^{1}H NMR (360 MHz, CDCl$_3$) 9.92 (s, 1H), 7.77 (s, 1H), 7.34–7.18 (m, 7H), 7.01 (t, $J = 9.2$ Hz, 2H); ^{13}C NMR (90 MHz, CDCl$_3$) 182.9, 164.0, 160.7, 148.8, 141.6, 138.9, 138.5, 133.0, 131.2, 130.8 (d, $J = 32$ Hz), 129.2 (d, $J = 100$ Hz), 128.8, 115.8 (d, $J = 86$ Hz). HRMS (EI) Calcd for $C_{17}H_{11}FOS$ 390.0515; found, 390.0517. *4-(3′,4′-Dimethoxyphenyl)-5-phenylthiophene-2-carboxaldehyde*: Tan solid. Mp 152–155 °C. IR (cm^{-1}, neat) 2860, 2820, 1668, 1513, 1465, 1432, 1251, 1027, 845; ^{1}H NMR (360 MHz, CDCl$_3$) 9.92 (s, 1H), 7.80 (s, 1H), 7.36–7.30 (m, 5H), 6.86 (d, $J = 6.8$ Hz, 1H), 6.85 (s, 1H), 6.68 (d, $J = 6.8$ Hz, 1H), 3.89 (s, 3H), 3.63 (s, 3H); ^{13}C NMR (90 MHz, CDCl$_3$) 182.9, 148.8, 141.3, 139.4, 138.9, 129.4, 128.9, 128.8, 127.7, 121.3, 119.2, 112.3, 111.5, 111.2, 110.4, 55.9, 55.7. HRMS (EI) Calcd for $C_{19}H_{16}O_3S$ 432.0820; found, 432.0818. *5-(2′-Methoxyphenyl)-4-phenylthiophene-2-carboxaldehyde*: Tan wax. Mp 77–78 °C. IR (cm^{-1}, neat) 2860, 2820, 1164, 1460, 1248, 1025, 831; ^{1}H NMR (360 MHz, CDCl$_3$) 9.94 (s, 1H), 7.85 (s, 1H), 7.28–7.22 (m, 6H), 7.08–7.00 (m, 1H), 6.93 (t, $J = 6.8$ Hz, 1H), 6.86 (d, $J = 6.8$ Hz, 1H), 3.49 (s, 3H); ^{13}C NMR (90 MHz, CDCl$_3$)183.1, 156.7, 142.0, 141.2, 138.1, 136.2, 132.0, 131.5, 130.7, 128.4, 128.0, 127.4, 120.8, 120.6, 111.6, 55.2. HRMS (EI) Calcd for $C_{18}H_{14}O_2S$ 402.0784; found, 402.0783. *5-(trans-Heptenyl)-4-(4′-methoxyphenyl)thiophene-2-carboxaldehyde*: Yellow solid. Mp 74–75 °C. IR (cm^{-1}, neat) 2860, 2820, 1164, 1508, 1437, 1289, 1246, 1177, 835, 741; ^{1}H NMR (360 MHz, CDCl$_3$) 9.83 (s, 1H), 7.63 (s, 1H), 7.30 (d, $J = 6.6$ Hz, 2H), 6.98 (d, $J = 6.6$ Hz, 2H), 6.54 (d, $J = 14.4$ Hz, 1H), 6.36 (dt, $J = 6.7, 14.4$ Hz, 1H), 3.86 (s, 3H), 2.18 (q, 2H), 1.46–1.24 (m, 6H), 0.89 (t, 3H); ^{13}C NMR (90 MHz, CDCl$_3$) 182.8, 159.3, 147.2, 139.5, 139.2, 139.0, 137.1, 130.2, 128.5, 122.2, 114.2, 55.4, 33.3, 31.5, 28.7, 22.6, 14.1. HRMS (EI) Calcd for $C_{19}H_{22}OS$ 406.1391; found, 406.1390.