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STILLE CROSS-COUPLING REACTIONS OF ARYL MESYLATES AND TOSYLATES USING A BIARYLPHOSPHINE BASED CATALYST SYSTEM[‡]

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Abstract – A catalyst system for the Stille cross-coupling reactions of aryl mesylates and tosylates is reported. Using the combination of $Pd(OAc)_2$, XPhos, and CsF in *t*-BuOH an array of aryl and heteroaryl sulfonates were successfully employed in these reactions. Morever, heteroarylstannanes, such as furyl, thienyl, and *N*-methylpyrrolyl, which are often prone to decomposition, were efficiently coupled under these conditions. *Ortho*-substitution on the stannane coupling partner was well tolerated; however, the presence of *ortho* substituents on the aryl sulfonates greatly reduced the efficiency of these reactions.

INTRODUCTION

The Stille cross-coupling reaction is a versatile method for the formation of carbon–carbon bonds and the construction of molecules containing sp^2-sp^2 bonds.[1] Since its introduction by Migita[2] and its subsequent exploration by Stille,[3] it has evolved into one of the most robust of the palladium-catalyzed cross-coupling reactions and has found applications in drug discovery,[4] natural products synthesis,[5] and materials chemistry.[6] The toxicity of organostannanes,[7] and the difficulty in the removal of the tin byproducts have lead to an increase in the popularity of other C–C cross-coupling methods, specifically the Suzuki-Miyaura reaction,[8] but for difficult cases and late stage synthetic transformations the Stille reaction is still widely employed due to its reliable nature.

A great deal of effort in the field of Pd-catalyzed cross-coupling has been devoted to the development of catalysts that allow for less reactive and more stable aryl halides or pseudohalides to be employed in these reactions. Early methods utilized activated electrophilic coupling partners, such as aryl iodides, electron-deficient aryl bromides, and in the case of the Stille reaction, acid chlorides.[3] The advent of more

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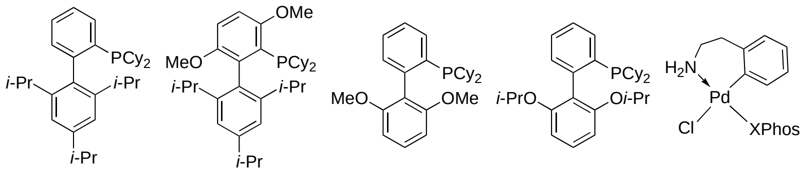
[‡] This paper is dedicated to Prof. Akira Suzuki on the occasion of his 80^{th} birthday.

active catalysts, based on electron-rich phosphine ligands, has allowed for reactions of unactivated aryl bromides, aryl chlorides, and aryl sulfonates to be carried out efficiently.[9] Aryl triflates were initially the most successfully employed aryl sulfonates for cross-coupling reactions.[10] However, due to the fact that aryl tosylates and mesylates are less expensive and more stable than the corresponding aryl triflates, recent research has focused on utilizing these substrates in many cross-coupling reactions.[11] Specifically, aryl tosylates have been shown to be effective coupling partners in Suzuki-Miyaura, Kumada-Corriu, and C-N cross-coupling reactions;[12] aryl mesylates have been efficiently employed in Hiyama, Suzuki-Miyaura, and C–N cross-coupling reactions, as well as Pd-catalyzed carbonylation reactions.[13] Further, vinyl tosylates have also been utilized in Stille cross-coupling reactions;[14] however, to date no examples of the Stille cross-coupling reactions of aryl tosylates and mesylates have been reported. Herein, we report a catalyst, based on **1** (XPhos), for the Pd-catalyzed Stille cross-coupling reactions of aryl mesylates and tosylates.

RESULTS AND DISCUSSION

We began our studies by investigating the reaction of 3-methoxyphenyl methanesulfonate and tri-*n*-butyl(phenyl)stannane. Attempts to use reaction conditions previously reported by our group for the Stille reaction of aryl chlorides,[15] employing Pd(OAc)$_2$ and **1** in either 1,4-dioxane or DME as solvent provided very low yields (Table 1, entries 1 and 2). An examination of the use of non-ethereal solvents showed that a polar aprotic solvent, DMF, gave no desired product; while alcoholic solvents proved to be the best, with *t*-BuOH giving the highest yield (Table 1, entries 3-5).

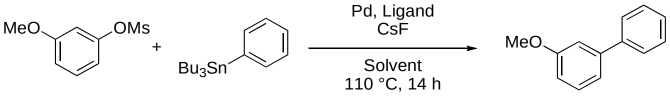


XPhos - 1 **BrettPhos - 2** **SPhos - 3** **RuPhos - 4** **5**

Figure 1: Biaryl-monophosphine Ligands

We next explored other biarylphosphine ligands and Pd sources in this reaction. Catalysts based on **2** (BrettPhos), which has been shown to form an efficient catalyst for the C–N cross-coupling of aryl mesylates, and **3** (SPhos) provided yields of 60% and 52% respectively (table 1, entries 6 and 7). Using a catalyst comprised of Pd(OAc)$_2$ and **4** (RuPhos) increased the yield of the reaction to 76% (Table 1, entry 8); however, **1** formed the most efficient catalyst system and furnished the desired product in 93% yield (Table 1, entry 3). While other Pd sources, such as allylpalladium chloride dimer and **5**, a single component precatalyst developed in our group,[16] gave results similar to palladium acetate for this reaction, we chose to continue our studies with the latter because of its low cost and stability (Table 1, entries 8 and 9). Pd_2dba_3 was also examined, and its use only produced a 22% yield of the desired product (Table 1, entry 10). Finally, we wanted to explore the effect of increasing the L:Pd ratio on the efficiency of the reaction. Entries 12-14 show these results. While the yields of the three ratios of L:Pd examined were similar, we found that a 2:1 ratio was optimal (Table 1, entries 11-13).

Table 1: Palladium-catalyzed Stille couplings of 3-methoxyphenyl methanesulfonate

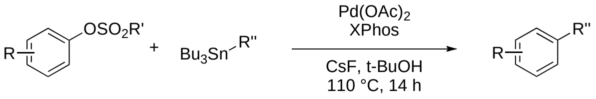


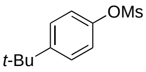
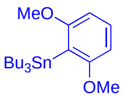
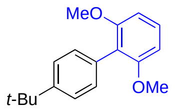
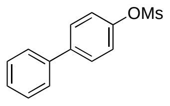
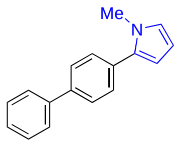
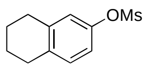
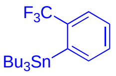
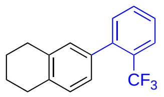
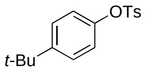
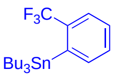
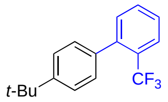
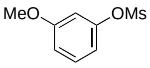
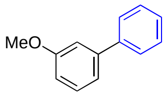
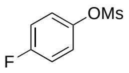
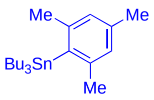
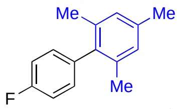
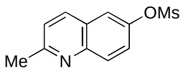
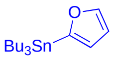
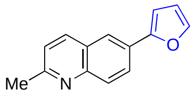
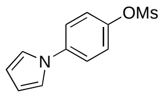
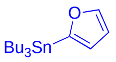
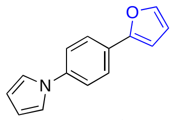
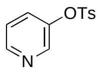
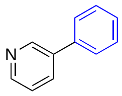
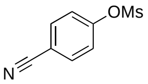
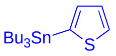
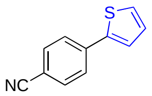
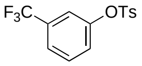
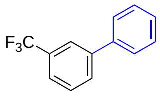
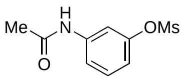
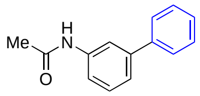
Entry	Solvent	Ligand	Pd Source	L:Pd	Yield[b]
1	1,4-dioxane	**1**	$Pd(OAc)_2$	1.5:1	4
2	DME	**1**	$Pd(OAc)_2$	1.5:1	0
3	*t*-BuOH	**1**	$Pd(OAc)_2$	1.5:1	93
4	*n*-BuOH	**1**	$Pd(OAc)_2$	1.5:1	48
5	DMF	**1**	$Pd(OAc)_2$	1.5:1	0
6	*t*-BuOH	**2**	$Pd(OAc)_2$	1.5:1	60
7	*t*-BuOH	**3**	$Pd(OAc)_2$	1.5:1	52
8	*t*-BuOH	**4**	$Pd(OAc)_2$	1.5:1	76
9	*t*-BuOH	**1**	$(AllylPdCl)_2$	1.5:1	88
10	*t*-BuOH	**1**	Pd_2dba_3	1.5:1	22
11	*t*-BuOH	**1**	**5**	1.5:1	86
12	*t*-BuOH	**1**	$Pd(OAc)_2$	1.1:1	83
13	*t*-BuOH	**1**	$Pd(OAc)_2$	2:1	96
14	*t*-BuOH	**1**	$Pd(OAc)_2$	3:1	95

(a) *Reaction Conditions*: 0.5 mmol of Ar-OMs, 0.6 mmol of $Ar-SnBu_3$, 1.1 mmol of CsF, 1.0 mL of *t*-BuOH, 2.0 mol% of [Pd], DME = dimethoxyethane, DMF = dimethylformamide.
(b) GC Yield.

With these conditions in hand, we wanted to explore the scope of the Stille cross-coupling reaction of aryl sulfonates using $Pd(OAc)_2$ and XPhos. The results are summarized in Table 2. We found that a variety of aryl and heteroaryl mesylates and tosylates could be coupled in moderate to good yields with aryl stannanes. These results represent the first reported Stille couplings of these sulfonates. Unactivated aryl mesylates and tosylates were coupled in good yields (Table 2, entries 1-4). Slightly activated aryl mesylates, such as 3-methoxyphenyl mesylate and 4-fluorophenyl mesylate were also suitable coupling partners (Table 2, entries 5-6). Heteroaryl containing mesylates (Table 2, entries 7-8), which have been difficult substrates in other cross-coupling reactions, and a heteroaryl tosylate (Table 2, entry 9) were successfully combined with arylstannanes in good to moderate yields.

Table 2: Stille couplings of aryl sulfonates with XPhos



Entry	Sulfonate	Stannane	Product	Yield^{b}
1				78
2				63^{d}
3				64
4				58^{c}
5				78
6				51
7				78
8				58
9				60^{c}
10				64
11				84
12				61^{c}

[a] *Reaction Conditions*: 1.0 mmol of Ar-OMs, 1.2 mmol of Ar-$SnBu_3$, 2.2 mmol of CsF, 2.0 mol% of $Pd(OAc)_2$, 4.0 mol% of XPhos, 2.0 mL of *t*-BuOH.
[b] Isolated yields (average of two runs).
[c] 2.0 mol% of pre-milled $Pd(OAc)_2$:XPhos (1:2)
[d] 4.0 mol% of $Pd(OAc)_2$, 8.0 mol% of XPhos

For example, the reaction of 2-methylquinolin-6-yl methanesulfonate and tri-*n*-butyl(furan-2-yl)stannane provided the desired product in 78% yield. Finally, reactions were carried out with aryl sulfonates containing functional groups. Electron-withdrawing groups such as nitriles and trifluoromethyl groups were tolerated in this reaction (Table 2, entries 10-11), as well as an acetamide that contained a free N-H(Table 2, entry 12).

A range of tri-*n*-butylarylstannanes were also explored and found to work well in these coupling reactions. The simplest arylstannane, tri-*n*-butyl(phenyl)stannane, was combined with weakly activated mesylates (Table 2, entry 5), functional group containing mesylates (Table 2, entries 11-12) and heteroaryl tosylates (Table 2, entry 9) with high efficiency. Arylstannanes containing *ortho* substitution, such as tri-*n*-butyl(2,6-dimethoxyphenyl)stannane (Table 2, entry 1), tri-*n*-butyl(2-(trifluoromethyl)-phenyl)stannane (Table 2, entries 3-4), and tri-*n*-butyl(mesityl)-stannane (Table 2, entry 6) were effectively reacted with unactivated mesylates and tosylates. Additionally, heteroarylstannanes such as 2-furyl-, 2-thienyl-, and 2-(*N*-methylpyrrolyl)tri-*n*-butylstannane were shown to be proficient substrates in these reactions. (Table 2, entries 2, 7, 8 and 10).

While we have revealed that this method tolerates a range of substrates, we also discovered some limitations in its scope. As described above, steric hindrance was well tolerated on the arylstannane, as shown by the reactions of tin reagents containing an *o*-CF_3 group, two *o*-OMe groups, and even two *o*-Me groups. However, attempts to utilize *ortho*-substituted aryl sulfonate resulted in greatly reduced reaction rates.[17] In addition, there were certain classes of heterocycles that were not tolerated under these reaction conditions. While 3-pyridyltosylate was successfully coupled, the analogous mesylate, along with 2-pyridylmesylate provided no product; in both cases only the products of hydrolysis (3-hydroxypyridine and 2-pyridone, respectively) were observed. Similarly, use of several heteroarylstannanes provided no coupling product and only decomposition of the mesylate coupling partners to their parent phenols were observed. These stannanes included the 2-thiazole, 2-oxazole, 2-pyrazinyl and 2-pyridyl derivatives.

In conclusion, a catalyst system comprised of XPhos and $Pd(OAc)_2$ used with CsF in t-BuOH was developed for the Stille cross-coupling of aryl mesylates and aryl tosylates with aryl- and heteroaryl-stannanes. A total of 11 examples were reported including unactivated aryl mesylates and aryl tosylates, functional group containing aryl mesylates and both heteroaryl mesylates and heteroaryl tosylates. The biaryl products were obtained in yields that ranged from 51-84%, and represent the first biaryl compounds made by Stille cross-coupling of aryl mesylates and tosylates.

EXPERIMENTAL

General Reagent Information

All reactions were carried out under an argon atmosphere. The *tert*-butanol, 1,4-dioxane, DME, and DMF were purchased from Aldrich Chemical Company in Sure-Seal bottles and were used as received. Toluene was purchased from J.T. Baker in CYCLE-TAINER® solvent-delivery kegs and vigorously purged with argon for 2 h. The solvent was further purified by passing it under argon pressure through two packed columns of neutral alumina and copper (II) oxide. Aryl mesylates, tosylates, and benzenesulfonates were synthesized using literature procedures. Aryl tin reagents were purchased from Aldrich Chemical

Company, Alfa Aesar, and Gelest and were used as received. **2**,[14] **4**,[18] and **5**[17] were synthesized using literature procedures. Ligands **1**[19] and **3**[20] were purchased from Strem Chemicals and the CsF, $Pd_2(dba)_3$, $PdCl_2(CH_3CN)_2$, and $[(allyl)PdCl]_2$ were purchased from Aldrich Chemical Company. $Pd(OAc)_2$ was received as a gift from BASF. Flash chromatography was performed using a Biotage SP4 instrument with prepacked silica cartridges.

General Analytical Information

All compounds were characterized by ^1H NMR, ^{13}C NMR, and IR spectroscopy. Copies of the ^1H and ^{13}C spectra can be found in the Supporting Information. Nuclear Magnetic Resonance spectra were recorded on a Varian 300 MHz instrument or a Bruker 400 MHz instrument. All ^1H NMR experiments are reported in δ units, parts per million (ppm), and were measured relative to the signals for residual chloroform (7.26 ppm) in the deuterated solvent, unless otherwise stated. All ^{13}C NMR spectra are reported in ppm relative to deuterochloroform (77.23 ppm), unless otherwise stated, and all were obtained with ^1H decoupling. All IR spectra were taken on a Perkin – Elmer 2000 FTIR. All GC analyses were performed on a Agilent 6890 gas chromatograph with an FID detector using a J & W DB-1 column (10 m, 0.1 mm I.D.).

General Procedure for Table 1

An oven-dried test tube, which was equipped with a magnetic stir bar and fitted with a Teflon screw-cap septum, was charged with the Pd source (2 mol% Pd), ligand (4 mol%), and CsF (1.1 mmol). The vessel was evacuated and backfilled with argon (this process was repeated a total of 3 times) and then the 3-methoxyphenyl methanesulfonate (101 mg, 0.5 mmol), tri-*n*-butyl(phenyl)stannane (221 mg, 0.6 mmol), and *t*-BuOH (1 mL) were added via syringe. The solution was heated to 110 °C for 14 h and then the reaction mixture was cooled to room temperature and filtered through a plug of silica (eluting with EtOAc). Biphenyl was then added as an internal standard and the reaction was analyzed by GC.

General Procedure for Table 2

An oven-dried test tube, which was equipped with a magnetic stir bar and fitted with a Teflon screw-cap septum, was charged with the $Pd(OAc)_2$ (2 mol%), **1** (4 mol%), and CsF (2.2 mmol). The vessel was evacuated and backfilled with argon (this process was repeated a total of 3 times) and then the aryl sulfonate (1.0 mmol), stannane (1.2 mmol), and *t*-BuOH (2 mL) were added via syringe (aryl mesylates, tosylates, or benzenesulfonates that were solids at room temperature were added with the catalyst and base). The solution was heated to 110 °C for 44 h and then the reaction mixture was cooled to room temperature, filtered through a plug of silica (eluting with EtOAc), concentrated in vacuo, and purified via the Biotage SP4 (silica-packed 50 or 100 g snap cartridge).

4'-*tert*-Butyl-2,6-dimethoxybiphenyl[21] (Table 2, entry 1) Following the general procedure, a mixture of 4-*tert*-butylphenyl methanesulfonate (228 mg, 1.0 mmol), tri-*n*-butyl(2,6-dimethoxyphenyl)stannane (514 mg, 1.2 mmol), $Pd(OAc)_2$ (4.4 mg, 2.0 mol%), **1** (19 mg, 4 mol%), CsF (334 mg, 2.2 mmol), and *t*-BuOH (2 mL) was heated to 110 °C for 14 h. The crude product was purified via the Biotage SP4 (silica-packed 50 g snap column; 0-5% EtOAc/hexanes) to provide the title compound as a white solid (211 mg, 87%), mp = 129 – 130 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.43 (d, J = 8.7 Hz, 2H), 7.32 – 7.22 (m, 3H), 6.46 (d, J = 8.4 Hz, 2H), 3.75 (s, 6H), 1.37 (s, 9H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 157.9, 149.3, 131.0, 130.6, 128.6, 124.8, 119.5 ppm. IR (neat, cm^{-1}): 2961, 1587, 1471, 1430, 1384, 1245, 1109, 825, 723, 563.

2-(Biphenyl-4-yl)-1-methyl-1*H*-pyrrole (Table 2, entry 2) Following the general procedure, a mixture of biphenyl-4-yl methanesulfonate (248 mg, 1.0 mmol), 1-methyl-2-(tri-*n*-butylstannyl)-1*H*-pyrrole (445 mg, 1.2 mmol), $Pd(OAc)_2$ (8.8 mg, 4.0 mol%), **1** (38 mg, 8 mol%), CsF (334 mg, 2.2 mmol), and *t*-BuOH (2 mL) was heated to 110 °C for 14 h. The crude product was purified via the Biotage SP4 (silica-packed 50 g snap column; 0-40% EtOAc/hexanes) to provide the title compound as a white solid (151 mg, 65%), mp = 125 – 127 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.64 (m, 4H), 7.49 (m, 4H), 7.39 (m, 1H), 6.76 (t, J =2.4 Hz, 1H), 6.30 (m, 1H), 6.25 (t, J = 2.4 Hz, 1H), 3.73 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 140.9, 139.6, 134.4, 132.5, 129.1, 129.0, 127.5, 127.3, 127.2, 124.1, 109.0, 108.1, 35.4 ppm. IR (neat, cm^{-1}): 2953, 1478, 1446, 1408, 1309, 1061, 846, 765, 713, 695.

6-(2-(Trifluoromethyl)phenyl)-1,2,3,4-tetrahydronaphthalene (Table 2, entry 3) Following the general procedure, a mixture of 5,6,7,8-tetrahydronaphthalen-2-yl methanesulfonate (237 mg, 1.0 mmol), tri-*n*-butyl(2-(trifluoromethyl)phenyl)stannane (522 mg, 1.2 mmol), $Pd(OAc)_2$ (4.4 mg, 2.0 mol%), **1** (19 mg, 4 mol%), CsF (334 mg, 2.2 mmol), and *t*-BuOH (2 mL) was heated to 110 °C for 14 h. The crude product was purified via the Biotage SP4 (silica-packed 50 g snap column; 0-10% EtOAc/hexanes) to provide the title compound as a yellow oil (152 mg, 55%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.78 (d, J = 7.8 Hz, 1H), 7.58 (t, J = 7.5 Hz, 1H), 7.47 (t, J = 7.5 Hz, 1H), 7.38 (d, J = 6.9 Hz, 1H), 7.14 (m, 2H), 7.09 (s, 1H), 2.86 (m, 4H), 1.89 (m, 4H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 141.9, 141.8, 137.2, 136.7, 136.7, 132.4, 131.4, 131.4, 129.8, 129.8, 129.8, 129.8, 129.3, 128,8, 128.6, 128.4, 127.2, 126.3, 126.2, 126.1, 126.1, 125.6, 122.6, 29.6, 29.4, 23.6, 23.4 ppm. IR (neat, cm^{-1}): 2931, 1604, 1486, 1449, 1315, 1168, 1127, 1036, 768, 650.

4'-*tert*-Butyl-2-(trifluoromethyl)biphenyl[22] (Table 2, entry 4) Following the general procedure, a mixture of 4-*tert*-butylphenyl 4-tolylsulfonate (304 mg, 1.0 mmol), tri-*n*-butyl(2-(trifluoromethyl)-phenyl)stannane (522 mg, 1.2 mmol), Pd(OAc)$_2$ (2.0 mol%) and **1** (4 mol%) as a pre-milled mixture (23.6 mg), CsF (334 mg, 2.2 mmol), and *t*-BuOH (2 mL) was heated to 110 °C for 14 h. The crude product was purified via the Biotage SP4 (silica-packed 50 g snap column; hexanes) to provide the title compound as a colorless oil (170 mg, 61%). ^{1}H NMR (400 MHz, CDCl$_3$) δ: 7.75 (d, *J* =7.5 Hz, 1H), 7.54 (t, *J* =7.5 Hz, 1H), 7.44 (m, 3H), 7.34 (d, *J* =7.5 Hz, 1H), 7.28 (d, *J* =7.5 Hz, 2H), 1.38 (s, 9H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$) δ: 150.7, 141.7, 141.7, 137.1, 132.4, 131.5, 129.1, 128.8, 128.8, 128.5, 128.2, 127.3, 126.3, 126.3, 126.2, 126.2, 125.8, 124.9, 123.1, 34.8, 31.6 ppm. IR (neat, cm^{-1}): 2965, 2869, 1606, 1488, 1315, 1171, 1131, 1069, 1036, 768.

3-Methoxybiphenyl[23] (Table 2, entry 5) Following the general procedure, a mixture of 3-methoxyphenyl methanesulfonate (202 mg, 1.0 mmol), tri-*n*-butyl(phenyl)stannane (440 mg, 1.2 mmol), Pd(OAc)$_2$ (4.4 mg, 2.0 mol%), **1** (19 mg, 4 mol%), CsF (334 mg, 2.2 mmol), and *t*-BuOH (2 mL) was heated to 110 °C for 14 h. The crude product was purified via the Biotage SP4 (silica-packed 50 g snap column; 0-10% EtOAc/hexanes) to provide the title compound as a yellow oil (145 mg, 79%). ^{1}H NMR (300 MHz, CDCl$_3$) δ: 7.60 (d, *J* = 6.9 Hz, 2H), 7.45 (t, *J* = 7.2 Hz, 2H), 7.37 (m, 2H), 7.19 (d, *J* = 7.8 Hz, 1H), 7.14 (m, 1H), 6.91 (m, 1H), 3.89 (s, 3H) ppm. ^{13}C NMR (75 MHz, CDCl$_3$) δ: 160.1, 143.0, 141.3, 130.0, 128.9, 127.6, 127.4, 119.9, 113.1, 112.8, 55.5 ppm. IR (neat, cm^{-1}): 2937, 1599, 1573, 1479, 1421, 1296, 1213, 1020, 757, 697.

4'-Fluoro-2,4,6-trimethylbiphenyl[24] (Table 2, entry 6) Following the general procedure, a mixture of 4-fluorophenyl methanesulfonate (190 mg, 1.0 mmol), tri-*n*-butyl(mesityl)-stannane (491 mg, 1.2 mmol), Pd(OAc)$_2$ (4.4 mg, 2.0 mol%), **1** (19 mg, 4 mol%), CsF (334 mg, 2.2 mmol), and *t*-BuOH (2 mL) was heated to 110 °C for 14 h. The crude product was purified via the Biotage SP4 (silica-packed 50 g snap column; 0-5% EtOAc/hexanes) to provide the title compound as a white solid (116 mg, 54%), mp = 65 – 67 °C (literature 64 – 65 °C). ^{1}H NMR (300 MHz, CDCl$_3$) δ: 7.14 (s, 2H), 7.11 (s, 2H), 6.97 (s, 2H) ppm. ^{13}C NMR (75 MHz, CDCl$_3$) δ: 163.5, 160.3, 138.2, 137.0, 137.0, 136.4, 131.1, 130.9, 128.3, 115.7, 115.4, 109.9, 21.2, 21.0 ppm. IR (neat, cm^{-1}): 2921, 1601, 1511, 1478, 1217, 1151, 1087, 1008, 854, 815.

6-(Furan-2-yl)-2-methylquinoline (Table 2, entry 7) Following the general procedure, a mixture of 2-methylquinolin-6-yl methanesulfonate (237 mg, 1.0 mmol), tri-*n*-butyl(furan-2-yl)stannane (430 mg, 1.2 mmol), Pd(OAc)$_2$ (4.4 mg, 2.0 mol%), **1** (19 mg, 4 mol%), CsF (334 mg, 2.2 mmol), and *t*-BuOH (2 mL) was heated to 110 °C for 14 h. The crude product was purified via the Biotage SP4 (silica-packed 50 g snap column; 0-40% EtOAc/hexanes) to provide the title compound as a white solid (175 mg, 84%), mp = 57 – 59 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.97 (m, 4H), 7.48 (s, 1H), 7.19 (d, *J* =8.4 Hz, 1H), 6.71 (d, *J* = 3.3 Hz, 1H), 6.47 (m, 1H), 2.69 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 158.9, 153.5, 147.3, 142.6, 136.3, 129.1, 128.1, 126.7, 125.9, 122.6, 121.5, 112.0, 106.1 ppm. IR (neat, cm^{-1}): 1640, 1385, 1125, 1385, 1125, 885, 816, 744, 596, 456.

1-(4-(Furan-2-yl)phenyl)-1*H*-pyrrole (Table 2, entry 8) Following the general procedure, a mixture of 4-(1*H*-pyrrol-1-yl)phenyl methanesulfonate (237 mg, 1.0 mmol), tri-*n*-butyl(furan-2-yl)stannane (430 mg, 1.2 mmol), $Pd(OAc)_2$ (4.4 mg, 2.0 mol%), **1** (19 mg, 4 mol%), CsF (334 mg, 2.2 mmol), and *t*-BuOH (2 mL) was heated to 110 °C for 14 h. The crude product was purified via the Biotage SP4 (silica-packed 50 g snap column; 0-40% EtOAc/hexanes) to provide the title compound as a white solid (123 mg, 59%), mp = 189 – 191 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.72 (d, *J* = 9.0 Hz, 2H), 7.49 (d, *J* = 1.8 Hz, 1H), 7.41 (d, *J* = 9.0 Hz, 2H), 7.12 (t, *J* = 2.4 Hz, 2H), 6.65 (d, *J* = 3.3 Hz, 1H), 6.49 (m, 1H), 6.37 (t, *J* = 2.4 Hz, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 153.4, 142.3, 139.8, 128.5, 125.1, 120.7, 119.3, 112.0, 110.8, 105.1 ppm. IR (neat, cm^{-1}): 2360, 1523, 1329, 1250, 1007, 831, 718, 594.

3-Phenylpyridine[25] (Table 2, entry 9) Following the general procedure, a mixture of pyridin-3-yl 4-methylbenzenesulfonate (249 mg, 1.0 mmol), tri-*n*-butyl(phenyl)stannane (440 mg, 1.2 mmol), $Pd(OAc)_2$ (2.0 mol%) and **1** (4 mol%) as a pre-milled mixture (23.6 mg), CsF (334 mg, 2.2 mmol), and *t*-BuOH (2 mL) was heated to 110 °C for 14 h. The crude product was purified via the Biotage SP4 (silica-packed 25 g snap column; 20% EtOAc/hexanes) to provide the title compound as a pale yellow oil (85 mg, 55%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.82 (s, 1H), 8.55 (d, *J* =5.0 Hz, 1H), 7.82 (d, *J* =7.5 Hz, 1H), 7.54 (d, *J* =7.5 Hz, 2H), 7.44 (t, *J* =7.5 Hz, 2H), 7.37 (m, 1H), 7.31 (dd, *J* = 7.5, 5.0 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 148.7, 148.5, 138.0, 136.8, 134.6, 129.3, 128.3, 127.3, 123.8 ppm. IR (neat, cm^{-1}): 3400, 3031, 1581, 1473, 1450, 1407, 1006, 754, 711, 698.

4-(Thien-2-yl)benzonitrile[26] (Table 2, entry 10) Following the general procedure, a mixture of 4-cyanophenyl methanesulfonate (197 mg, 1.0 mmol), tri-*n*-butyl(thiophen-2-yl)stannane (448 mg, 1.2 mmol), $Pd(OAc)_2$ (4.4 mg, 2.0 mol%), **1** (19 mg, 4 mol%), CsF (334 mg, 2.2 mmol), and *t*-BuOH (2 mL) was heated to 110 °C for 14 h. The crude product was purified via the Biotage SP4 (silica-packed 50 g snap column; 0-40% EtOAc/hexanes) to provide the title compound as a white solid (120 mg, 65%), mp = 90 – 92 °C (literature 91 – 92 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.68 (m, 4H), 7.41 (m, 2H), 7.13 (m, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 142.1, 138.7, 132.8, 128.7, 119.0, 110.6 ppm. IR (neat, cm^{-1}): 2218, 1600, 1424, 852, 821, 718, 551.

3-(Trifluoromethyl)biphenyl[24] (Table 2, entry 11) Following the general procedure, a mixture of 3-trifluoromethylphenyl tosylate (300 mg, 1.0 mmol), tri-*n*-butyl(phenyl)stannane (442 mg, 1.2 mmol), $Pd(OAc)_2$ (4.4 mg, 2.0 mol%), **1** (19 mg, 4 mol%), CsF (334 mg, 2.2 mmol), and *t*-BuOH (2 mL) was heated to 110 °C for 14 h. The crude product was purified via the Biotage SP4 (silica-packed 50 g snap column; 0-3% EtOAc/hexanes) to provide the title compound as a clear oil (194 mg, 86%). ^1H NMR (300 MHz, $CDCl_3$) δ: 7.93 (s, 1H), 7.82 (d, J = 7.5 Hz, 1H), 7.70 – 7.47 (m, 7H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 142.3, 140.0, 131.6, 131.2, 130.7, 130.7, 129.5, 129.3, 128.3, 127.5, 126.3, 124.3, 124.2, 124.2, 124.1, 124.1, 122.7 ppm. IR (neat, cm^{-1}): 3037, 1425, 1335, 1262, 1167, 1097, 1047, 899, 759, 702.

***N*-(Biphenyl-3-yl)acetamide**[27] (Table 2, entry 12) Following the general procedure, a mixture of 3-acetamidophenyl methanesulfonate (229 mg, 1.0 mmol), tri-*n*-butyl(phenyl)stannane (440 mg, 1.2 mmol), $Pd(OAc)_2$ (2.0 mol%) and **1** (4 mol%) as a pre-milled mixture (23.6 mg), CsF (334 mg, 2.2 mmol), and *t*-BuOH (2 mL) was heated to 110 °C for 14 h. The crude product was purified via the Biotage SP4 (silica-packed 50 g snap column; 20-60% EtOAc/hexanes) to provide the title compound as a white solid (120 mg, 57%), mp = 143 - 145 °C (literature 146 °C). ^1H NMR (400 MHz, $CDCl_3$) δ: 7.98 (s, 1H), 7.73 (s, 1H), 7.50 (m, 3H), 7.37 (t, J =7.2 Hz, 2H), 7.30 (m, 3H), 2.14 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.1, 142.2, 140.9, 138.6, 129.5, 129.0, 127.7, 127.3, 123.3, 119.1, 119.0, 24.7 ppm. IR (neat, cm^{-1}): 3294, 1665, 1555, 1480, 1402, 1317, 1013, 891, 759, 700.

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REFERENCES AND NOTES

1. For reviews of the Stille reaction see: T. N. Mitchell, in: 'Metal-catalyzed Cross-coupling Reactions, 2nd edn.', ed. by A. de Meijere and F. Diederich, Wiley-VCH, Weinheim, 2004, p. 125; P. Espinet and A. M. Echavarren, *Angew. Chem. Int. Ed.*, 2004, **43**, 4704.
2. M. Kosugi, K, Sasazawa, Y. Shimizu, and T. Migita, *Chem. Lett.*, 1977, 301.
3. D. Milstein and J. K. Stille, *J. Am. Chem. Soc.*, 1978, **100**, 3636; D. Milstein and J. K. Stille, *J. Org. Chem.*, 1979, **44**, 1613; J. K. Stille, *Pure Appl. Chem.*, 1985, **57**, 1771.
4. A.-M. Lord, M. F. Mahon, M. D. Lloyd, and M. D. Threadgill, *J. Med. Chem.*, 2009, **52**, 868; D. Amans, V. Bellosta, and J. Cossy, *Org. Lett.*, 2007, **9**, 4761; M. D. Cullen, B. L. Deng, T. L.

Hartman, K. M. Watson, R. W. Buckheit, C. Pannecouque, E. DeClercq, and M. Cushman, *J. Med. Chem.*, 2007, **50**, 4854; V. Uchil, B. Seo, and V. Nair, *J. Org. Chem.*, 2007, **72**, 8577.

5. V. Sofiyev, G. Navarro, and D. Trauner, *Org. Lett.*, 2008, **10**, 149; S. Lopez, J. Montenegro, and C. Saa, *J. Org. Chem.*, 2007, **72**, 9572; D. Schweitzer, J. J. Kane, D. Strand, P. McHenry, M. Tenniswood, and P. Helquist, *Org. Lett.*, 2007, **9**, 4619.
6. C. Song and T. M. Swager, *Macromolecules*, 2009, **42**, 1472; T. Qi, Y. Liu, W. Qiu, H. Zhang, X. Gao, Y. Liu, K. Lu, C. Du, G. Yu, and D. Zhu, *J. Mater. Chem.*, 2008, **18**, 1131; J. Gau, L. Li, Q. Meng, R. Li, H. Jiang, H. Li, and W. Hu, *J. Mater. Chem.*, 2007, **17**, 1421; K. R. J. Thomas, J. T. Lin, Y.-T. Tao, and C. H. Chuen, *J. Mater. Chem.*, 2002, **12**, 3516.
7. S. M. Jenkins, K. Ehman, and S. Barone Jr., *Dev. Brain Res.*, 2004, **151**, 1; A. S. Stasinakis, N. S. Thomaidis, and T. D. Lekkas, *Ecotox. Environ. Safe.*, 2001, **49**, 275; N. J. Snoeij, A. H. Penninks, and W. Seinen, *Environ. Res.*, 1987, **44**, 335.
8. For recent reviews of the Suzuki-Miyaura reaction see: R. Martin and S. L. Buchwald, *Acc. Chem. Res.*, 2008, **41**, 1461; H. Doucet, *Eur. J. Org. Chem.*, 2008, 2013.
9. A. F. Littke and G. C. Fu, *Angew. Chem. Int. Ed.*, 2002, **41**, 4176.
10. J. Corbet and G. Mignani, *Chem. Rev.*, 2006, **106**, 2651; A. L. Casado, P. Espinet, and A. M. Gallego, *J. Am. Chem. Soc.*, 2000, **122**, 11771; V. Farina, V. Krishnamurthy, and W. J. Scott, 'The Stille Reaction', John Wiley & Sons, New York, NY, 1998.
11. R. H. Munday, J. R. Martinelli, and S. L. Buchwald, *J. Am. Chem. Soc.*, 2008, **130**, 2754.
12. Coupling of aryl tosylates, for the Suzuki-Miyaura reaction, see: H. N. Nguyen, X. Huang, and S. L. Buchwald, *J. Am. Chem. Soc.*, 2003, **125**, 11818; L. Ziang, T. Meng, and J. Wu, *J. Org. Chem.*, 2007, **72**, 9346; C. M. So, C. P. Lau, A. S. C. Chan, and F. Y. Kwong, *J. Org. Chem.*, 2008, **73**, 7731; for the Kumada-Corriu reaction, see: A. M. Roy and J. F. Hartwig, *J. Am. Chem. Soc.*, 2003, **125**, 8704; L. Ackermann and A. Althammer, *Org. Lett.*, 2006, **8**, 2457; for C–N cross-coupling, see: B. C. Hamann and J. F. Hartwig, *J. Am. Chem. Soc.*, 1998, **120**, 7369; X. Huang, K. W. Anderson, D. Zim, L. Jiang, A. Klapars, and S. L. Buchwald, *J. Am. Chem. Soc.*, 2003, **125**, 6653.
13. Coupling of aryl mesylates, for the Hiyama reaction, see: L. Zhang, J. Qing, P. Yang, and J. Wu, *Org. Lett.*, 2008, **10**, 4971; for the Suzuki-Miyaura reaction, see: C. M. So, C. P. Lau, and F. Y. Kwong, *Angew. Chem. Int. Ed.*, 2008, **47**, 8059; for the C–N cross-coupling, see: C. M. So, C. P. Lau, and F. Y. Kwong, *Angew. Chem. Int. Ed.*, 2008, **47**, 8059; B. P. Fors, D. A. Watson, M. R. Biscoe, and S. L. Buchwald, *J. Am. Chem. Soc.*, 2008, **130**, 13552.
14. L. Schio, F. Chatreaux, and M. Klich, *Tetrahedron Lett.*, 2000, **41**, 1543; D. Steinhuebel, J. M. Baxter, M. Palucki, and I. W. Davies, *J. Org. Chem.*, 2005, **70**, 10124.
15. J. R. Naber and S. L. Buchwald, *Adv. Synth. Catal.*, 2008, **250**, 957.

16. M. R. Biscoe, B. P. Fors, and S. L. Buchwald, *J. Am. Chem. Soc.,* 2008, **130**, 6686.
17. For the coupling of 2-methylphenyltosylate and 2,4,6-trimethylphenyltributylstannane the GC conversion was measured to be 40% after the standard reaction conditions of 14 h at 110 °C with 2 mol% Pd.
18. J. E. Milne and S. L. Buchwald, *J. Am. Chem. Soc.,* 2004, **126**, 13028.
19. X. Huang, K. W. Anderson, D. Zim, L. Jiang, and S. L. Buchwald, *J. Am. Chem. Soc.,* 2003, **125**, 6653.
20. T. E. Barder, S. D. Walker, J. R. Martinelli, and S. L. Buchwald, *J. Am. Chem. Soc.,* 2005, **127**, 4685.
21. J. Becht and C. Le Drian, *Org. Lett.,* 2008, **10**, 3161.
22. K. Fuchibe and T. Akiyama, *J. Am. Chem. Soc.,* 2006, **128**, 1434.
23. D. Saha, K. Chattopadhyay, and B. C. Ranu, *Tetrahedron Lett.,* 2009, **50**, 1003.
24. B. H. Lipshutz, T. B. Petersen, and A. R. Abela, *Org. Lett.,* 2008, **10**, 1333.
25. E. Alacid and C. Najera, *Org. Lett.,* 2008, **10**, 5011.
26. S. E. Denmark and J. D. Baird, *Org. Lett.,* 2006, **8**, 793.
27. Z. Bosshand, *Helv. Chim. Acta,* 1961, **44**, 1985.