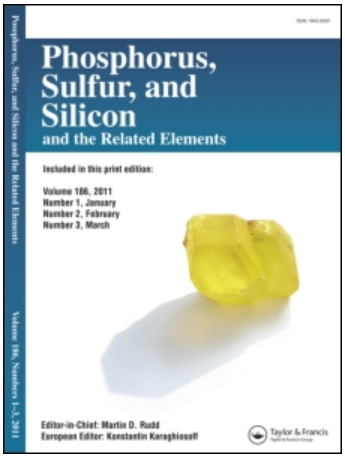

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STUDIES OF (Pd^0-MEDIATED) STILLE CROSS-COUPLING REACTIONS OF THIOPHENESTANNANE WITH ARYL HALIDE DERIVATIVES

Abdel-Sattar S. Hamad Elgazwy[a]
[a] Department of Chemistry, Faculty of Science, University of Ain Shams Abbassia, Cairo, Egypt

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STUDIES OF (Pd^0-MEDIATED) STILLE CROSS-COUPLING REACTIONS OF THIOPHENESTANNANE WITH ARYL HALIDE DERIVATIVES

ABDEL-SATTAR S. HAMAD ELGAZWY

Department of Chemistry, Faculty of Science, University of Ain Shams Abbassia 11566, Cairo, Egypt. *

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Stille (arylstannane) conditions used Pd^0-mediated cross-coupling reactions for preparation of thiophene/aryl analogs. Different arylhalides were compared when coupled with hetero-metal (thiophenestannane) system. Comparable yields have now been obtained by Stille (arylstannane) couplings with different reactivity of arylhalides.

Keywords: Stille Cross-Coupling; Thiophenestannane; 2(Tri-n-butylstannyl) thiophene

INTRODUCTION

Thiophenes isolated from plants in the family *Compositae* have recently stimulated much interest owing to their wide range of photobiological effect.[1-3] Aryl-substituted aromatic heterocycles such as 2-phenyl propynylthiophene[4] are also of interest as naturally occurring compounds. Palladium-catalyzed cross-coupling reactions between organometallic reagents and organic halides are now very efficient means for carbon-carbon bond formation.[5]

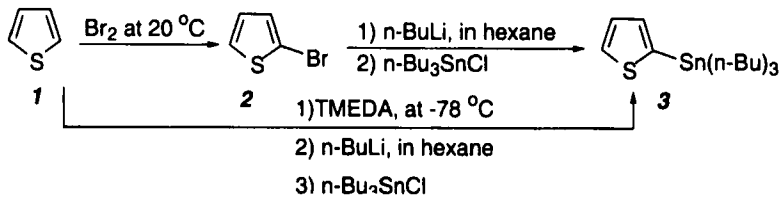
RESULTS AND DISCUSSION

In the present study, palladium-catalyzed direct cross-coupling reactions of aryl halides were conducted with π-electron sufficient aromatic hetero-

* Corresponding Author. E-mail; Hamad@asunet.shams.eun.eg

cycles such as thiophene. These prompted our efforts towards the study of (Pd^0-mediated) Stille[6] cross-coupling reactions of thiophenestannane **3** with different aryl halides to provide the corresponding cross-coupling products in moderate yields and in order to synthesize thiophene-isoquinoline analogs.

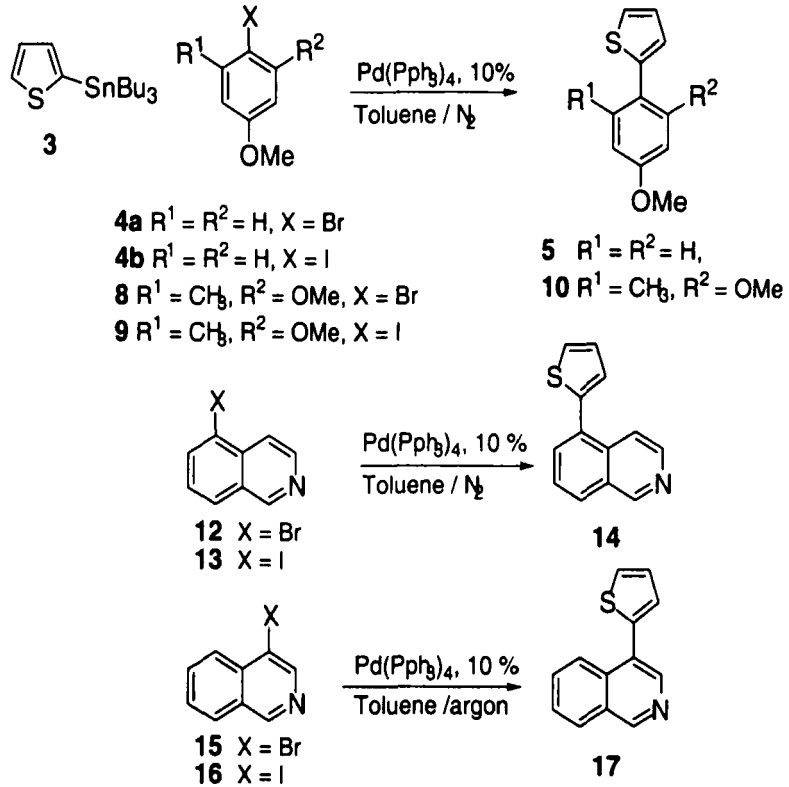
The transition metal catalyzed cross-coupling reaction is one of the most versatile and widely used methods of forming symmetrical and unsymmetrical heteroaryls. Cross-coupled heteroaryls are formed by the coupling of electrophilic and nucleophilic aromatic partners. In this method the organometallic species acts as a nucleophile for the palladium(0)-catalyzed heteroaryl cross-coupling reaction with an electrophilic species, such as an aryl halide. Stannane **3** was isolated in 79% yield after chromatographic purification of the reaction mixture obtained by metal-halogen exchange of (**2**)[7] with n-BuLi followed by the reaction with tributyltin chloride. The stannane **3** was also prepared by a different route in 79% yield, by treatment of thiophene **1** with TMEDA, at – 78°C followed by lithiation with n-BuLi and then metal-metal exchange with n-tributyltin chloride.



A variety of arylbromides **4a, 8, 12** and **15** were reacted with 2 equivalents of stannane **3**, in the presence of 10 mol % of $Pd(Pph_3)_4$ in toluene (0.1 M) at 110°C for 24 hours in a sealed culture tube under N_2 (Method A). Cross-coupled products **5, 10, 14** and **17** were formed respectively in moderate yield as shown in (Table I).

As model compounds of 2-bromo and 2-iodo-3,5-dimethoxytoluene (**8** and **9**) were used because both the steric hindrance and electron density at the coupling positions are very similar to **12** and **13**, the ideal isoquinoline building block (Scheme 1). The isolated product **5** was purified by flash chromatography (hexane/EtOAc, 9:1) to provide colorless needles solid in 55% yield (in case arylbromide). The cross-coupling isolated product **10** was purified by flash chromatography to provide colorless oil in 67% yield. This isolated yield was opposite to the result suggested by Thomas

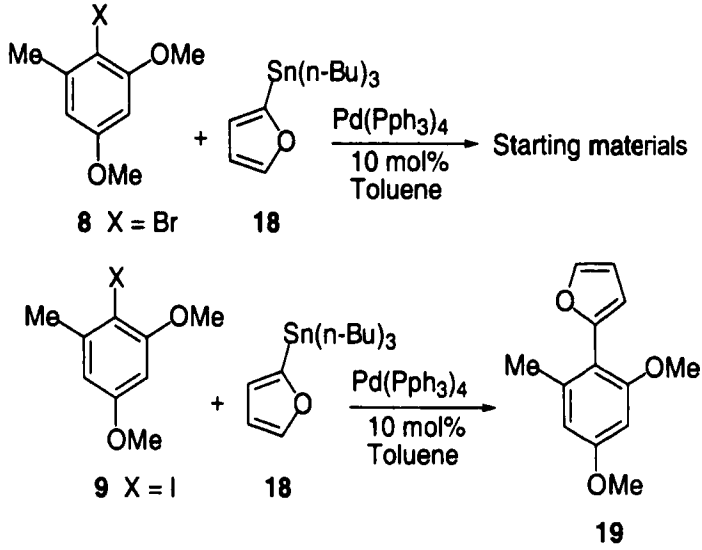
R. Hoye and Minzhang Chen[8] with the same arylhalide as shown in (Scheme 2) It was suggested that the reaction of 2-(tributylstannyl)furan **18** and arylbromide **8** gave only starting materials under identical reaction condition. But in the reaction of 2-(tributylstannyl)furan **18** and aryliodide **9** under the same identical reaction conditions, the isolated coupling product **19** was in excellent yield (90%) these was consistent with our results. Which was isolated too in 89% yield with the same aryliodide **9** as shown in (Scheme 1)



SCHEME 1

These indicate that the aryl iodide **9** is more reactive than bromide **8**. Ortho-disubstituted halides and *t*-butysubstannane thiophene were presumably too hindered to enter into the coupling event. Cross-coupling

product **14** was isolated in 52 % yield as colorless oil after flash chromatography (hexane/EtOAc, 2:1), and cross-coupling product **17** was also purified by flash chromatography (hexane/EtOAc, 3:1) to give as colorless oil in 45% yield. Compound (**17**) was produced in a low yield and the rate of reaction was slowly as monitored by TLC test and GC/MS after 12 hrs. the reaction mixture was continued for another 12 hrs.



SCHEME 2

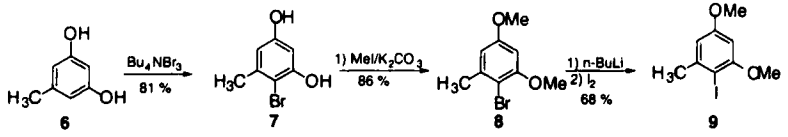
When the aryl iodides **4b, 9, 13** and **16** were coupled with 2-(*t*-tributylstannyl)thiophene (**3**) under identical reaction conditions, the corresponding products **5, 10, 14** and **17** were isolated in excellent yield as shown in (Table I).

This clearly indicates that the aryl iodide is more reactive than its bromide analogue and that iodide can be efficiently processed through the catalytic cycle when there is a sufficiently reactive, heterometal species present to capture the intermediate arylpalladium iodide. It was not clear at this stage whether the aryl bromide **8** was less capable of supporting the oxidative addition step or whether the resulting arylpalladium bromide was less sufficiently reactive to continue the catalytic cycle, These would explain the consistently lower isolated yield of the coupled product when

the arylbromides were used instead of the aryliodides. Firstly, The 2-bromo-3,5-dimethoxytolune **8** used in the Still coupling reaction was prepared by bromination[9,10]of orcinol **6** with one equivalent tetrabutylammonium tribromide to give the bromoorcinol **7** (79%, Scheme 3, flash chromatography) and methylation of the product with MeI/K_2CO_3. The product **8** was purified by flash chromatography using silica gel (hexane / EtOAc, 15:1), 1 to give a white solid in 82 % yield.

TABLE I Palladium-Catalyzed Cross-Coupling Reactions of Aryl halides with 2-n-tributylstannylthiophene **3**

Stannane	*$Pd^0(Pph_3)_4$ mole%*	*Aryl halides (Ar-X)*		*Products*	*Yield/24hrs.*
3	10 mole%	**4**	x = Br	**5**	55%
			x = I		68%
3	10 mole%	**8**	x = Br	**10**	67%
		9	x = I		89%
3	10 mole%	**12**	x = Br	**14**	52%
		13	x = I		70%
3	10 mole%	**15**	x = Br	**17**	45%
		16	X=I		68%

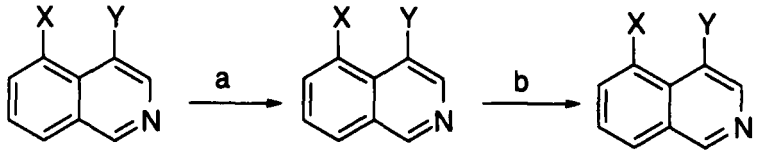


SCHEME 3

Compound **8** was lithiated via n-BuLi followed by addition of solution of I_2. provided 2-iodo-3,5-dimethoxytoluene **9** in 68 % yield.

In order to study the activation of the position C-4 and C-5 of isoquinoline when it was coupled with 2(tri-n-butylstannyl)thiophene **3** this compound had to be selectively functionalized at the C-4 or C-5-position. This was done using the "swamping catalyst" method.[11] In a variation of Pierson's swamping catalyst method, isoquinoline **11** and $AlCl_3$ with passing bromine vapors (1 equiv.) were slowly diffused into the reaction pot. Vac-

uum distillation provided pure 5-bromo-isoquinoline **12** in 24 % yield. Lithiation-iodination exchange with n-BuLi followed by immediate addition of solution of I_2 to compound **12** to give compound **13**, as shown in Scheme 4The 4-iodoisoquinoline **16** was prepared from the commercially available 4-bromoisoquinoline **15** following the same experimental procedure.



11 X = Y = H **11** X = Br, Y = H **13** X = I, Y = H
14 X = H, Y = Br **15** X = H, Y = I

a) Br_2 / $AlCl_3$, at 75 °C; b) i) n-BuLi, ii) I_2

SCHEME 4

EXPERIMENTAL SECTION

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 is reported along with the capillary column.

Method A

In a screw-capped culture tube were placed aryl halide (0.1 M), 2 equiv. of aryl stannane, and 10 mol % of $Pd(PPh_3)_4$ in toluene. The reaction mixture

was sealed under N_2 and heated to 110°C for 24 hrs., then cooled to room temperature. The product was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated. The crude product was purified by column chromatography on silica gel.

Method B

In an oven-dried flask (100 ml r.b.) were placed aryl halide (0.1 mmol) dissolved in THF. The mixture was cooled to −78°C under argon with magnetic stirring. The n-BuLi (1.3 equiv., 2.5 M in hexane) was added via syringe followed immediately by a solution of I_2 (1.3 equiv. in THF). The reaction mixture was allowed to warm to room temperature and stirring was continued for 15 min. The reaction was quenched with aqueous sodium bicarbonate and decolorized with solid $NaHSO_3$. The aqueous phase was extracted with Et_2O (2X30 mL) and combined organics were dried over $MgSO_4$. The crude product was purified by column chromatography on silica gel with 3% Et_3N).

2-(Tri-n-butylstannyl)thiophene (3)

A solution of thiophene 1 (1.68 mg, 20 mmol, 1.0 equiv.) in ether (20 mL) was cooled to −78°C. TMEDA (3 mL, 20.1 mmol, 1.1 equiv.) was introduced. n-BuLi (22 mmol, 8.8 mL, 2.5 M in hexane, 1.1 equiv.) was slowly added and stirred under N_2 at −78°C for 1 h. The reaction mixture was allowed too warm to room temperature and stirred for 3 h. and then cooled to −78°C. for 1 h., with continue stirring. The n-Bu_3SnCl (6,5 mL, 7.8 g, 24 mmol, and 1.2 equiv.) was added dropwise via syringe and the reaction mixture was stirred for 2 hour at −78°C. The reaction mixture was quenched with 10 % aqueous NH_4Cl (25 mL) and extracted with (3 × 70 mL) ether. The organic layers were combined, washed with aqueous NH_4Cl and sat. aq. NaCl, dried over Na_2SO_4 and evaporate the solvent to oil. The resulting crude oil of 2-(tri-n-butytin) thiophene **3** was purified by dissolving in nonpolar organic solvent (Hexane) and stirred for 10 hrs. with potassium fluoride to remove the unreacted tributyltin chloride and then filtered, evaporated the solvent to got the crude oil product was loaded on neutral Alumnina columns and the columns were eluted with hexane to remove unwanted and unreacted tin compounds then the isolated oil product was distilled gave a clear yellow oil in 79% yield of (bp

155°C /0.1 mmHg). LRMS (EI): m/z 317 (M^+-C_4H_9, 75), 261 (32), 203 (69), 177 (15), 153 (12), 121 (18), 55 (12), and 44 (100). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.631 (dd, J = 5.19 and 0.6 Hz, Ar-H_5), 7.25 (dd, J = 4.6 and 3.2 Hz, Ar-H_4), 7.18 (dd, J = 3.3 and 0.6 Hz, Ar-H_3), 1.56 (tt, J = 7.86 and 7.79 Hz, 6H of $ArSnCH_2C\underline{H}_2CH_2CH_3$), 1.36 (tq, J = 6.9 and 7.33 Hz, 6H of $ArSn(CH_2)_2C\underline{H}_2CH_3$), 1.13 (t, J = 7.8 Hz, 6H of $ArSnC\underline{H}_2CH_2CH_2CH_3$), 0.92 (t, J = 7.13 Hz, 6H of $ArSn(CH2)_3C\underline{H}_3$) ppm. GC: t_R = 9.54 min.; column; DB-5 6 m × 0.01 mm + 1 m guard column: temp. prog.: 50°C / 2 min. / 20°C min.$^{-1}$ / 250°C / 5 min.

4-Bromo-5-methylresorcinol (7)

In a round bottomed flask was placed the orcinol monohydrate **6** (0.5807 g, 4.09 mmol) in CH_2Cl_2 (30 mL)-methanol (20 mL), and a solution of $BuNBr_3$ (2.0 g, 4.13 mmol) was added dropwise under stirring at room temperature. The reaction mixture was stirred for 30 min until a decoloration of the orange solution took place. The solvent was distilled the residue was treated with water (30 mL). The reaction mixture was extracted with ether (4 × 40 mL). The ether layer was then dried with anhydrous $MgSO_4$, and evaporated in vacuum to give a residue which was recrystallized from methanol-water (1:3) as colorless crystals and was purified by flash chromatography (hexane / EtOAc, 3:1); 0.66 g, 3.25 mmol, 79 % yield), m.p.: (range): 132–134°C, colorless solid crystal. TLC: R_f (hexane / EtOAc, 3:1); 0.6; LRMS (EI): m/z (relative intensity %) 202 (M^+, 100), 185 (10), 123 (35), 98 (10), 77 (15), 69 (15), 51 (20), and 44 (35). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 6.51 [d, J = 2.7 Hz, 1H, Ar-H(2)], 6.48 [d, J = 2.7 Hz, 1H, Ar-H (6)], 8.7 [s, 1H, Ar-OH(3)], 8.02 [s, 1H, Ar-OH(1)], 2.85 (s, 3H, Ar-$\underline{C}H_3$) ppm. GC: t_R = 7.463 min.; column: DB-5 6m × 0.01 mm + 1 m guard column: temp. prog: 50°C / 2 min. / 20°C min.$^{-1}$ / 250°C / 5 min.

2-Bromo-3,5-dimethoxytoluene (8)

Bromo-orcinol **7** (2.03 g, 10 mmol) was dissolved in (35 mL) of acetone. Methyl iodide (5.67 g, 40 mmol) and K_2CO_3 (5.528 g, 40 mmol) were slowly added and stirred at room temperature for 24h. The reaction mixture was passed through a celite bed, and the celite bed was washed with methylene chloride. The combined filtrates were washed with water, dried

with anhydrous Na_2SO_4, and concentrated. Purification of the residue by silica gel flash chromatography with (15:1:hexane / EtOAc) to give (1.89 g, 8.18 mmol, 81.8 % yield) of compound **8**, m.p. (range): 39–41°C, white solid. TLC: R_f (hexane / EtOAc; 15:1): 0.422; LRMS (EI): m/z (relative intensity) 230 (M^+-1, 100), 187 (15), 136 (10), 122 (15), 108 (20), 93 (12), 78 (10), and 44 (25). GC: t_R = 7.98 min.; column: DB-5 6m × 0.01 mm + 1m guard column: temp. prog: 50°C / 2 min. / 20°C $min.^{-1}$ / 250°C / 5 min. ^1H NMR ($CDCl_3$ 500 MHz): δ 6.43 [bs, 1H, Ar-H (4)], 6.35 [bs, 1H, Ar-H (6)], 3.86 [s, 3H, Ar-OC$\underline{H}_3$(3)], 3.79 [s, 3H, Ar-OC$\underline{H}_3$ (5)], 2.39 (s, 3H, Ar-C$\underline{H}_3$) ppm.

2-Iodo-3,5-dimethoxytoluene (9)

Method B was used to prepare compound **9** from **8**. The product was obtained after purification by flash chromatography (9:1::hex:EtOAc with 3% Et_3N)) to give (1.89 g, 6.79 mmol, in 68 % yield) of compound **9**. m.p. (range): 59–61°C, white solid. TLC: R_f (hexane / EtOAc; 20:1): 0.52; LRMS (EI): m/z (relative intensity) 277 (M^+-1, 100), 187 (15), 136 (10), 122 (15), 108 (20), 93 (12), 78 (10), and 44 (25). GC: t_R = 8.88 min.; column: DB-5 6m × 0.01 mm + 1m guard column: temp. prog: 50°C / 2 min. / 20°C $min.^{-1}$ / 250 °C / 250°C / 5 min. ^1H NMR ($CDCl_3$, 500 MHz): δ 6.44 [bs, 1H, Ar-H (4)], 6.34 [bs, lH, Ar-H (6)], 3.87 [s, 3H, Ar-OC$\underline{H}_3$(3)], 3.80 [s, 3H, Ar-OC$\underline{H}_3$ (5)], 2.37 (s, 3H, Ar-C$\underline{H}_3$) ppm.

2-[1-(4-Methoxyphenyl)]thiophene (5)

Method A was used to prepare compound **5** from **3** and **4**. The product was obtained after purification by flash chromatography (9:1:hexane/EtOAc) to give (130 mg, 0.68 mmol, 68 % yield) of compound **5**, m.p. (range): 106–108°C, as colorless needles solid. TLC: R_f (hexane/EtOAc; 9:1): 0.36; LRMS (EI): m/z 190 (M^+, 100), 175 (100), 160 (<2), 147 (35), 145 (4), 121 (5), 115 (7), 102 (4), 77 (7), 69 (5), 51 (<3), and 45 (8). ^1H NMR ($CDCl_3$, 200 MHz): δ 6.82 (d, J = 1.8 and 3.6 Hz, 1H of Th-H_3), 7.29 (dd, J = 3.6 and 5.7 Hz, 1H of Th-H_4), 7.33 (dd, J = 1.7 and 5.7 Hz, 1H of Th-H_5), 7.65 (d, J = 8.0 Hz, 2H of Ar-H), 7.93 (d, J = 8.0 Hz, 2H of Ar-H), 3.89 (s, 3H, Ar-O$\underline{C}H_3$) ppm.

GC: tR = 8.477 min.; column DB-5 6m × 0.01 mm + 1m guard column; temp. prog: 50°C / 2 min. / 20°C $min.^{-1}$ / 270°C / 5 min.

2-[2-(3,5-Dimethoxy)toluene]thiophene (10)

Method A was used to prepare compound **10** from **3** and **8** or **9**. The product was obtained after purification by flash chromatography. Purification via flash chromatography (silica gel, 15:1::hexane:EtOAc) afforded the cross-coupled product **10** (208 mg, 0.89 mmol, 89% yield) as a colorless oil. TLC: R_f (hexane / EtOAc; 15:1): 0.33; LRMS (EI): m/z (relative intensity %) 234 (M^+, 100), 217 (7), 203 (15), 189 (25), 175 (35), 157 (4), 121 (40), 108 (20), 93 (15), 77 (20), 51 (21), and 44 (15). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.73–7.75 [dd, J = 5.1 and 1.2 Hz, lH, Ar-H (5)], 7.29 [dd, J = 3.8 and 1.2 Hz, 1H, Ar-H(3)], 7.11 [dd, J = 5.1 and 3.8 Hz, 1H, Ar-H(4)], 6.51 [bs, 1H, Ar-H (4)], 6.44 [bs, 1H, Ar-H(6)], 3.94 [s, 3H, Ar-OCH_3(3)], 3.85 [s, 3H, Ar-OCH_3(5)], 2.4 (s, 3H, Ar-CH_3) in ppm.

^{13}C NMR ($CDCl_3$, 125 MHz) d 160.8, 159.6, 141.5, 140.8, 113.4, 110.5, 109.9, 106.9, 105.2, 96.2, 55.9, 55.4, and 22.2; GC: t_R = 9.78 min.; column: DB-5 6m × 0.01 mm + 1m guard column: temp. prog.: 50°C / 2 min. / 20°C min.$^{-1}$ / 250°C / 5 min. Anal. Calcd for $C_{13}H_{14}SO_2$: C, 66.66; H, 5.98. Found: C, 66.91; H, 6.32.

5-Bromoisoquinoline (12)

Isoquinoline **11** (51.48g, 399.0 mmol) and $AlCl_3$ (111.0 g, 1.2 eq.) were placed into an oven dried flask (250 mL r.b.) fitted with a short-path distillation apparatus. Br_2 (19.5 mL, 95 eq.) was placed in an oven-dried flask (25 mL r.b.) and the flask was fixed to the other end of the distillation apparatus. Carefully heating the flask with Br_2, the vapors were allowed to slowly diffuse into the reaction pot over a period of 30hrs. The reaction pot was maintained at 75°C. After the Br_2 transfer was complete, the reaction mixture was stirred at 75°C for another 48h. after which time it was cooled to room temperature and allowed to sit for 48hrs. The resulting slurry was poured over water (500 mL), treated with 15 % NaOH until all solids were dissolved, and extracted with ether (3x100 mL). The combined organic extracts were washed with brine and concentrated to yield a crude mixture containing 45 % of the desired product. Vacuum distillation (0.1 mmHg) afforded 5-bromoisoquinoline (20.15 g, 24% yield), m.p. (range): 80–82°C, as a white solid. LRMS (EI): m/z (relative intensity %) 209 (M^+, 95), 207 (M^+, 100), 129 (5), 128 (52), 127 (10), 104 (5), 101 (25), 100 (7), 91 (7), 90 (8), 77 (22), 74 (15), 51 (9), and 50 (14). ^{1}H NMR (500 MHz,

$CDCl_3$): δ 9.20 [s, 1H, Ar-H1], 8.62 [d, J = 6.0 Hz, 1H, Ar-H3], 7.92 [d, J = 6.0 Hz, 1H, Ar-H6], 7.89 [d, J = 7.9 Hz, 1H, Ar-H8], and 7.41 [dd, J = 7.9 and 7.6 Hz, 1H, Ar-H7] ppm. ^{13}C NMR (125 MHz, CDCl3): δ 151.87, 143.69, 133.88, 133.02, 128.65, 126.84, 126.49, 120.66, and 118.39 ppm. GC: t_R = 7.4 min; column DB-5 6m × 0.01 mm+ 1m guard column; temp. prog.; 50°C / 2 min / 20°C min^{-1} / 270°C / 5 min. IR (KBr pellet): 3017 (w) cm^{-1}.

5-Iodoisoquinoline (13)

Method B was used to prepare compound **13** from **12**. The product was obtained after purification by flash chromatography (6:1:hex:EtOAc with 3% Et_3N) to give 5-iodoisoquinoline (2.76 g, m.p. (range): 90–91°C, 77 % yield) of compound **13**., as an orange solid.Tlc; R_f (6:1:hexane/EtOAc with 3% Et_3N); 0.17; LRMS (EI): m/z (relative intensity %) 255 (M^+, 100), 129 (3), 128 (39), 127 (5), 114 (4), 102 (3), 101 (17), 100 (3), 99 (2), 98 (2), 77 (5), 76 (2), 75 (13), 74 (7), 64 (2), 63 (2), 62 (2), 51 (6), and 50 (4). ^1H NMR (300 MHz, $CDCl_3$): δ 9.12 [s, 1H, Ar-H1], 8.62 [d, J = 6.0 Hz, 1H, Ar-H3], 8.24 [d, J = 7.5 Hz, 1H, Ar-H8], 7.96 [d, J = 8.2 Hz, 1H, Ar-H6], and 7.82 [d, J = 6.1, 1H, Ar-H4], and 7.33 [dd, J = 8.2 and 7.5 Hz, Ar-H7] ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 152.84, 144.65, 141.05, 137.22, 129.16, 128.17 (2C), 123.84, and 97.53 ppm. Gc: t_R = 8.1 min.; column DB-5 6m × 0.01 mm+ 1m guard column; temp. prog.; 50°C / 2 min. / 20°C $min.^{-1}$ / 270°C / 5 min. IR (KBr pellet): 2921 (w), 2854 (w), 1617 (w), 1576 (w), 1480 (w), 1258 (w), and 827 (m), cm^{-1}.

2-[5(-Isoquinoline)thiophene (14)

A flask was charged with 2-(Tri-n-butylstannyl)thiophene **3** (37.3 mg, 0.1 mmol), 5-bromoisoquinoline **12** (20.8 mg, 0.1 mmol), tetrakis (triphenylphosphine)palladium(0) (11.55 mg, 0.01 mmol, 10 mol %), and toluene (3 mL). The reaction mixture was first purged with argon for 20 min. and then heated to 100–110°C for 24 hrs. The reaction mixture poured into saturated KF solution stirred for 5 h and then washed with saturated NH_4Cl solution. The aqueous layer was extracted with ether, and the organic extracts were washed with brine and the combined organic layer was dried over anhydrous Na_2SO_4. Solvent was removed by rotary evaporator, and

the residue was purified by MPLC (2:1:hexane/EtOAc) afforded the cross-coupled product **237** (148 mg, 0.7 mmol, 70 % yield) as a colorless oil. TLC; R_f (hexane / EtOAc; 2:1): o.17 LRMS (EI): m/z (relative intensity %) 211 (M+, 100), 210 (30), 186 (5), 184 (10), 166 (10), 152 (<3), 139 (12), 126 (<3), 113 (<3), 105 (<3), 91 (4), 83 (12) 63 (5), 51 (<3), and 45 (<3). GC: t_R= 10.034 min.; column: DB-5 6 m × 0.01 mm + 1 mguard column: temp. prog.: 50°C / 2 min. / 20°C $min.^{-1}$ / 250°C / 5 min. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.26 [s, 1H, Ar-H(1)], 8.54 [d, J = 6.4 Hz, 1H, Ar-H(3)], 8.04 [d, J = 5.87, 1H, Ar-H(8)], 7.96 [d, J = 8.09 Hz, 1H, Ar-H(6)]. 7.77 [d, J = 6.9 Hz, 1H, Ar-H(4)], 7.62 [t, J = 7.62 and 7.67 Hz, 1H, Ar-H(7)], 7.46 [dd, J = 3.4 and 4.9 Hz, 1H, Th-H(5)], 7.25 [dd, J = 3.5 and 5.22 Hz, 1H, Th-H(3)], 7.21 [dd, J = 3.5 and 5.37 Hz, 1H, Th-H(4)] ppm. Anal. Calcd for $C_{13}H_9NS$: C, 73.93; H, 4.26. Found: C, 74.22; H, 5.32.

2-(4-Isoquinoline)thiophene (17)

Method A to prepare compound 17 from reactions of **3** and **15** or **16**. The reaction mixture was cooled and quenched with water (10 mL). KF (250 mg) was added and the mixture was stirred for 6hrs. The aqueous layer was extracted with ether, and the organic extracts were washed with NH_4Cl solution, with brine, dried over Na_2SO_4, and concentrated in vacuum. Purification via MPLC (Hexane / Ethylacetate, 2:1) afforded the cross-coupled isolated product **17**in 45 % yield for arylbromide and in 68% yield for aryliodide used. LRMS (EI): m/z (relative intensity %) 211 (M+, 100), 210 (30), 186 (5), 184 (10), 166 (10), 152 (<3), 139 (12), 126 (<3), 113 (<3), 105 (<3), 91 (4), 83 (12) 63 (5), 51 (<3), and 45 (<3). **Gc**: t_R = 10.54 min.; column: DB-5 5 m × 0.01 mm + 1 mguard column: temp. prog.: 50°C / 2 min. / 20°C $min.^{-1}$ / 250°C / 5 min. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.26 [s, 1H, Ar-H(1)], 8.54 [d, J = 6.4 Hz, 1H, Ar-H(3)], 8.04 [d, J = 5.87, 1H, Ar-H(8)], 7.96 [d, J = 8.09 Hz, 1H, Ar-H(6)], 7.77 [d, J = 6.9 Hz, 1H, Ar-H(4)], 7.62 [t, J = 7.62 and 7.67 Hz, 1H, Ar-H(7)], 7.27 [dd, J = 1.8 and 5.4 Hz, 1H, Ar-H(5)], 7.28 [dd, J = 1.8 and 3.5 Hz, 1H, Ar-H(3)], 7.22 [dd, J = 3.5 and 5.4 Hz, 1H, Ar-H(4)] ppm.

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References

1. G.H.N. Towers, *Can. J. Bot.*,**1984**, *62*, 2900.
2. J. Lam, H. Breteler, T. Arnason, L. Hansen Eds., "Chemistry and Biology of Naturally Occurring Acetylenes and Related Compounds (NOARC)", Elsevier, Amsterdam, **1988**.
3. J.R. Heitz, K.R. Downum Eds., "Light Activated Pesticides", A.C.S. Symposium Series, No. 339, American Chemical Society, Washington, D.C., **1987**.
4. J.S. Sorensen and N.A. Sorensen, *Acta. Chem. Scand.*, **1958**, *12*, 771.
5. R.F. Heck, "Palladium Reagents in Organic Synthesis," ed. by A.R. Katritzky, O. Meth-Cohn, and C.W. Rees, Academic Press, Inc., London, **1985**.
6. For a review, see: Stille, J.K. *Angew. Chem. Int. Ed. Engl.*, **1986**, *25*, 508.
7. Lambert, Brandsma and Herman Verkruijsse, Preparative polar organometallic chemistry, **1987**, *vol. 1*, QD 411. B67 pp. 186.
8. Thomas R. Hoye and Minzhang Chen, *J. Org. Chem.*, **1996**, *61*, 7940–7942.
9. Berthelot, J.; Guette, C.; Ouchefoune, M.; Desbene P. -L.; Basselier, J. -J. *J. Chem. Res.* **1986**, 381.
10. Kajigaeshi, S.; Kakinami, T.; Okamois, H.; Fujikawa, M. *Bull. Chem. Soc. Jpn.*, **1987**, *60*, 4187.
11. Gordon, M.; Pearson, D.E. *J. Org. Chem.*, **1964**, *29*, 329.