Improved Studies of Cross-Coupling Reactions of 5-(tri-*n*-butystannyl)- and 5,5'-bis(tri-*n*-butylstannyl)-2,2'-Bithiophene with Aryl halides

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Stille coupling under standard conditions proceeds in low yield when using hindered organostannanes (**1**) or (**2**) and aryl bromide partners. The inclusion of aryl iodide instead of aryl bromide with the same organostannanes, significantly improves the efficiency of the coupling, providing a variety of desired products in good to excellent yield. The yields of Stille coupling are compared to the different reactivity of aryl halides. This study of Stille coupling with different aryl halides are documented and rationalized.

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Introduction.

The 2,5-diaryl-thiophene nucleus has been shown to enhance non-linear optical properties [1-2]. Most of these 2,2-bithiophene, which are characterized by an aryl group linked to the 5-position, have been found also to be potent photo-toxic agents when tested against microorganisms [3]. Synthesis of unsymmetrical [4] and symmetrical 2,5-diarylthiophenes could use a double Heck arylation starting from thiophene [5]. It is known that the Heck arylation does not work very well when electron-donating groups are present on the aryl nucleus. In general, symmetrical 2,5-diarylthiophenes have been prepared by reaction of the corresponding 1,4-diketones with phosphorus penta-sulfide and hydrogen sulfide, Lawesson reagent or other sulfur transfer systems [6].

The most valuable three coupling methods of the Pd°-catalyzed construction of 5,5'-diaryl-2,2'-bithiophene bonds formation are the organostannanes or Stille [7], organoboranes or Suzuki [8], and organozincs or Negishi [9] coupling reactions. We explored one of them in the synthesis of our hetero-aryl compounds, that is the organostannane method (Stille coupling). In this method, the organometallic species acts as a nucleophile for the palladium (0)-catalyzed hetero-aryl cross-coupling reaction with an electrophilic species, such as aryl bromides or iodides. This reaction has the advantage of being slightly more general than the Suzuki reaction, since it does not require base. However, a major drawback is the toxic tin by-products.

Results and Discussion.

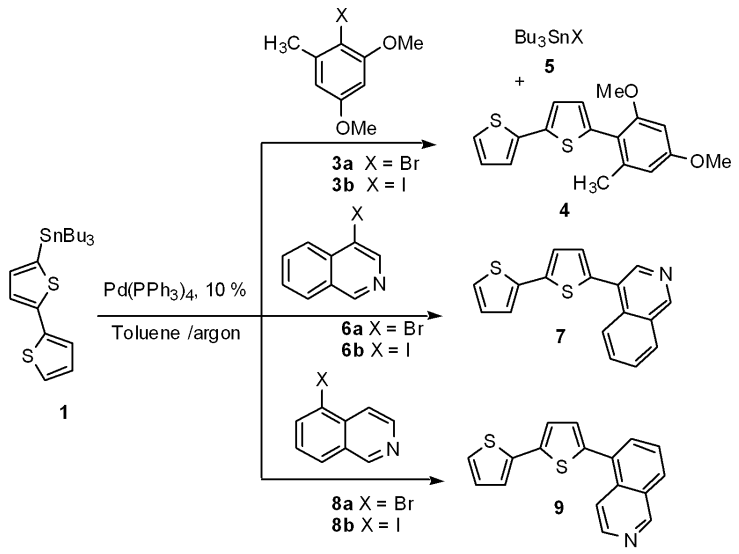
This work continues our previous studies on the palladium catalyzed cross-coupling (Stille reaction) of thiophene [10] and 2,2'-bithiophene [11,12] for carbon-carbon bond formation. The Stille coupling reaction is the palladium (0) catalyzed reaction of arylstannanes with aryl halides. This coupling reaction is well established as a useful method for formation of carbon-carbon bonds in organic synthesis [13]. Many reports disclosed the application, limitation and optimization of this coupling method [7,10,14-17].

Stannanes (**1**) and (**2**) were prepared in good yield after careful chromatographic separation [12]. 2-Bromo-, 2-iodo-3,5-dimethoxytoluene (**3a**,**b**) and halo-isoquinoline of (**6a**,**8a**) and (**6b**,**8b**) were prepared also following a previously described general [10,18,19].

We report here that a substantial improvement in yields in a variety of examples of this process can be obtained through the Stille coupling reactions of stannanes (**1**) or (**2**) with different aryl halides (**3a,b**,**6a,b** and **8a,b**) as shown in Scheme 1. Coupling of bromide (**3a**) and one equivalent of stannane (**1**) in toluene in the presence of 10 mol% $Pd(PPh_3)_4$ at 110°, in sealed culture tube gave the desired product (**4**) in 45% isolated yield as yellow oil after purified by flash chromatography over silica-gel (hexane: EtOAc (6:1). Coupling of (**3b**) with stannane (**1**) followed a similar trend to that of (**3a**), thus leading to an improved yield of desired product (**4**) in 70% yield. A model of 2-bromo and 2-iodo-3,5-dimethoxy toluene (**3a** and **3b**) were used first because both the steric hindrance and electron density at the coupling positions are very similar to that of the isoquinoline (IQ) building blocks (**6a**,**b**) and (**8a**,**b**). In making analogues, the most dramatic change made in this work is the selective halogenation of isoquinoline at the C-4 and C-5 positions, compounds **6a,b** and **8ab**, respectively, for coupling with stannanes (**1** or **2**). The ability to selectively halogenate isoquinoline at the C4 and C5 position prompted a more general survey of several representative substrates. As summarized in Table (1), changing the aryl halides from bromo to iodo gave consistently higher yields for Stille coupling of sterically hindered substrates.

Coupling of aryl bromides (**3a**,**6a**,**8a**) or aryl iodides (**3b**,**6b**,**8b**) with stannane (**1**) provided the corresponding products (**4**,**7**, and **9**) in moderate to excellent yields. Coupling of stannane (**1**) with (**6a**) in toluene at 110° furnished the desired product (**7**) in only 35% yield, as yellow oil after purified by flash chromatography over silica-gel (hexane: EtOAc (6:1). Coupling of (**8a**) with stannane (**1**) followed a similar trend to that of (**6a**) thus giving the expected product (**9**) in low (34%) yield. As discussed earlier, we examined stannane (**1**) against aryl iodides

Scheme 1



(**3b**,**6b**,**8b**), which was expected to exhibit increased reactivity compared to the aryl bromides (**3a**,**6a**,**8a**), and under identical conditions improved yields of 70%, 55%, 80% respectively were obtained.

Stannane (**2**) and aryl bromides (**3a**,**6a**,**8a**) were also examined in the Stille coupling under identical conditions to provide the desired products (**10**,**11**,**12**) in comparable yields (34%, 30%, 35%) respectively (Scheme 2). The yields in this case were the lowest even with increasing the reaction time or the addition of $Pd(PPh_3)_4$ catalysts for the Stille coupling. Hence, we repeated the coupling of stannane (**2**) using aryl iodides (**3b**,**6b**,**8b**) instead of aryl bromides and obtained the corresponding products (**10**,**11**,**12**), in, as expected, the higher yields of 60%, 65% and 80%, respectively, compared to that of the aryl bromides (Table 1).

In each case, the reductive products were contaminated with organotin halides R_3SnX (**5**) as by-products, the desired separation of reductive products and organotin halides R_3SnX (**5**) can be accomplished by conversion of the organotin halides (R_3SnX (**5**): X = Br, I) into the insoluble organotin fluoride (R_3SnF) by simply extracting the reduction mixture, dissolved in a non-polar solvent with a solution of potassium fluoride in water [10], which can be readily separated by filtration.

This report clearly indicates that aryl iodides are more reactive than their bromide analogue and that iodide can be efficiently processed through the catalytic cycle. When there is a sufficiently reactive hetero-metal species present to capture the intermediate of aryl palladium iodide.

Scheme 2

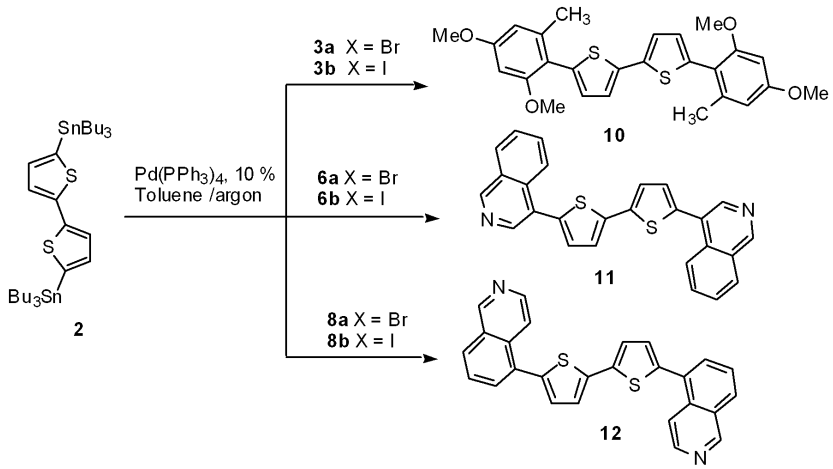


Table 1

Palladium-Catalyzed Cross-Coupling Reactions of Aryl Halides with 2-*n*-Tributylstannyl-2,2'-bithiophene (**1**) and 5,5'-Bis(*n*-tributylstannyl)-2,2'-bithiophene (**2**)

Stannanes	Pd°(PPh_3)$_4$, mole %	Aryl halides	Products	Yields
1	10 mol%	**3b** X = Br	**4**	45%
		3b X = I		70%
1	10 mol%	**6a** X = Br	**7**	35%
		6b X = I		55%
1	10 mol%	**8a** X = Br	**9**	36%
		8b X = I		80%
2	10 mol%	**3a** X = Br	**10**	34%
		3b X = I		60%
2	10 mol%	**6a** X = Br	**11**	30%
		6b X = I		65%
2	10 mol%	**8a** X = Br	**12**	35%
		8b X = I		80%

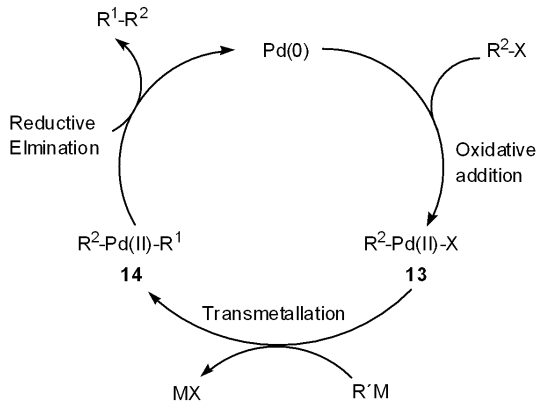


Figure 1. A general cycle for cross-coupling.

It was not clear at this stage whether the aryl bromides (**3a**,**6a** and **8a**) were less capable of supporting the oxidative addition step or whether the resulting aryl palladium bromide (**13** and **14**) was less sufficiently reactive to continue the catalytic cycle. These would explain the consistently lower isolated yield of the coupled product when the aryl bromides (**3a**,**6a** and **8a**) were used instead of the aryl iodides (**3b**, **6b** and **8b**).

A possible mechanism for these coupling reactions is described in Figures 1 and 2. A general catalytic cycle for the cross-coupling reaction of organometallics, which involves oxidative addition-transmetalation-reductive elimination sequences, is depicted in Figure 1. Although each steps involves further knotty processes including ligand exchanges, there is no doubt about the presence of those intermediates **13** and **14**, which have been characterized by isolation or spectroscopic analyses [20]. It is significant that the great majority of cross-coupling reactions catalyzed by Pd° is rationalized in terms of this common catalytic cycle.

Oxidative addition [21] of aryl halides to a palladium(0) complex affords a stable *trans*-σ-palladium (II) complex (**13**). The reaction proceeds with complete retention of configuration for aryl halides. Oxidative addition is often the rate-determining step in a catalytic cycle. The relative reactivity decreases in order of I>Br. Aryl halides activated by the proximity of electron-withdrawing groups are more reactive to the oxidative addition than those with donating groups.

The first step involves the oxidative addition of palladium into the carbon halogen bonds. The oxidative addition product is then scrambled to the intermediate (**16**) *via* a tetra-aryl phosphonium ion. Transmetallation then incorporates the aryl stannane into the coordination sphere of palladium. Finally, reductive elimination from the organopalladium (II) complex as intermediate produces the coupled product, as shown in Figure 2.

Reductive elimination could give homo-coupled biaryl (**5-12**), phenyl aryl (**18**) and protonated aryl (**19**). By-products **18**and **19** are observed in very small amounts in our system, however addition of excess aryl metal species usually gave the desired mix-coupled products in good yield. Electron rich aryl electrophiles and hindered substrates usually gave only moderate or poor yield.

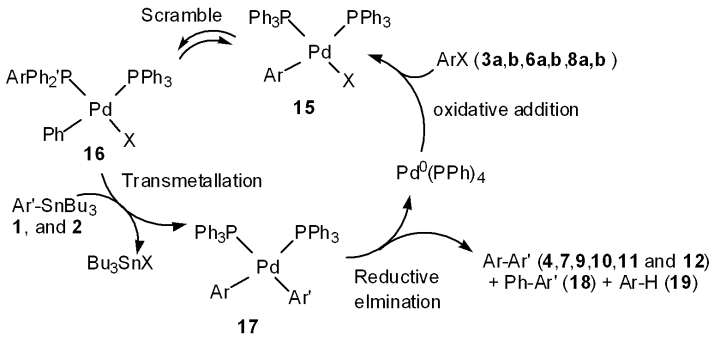


Figure 2. Catalytic cycle for Stille cross-coupling reaction.

EXPERIMENTAL

Products were characterized by comparison of their physical data with those of known samples. All yields refer to isolated products. IR spectra were recorded on a Perkin Elmer 781 and Pye Unicam 8725 spectrometers. NMR spectra were record on a Bruker DPX 250 spectrometer and the data obtained using an IBM NR-200, IBM NR-300-AF and a Varian VXR-500 (500 MHz) spectrometer. TLC accomplished the purity determination of the substrates and reaction monitoring on silica gel polygram SILG/UV 254 plates. M-H-W Laboratories (Phoenix, AZ) performed elemental analyses. Tandem gas chromatography/ low resolution mass spectrometry GC/LRMS using electron impact (EI) ionization was performed on a Hewlett-Packard 5890 series II gas chromatography and 5971A mass selective detector at 70 eV. Gas chromatography retention time reported along with the capillary column.

General Method.

In a screw-capped tube were placed aryl halide (0.1 *M*), 2 equivalents of aryl stannane, and 10 mole% of $Pd(PPh_3)_4$ in 25 ml of toluene. The reaction mixture was sealed under N_2 and heated to 110° for 20-24 hours. The mixture was cooled to room temperature and 25 ml of KF solution was added, the solution was then stirred for 30 minutes and neutralized with 10% aqueous ammonium chloride solution. The resultant mixture was filtered to remove unwanted Bu_3SnF. The filtrate was evaporated *in vacuo* to give an oily residue . The residue was isolated by extraction with ethyl acetate. The organic layer washed with brine, dried over $MgSO_4$, and evaporated to give an oil, which was purified by recrystallization or column chromatography on silica gel.

5-[2-(3,5-Dimethoxy)tolyl]-2,2'-bithiophene (**4**)

This compound was obtained using the general method as yellow oil after purification by column chromatography (silica gel, hexanes:EtOAc; 6:1 at R_f : 0.29). The cross-coupled product **5** (222 mg, 0.70 mmol, 45-70% yield; ir (Nujol) 839, 1602.4, 1631 cm^{-1}; lrms (EI): m/z (relative intensity %) 316 ($M^{+\cdot}$, 100), 254 (20), 202 (8), 189 (25), 165 (40), 151 (10), 121 (40), 108 (20), 82 (15), 77 (20), 51 (21), and 44 (100); ^1H nmr (deuteriochloroform): δ 7.29 (dd, J = 1.2 and 4.8 Hz, 1H, Ar-$H_{5'}$), 7.16 (d, J = 3.26 Hz, 1H, Ar-H_3), 7.02 (dd, J = 1.29 and 3.26 Hz, 1H, Ar-$H_{3'}$), 7.05 (d, J = 3.26 Hz, 1H, Ar-H_4), 7.003 (dd, J = 3.26 and 4.8 Hz, 1H, Ar-$H_{4'}$), 6.43 (bs, 1H, Ar-H_4), 6.39 (bs, 1H, Ar-H_6), 3.9 [s, 3H, ArO*C*H_3(3)], 3.85 [s, 3H, ArO*C*H_3(5)], 2.36 [s, 3H, Ar-CH3(1)] ppm. Gc**:** t_R = 13.317 min.; column: DB-5 6m x 0.01 mm + 1m guard column: temp. prog: 50°/2 min./20° $min.^{-1}$/250°/5 min.

Anal. Calcd. for $C_{17}H_{16}S_2O_2$: C, 64.55; H, 5.06; S, 20.25. Found: C, 64.22; H, 5.32; S, 20.01.

5-[4(Isoquinolinyl)]-2,2'-bithiophene (**7**).

This compound was obtained using the general method as yellow oil after purification by column chromatography (silica gel, hexanes:EtOAc; 6:1) to give 35-55% yield, ir (Nujol) 828, 1610.4, 1633 cm^{-1}; ^1H nmr (deuteriochloroform): δ 9.29 [s, 2H, Ar-H(1)], 8.58-8.56 [d, J = 6.0 Hz, 2H, Ar-H(3)], 8.12 [d, J = 6.0 Hz, 2H, Ar-H(8)], 7.99-7.97 [d, J = 8.14 Hz, 2H, Ar-H(5)], 7.83-7.80 [d, J = 7.16 Hz, 2H, Ar-H(6)], 7.68-7.61 [dd, J = 6.4 and 7.5 Hz, 2H, Ar-H(7)], 7.29 (dd, J = 1.2 and 4.8 Hz, 1H, Ar-$H_{5'}$), 7.16 (d, J = 3.26 Hz, 1H, Ar-H_3), 7.02 (dd, J = 1.29 and 3.26 Hz, 1H, Ar-$H_{3'}$), 7.05 (d, J = 3.26 Hz, 1H, Ar-H_4), 7.003 (dd, J = 3.26 and 4.8 Hz, 1H, Ar-$H_{4'}$) ppm.

Anal. Calcd. for $C_{17}H_{11}S_2N$: C, 69.62; H, 3.75; N, 4.77; S, 21.84. Found: C, 69.60; H, 3.74; N, 4.78, S, 21.85.

5-[5(Isoquinolinyl)]-2,2'-bithiophene (**9**).

This compound was obtained using the general method as yellow oil after purification by column chromatography (silica gel, hexanes:EtOAc; 6:1) to give 36-80% yield, ir (Nujol) 842, 1614.4, 1640 cm^{-1}; ^1H nmr (deuteriochloroform): δ 9.39 [s, 2H, Ar-H(1)], 8.63-8.60 [d, J = 6.08 Hz, 2H, Ar-H(3)], 8.18 [t, J = 6.0 Hz, 2H, Ar-H(8)], 7.97-7.93 [dd, J = 1.2 and 7.2 Hz, 2H, Ar-H(6)], 7.86-7.82 [d, J = 7.8 Hz, 2H, Ar-H(4)], 7.78-7,74 [d, J = 7.4 Hz, 2H, Ar-H(7)], 7.29 (dd, J = 1.2 and 4.8 Hz, 1H, Ar-$H_{5'}$), 7.16 (d, J = 3.26 Hz, 1H, Ar-H_3), 7.02 (dd, J = 1.29 and 3.26 Hz, 1H, Ar-$H_{3'}$), 7.05 (d, J = 3.26 Hz, 1H, Ar-H_4), 7.003 (dd, J = 3.26 and 4.8 Hz, 1H, Ar-$H_{4'}$) ppm.

Anal. Calcd. for $C_{17}H_{11}S_2N$: C, 69.62; H, 3.75; N, 4.77; S, 21.84. Found: C, 69.63; H, 3.74; N, 4.77, S, 21.86.

5,5' Bis [2-(3,5-dimethoxy)tolyl]-2,2'-bithiophene (**10**).

This compound was obtained using the general method as yellow oil after purification by column chromatography (silica gel, hexanes:EtOAc; 5:1, at R_f : 0.27) to give (165 mg, 0.34 mmol, 34-60% yield), ir (Nujol) 835, 1616.4, 1636 cm^{-1}; lrms (EI): m/z (relative intensity %) 482 ($M^{+\cdot}$, 80), 217 (7), 202 (8), 189 (25), 166 (40), 121 (40), 108 (20), 93 (15), 77 (20), 51 (21), and 44 (15); ^1H nmr (deuteriochloroform): δ 7.38 [d, J = 3.7 Hz, 2H, of Th-H(3,3')], 7.23 [d, J = 3.7 Hz, 2H, of Th-H(4,4')], 6.45 [bs, 2H, Ar-H(4,4')], 6.39 [bs, 2H, Ar-H(6,6')], 3.9 [s, 6H, ArO*C*H_3(3,3')*]*, 3.85 [s, 6H, ArO*C*H_3(5,5')*]*, 2.36 [s, 6H, Ar-CH3(1,1')] ppm. Gc**:** t_R = 14.3 min.; column: DB-5 6m x 0.01 mm + 1m guard column: temp. prog: 50°/2 min. /20° $min.^{-1}$/270° /5 min.

Anal. Calcd. for $C_{26}H_{26}S_2O_4$: C, 66.95; H, 3.58; S, 13.73. Found: C, 66.92; H, 3.55; S, 13.74.

5,5'-Bis(4-isoquinolyl)-2,2'-bithiophene (**11**).

This compound obtained as a yellow solid in an amorphous shape, by general method and Purified by crystallized from ethyl acetate to give (276 mg, 0.6 mmol, 30-65 %) mp. 189-192°, ir (Nujol) 844, 1621.4, 1643 cm^{-1}; ^1H nmr (deuteriochloroform): δ 9.29 [s, 2H, Ar-H(1)], 8.58-8.56 [d, J = 6.0 Hz, 2H, Ar-H(3)], 8.12 [d, J = 6.0 Hz, 2H, Ar-H(8)], 7.99-7.97 [d, J = 8.14 Hz, 2H, Ar-H(5)], 7.83-7.80 [d, J = 7.16 Hz, 2H, Ar-H(6)], 7.68-7.61 [dd, J = 6.4 and 7.5 Hz, 2H, Ar-H(7)], 7.33-7.32 [d, J = 3.6 Hz, 2H, Ar-H(3,3')], 7.21-7.2 [d, J = 3.66 Hz, 2H, Ar-H(4,4')] ppm.

Anal. Calcd. for $C_{26}H_{16}S_2N_2$: C, 74.28; H, 3.80; N, 6.66; S, 15.23. Found: C, 74.19; H, 3.81; N, 6.67; S, 15.20.

5,5' Bis(5-Isoquinolyl)-2,2'-Bithiophene (**12**).

This compound obtained using the general method as a yellow solid in an amorphous shape and was purified by recrystallized from ethyl acetate to give (350 mg, 0.8 mmol, 35-80 %), mp. 199-202°, ir (Nujol) 837, 1625.4, 1644 cm^{-1}; ^1H nmr (deuteriochloroform): δ 9.39 [s, 2H, Ar-H(1)], 8.63-8.60 [d, J = 6.08 Hz, 2H, Ar-H(3)], 8.18 [t, J = 6.0 Hz, 2H, Ar-H(8)], 7.97-7.93 [dd, J = 1.2 and 7.2 Hz, 2H, Ar-H(6)], 7.86-7.82 [d, *J* = 7.8 Hz, 2H, Ar-H(4)], 7.78-7,74 [d, J = 7.4 Hz, 2H, Ar-H(7)], 7.56-7.53 [d, J = 3.8 Hz, 2H, Ar-H(3,3')], 7.42-7.41[d, J = 3.8 Hz, 2H Ar-H(4,4')] ppm.

Anal. Calcd. for $C_{26}H_{16}S_2N_2$: C, 74.28; H, 3.80; N, 6.66; S, 15.23. Found: C, 74.18; H, 3.82; N, 6.69; S, 15.22.

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