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Palladium on charcoal-catalyzed ligand-free Stille coupling

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ABSTRACT

An efficient ligand-free Stille coupling reaction catalyzed by palladium on charcoal was developed. Tetraphenyltin was reacted with a variety of aryl halides including aryl chlorides using LiCl as an additive. The reactions of tributyl organotin compounds with aryl iodides were effectively expedited by the addition of LiF. These reactions efficiently proceeded without a phosphine or arsenic ligand and no leached palladium was detected in the reaction mixture.

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1. Introduction

Stille reaction,[1] a palladium-catalyzed cross-coupling between organotin compounds and aryl halides, has been widely used as a synthetic methods for functional and bioactive materials including natural products, agrochemicals, pharmaceuticals, and organic electroluminescent (EL) polymers.[2] Organostannanes are air- and moisture-stable and tolerate a wide variety of functional groups.[3] Stille coupling reaction was generally catalyzed by homogenous palladium catalysts together with expensive phosphine ligands. For example, Fu and Littke developed a powerful method for the cross-coupling between aryl chlorides and aryl or alkenyltributyltin compounds using $Pd_2(dba)_3$ and P(*n*-Bu)$_3$.[4] The use of homogeneous palladium catalysts unfortunately and frequently causes a contamination of the residual metal in the desired product due to the difficulty of its removal.[5] Palladium on charcoal (Pd/C), which has been employed as a common heterogeneous catalyst for hydrogenations, is attracting the interests of organic chemists as a practical catalyst for a variety of bond forming reactions[6] due to the air-stability, and non-residual properties. We have investigated the application of the Pd/C for the carbon–carbon,[7] carbon–nitrogen,[8] and carbon–oxygen[9] bond formation reactions. Although the Pd/C-catalyzed Stille coupling reaction was reported by Farina,[10,11] the use of $AsPh_3$ as a ligand and CuI was essential to the reaction progress. We here report two kinds of efficient protocols for the ligand-free, Pd/C-catalyzed Stille reaction under atmospheric conditions.

2. Results and discussion

The cross-coupling between ethyl 4-bromobenzoate (**1**) and 2 equiv of tetraphenyltin (**2**) was effectively catalyzed by 10% Pd/C (5 mol % as Pd metal)[12,13] in NMP at 90 °C without further additives to give ethyl 4-phenylbenzoate (**3**) in 87% yield, although a small amount of unreacted **1** remained (Table 1, entry 1). Since Fu[14] and Nolan[15] independently found that a fluoride salt as an additive played an important role in the activation of organotin compounds[16] by generating the corresponding 'ate' complex, we also examined the effect of fluoride as an additive (Table 1). Although AgF, KF·HF, CaF_2, CsF, NaF, and LiF never enhanced the reaction efficiency (entry 1 vs entries 2–8), tetra-*n*-butylammonium fluoride (TBAF) and LiCl were found to be effective to afford **3** in quantitative yields (entries 9 and 10). The addition of LiCl would lead to an in situ generation of a chloride-ligated zerovalent palladium species[17] facilitating the oxidative addition of aryl halide by the increased nucleophilicity of palladium atom.[18] Furthermore, **1** was successfully reacted with decreased amount of **2** (1 equiv) under atmospheric conditions in the presence of TBAF or LiCl without any declination of the yields (entries 11 and 12). Careful monitoring by TLC analysis revealed that the LiCl-promoted reaction was completed within 4 h (entry 13).[19]

The reaction of 4-iodoacetophenone with **2** using LiCl as an additive also afforded the corresponding 4-acetylbiphenyl in 88% yield, while the use of TBAF instead of LiCl remarkably reduced the

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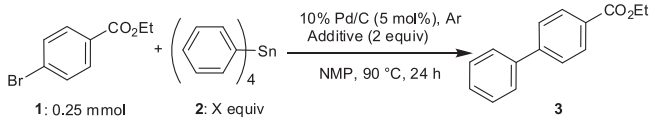
Table 1
Screening of additives in the cross-coupling between ethyl-4-bromobenzoate (**1**) and tetraphenyltin (**2**)[a]



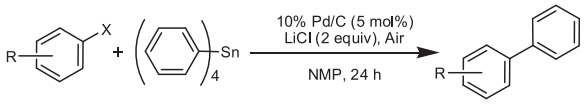
1: 0.25 mmol 2: X equiv 3

Entry	X	Additive	Yield[b] [%]
1	2	None	87
2	2	AgF	4[c]
3	2	KF·HF	21[c]
4	2	CaF_2	37[c]
5	2	CsF	46[c]
6	2	KF	58[c]
7	2	NaF	71
8	2	LiF	77
9	2	TBAF	99
10	2	LiCl	99
11	1	TBAF	99[d]
12	1	LiCl	99[d]
13	1	LiCl	99[e]

[a] All reactions were performed once.
[b] Isolated yield.
[c] Determined by ^{1}H NMR analysis.
[d] The reaction was carried out under atmospheric conditions.
[e] The reaction was quenched after 4 h.

yield (32%). The scope of the cross-coupling between aryl halides and **2** (1 equiv) was therefore investigated using LiCl (2 equiv) together with 10% Pd/C (5 mol %) in NMP after minor tuning of the reaction temperature (Table 2). Iodobenzenes bearing either an electron-withdrawing or -donating group smoothly underwent the cross-coupling regardless of the substitution pattern to give the desired biphenyl derivatives in good to excellent yields (entries 1–9).[20] The cross-coupling reactions using bromobenzene derivatives also proceeded efficiently (entries 10–13). The reaction scale was increased from 0.25 to 5.0 mmol with only slightly reduced yield of the desired biphenyl (entry 10). This protocol was furthermore applicable to the reaction of electron-withdrawing nitro or cyano-substituted aryl chlorides by increasing the amount of LiCl without the addition of phosphine or arsenic ligands (entries 14–16).

Table 2
Cross-coupling of aryl halides with tetraphenyltin (**2**)[a]



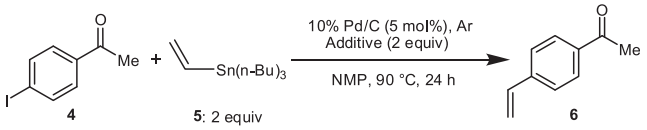
2: 1 equiv

Entry	X	R	Temp [°C]	Yield[b] [%]
1	I	4-COMe	50	88 (32)[c]
2	I	4-NO_2	50	63
3	I	3-NO_2	50	90
4	I	2-NO_2	50	60
5	I	4-CN	90	88
6	I	3-CN	50	85
7	I	4-OMe	120	79
8	I	3-OMe	110	90
9	I	2-OMe	110	86
10	Br	4-CO_2Et	90	99 (83)[d]
11	Br	3-NO_2	70	86
12	Br	2-CN	70	74
13	Br	4-OMe	110	68
14	Cl	2,4-NO_2	120	47[e]
15	Cl	4-NO_2	120	62[e]
16	Cl	4-CN	90	65[d,e]

[a] All reactions (0.25 mmol scale) were performed twice.
[b] Isolated yield.
[c] TBAF (2 equiv) instead of LiCl were used.
[d] Scale of ethyl 4-bromobenzoate (5 mmol) was used.
[e] LiCl (4 equiv) was used.

The cross-coupling between tributyl organotin compounds and aryl iodides was next explored (Table 3). 4-Iodoacetophenone (**4**) was reacted with 2 equiv of tributylvinyltin (**5**) in NMP at 90 °C to give 4-acetylstyrene (**6**) in only 36% yield (entry 1). The addition of LiCl or a fluoride salt increased the reaction efficiency (entries 1–8), and NaF and LiF were particularly effective (83% and 85%, entries 7 and 8). The usage of both **5** and LiF could be decreased to 1.5 equiv to **4**, and the reaction smoothly proceeded even under air conditions (83%, entry 9).

Table 3
Screening of additives in the cross-coupling between 4-iodoacetophenone (**4**) and tributylvinyltin (**5**)[a]



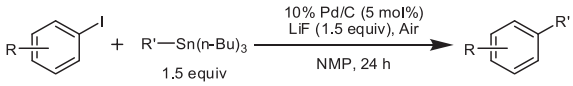
4 5: 2 equiv 6

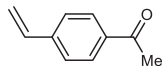
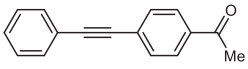
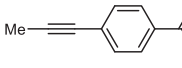
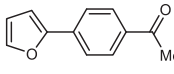
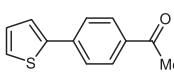
Entry	Additive	Yield[b] [%]
1	None	36
2	LiCl	65
3	TBAF	53
4	KF	52
5	CsF	69
6	CaF_2	73
7	NaF	83
8	LiF	85
9	LiF	83[c]

[a] All reactions were performed once.
[b] Isolated yield.
[c] 1.5 equiv of Tributylvinyltin and LiF were used. The reaction was carried out under atmospheric conditions.

Diverse aryl iodides possessing either an electron-withdrawing or -donating functionality on the benzene ring were effectively reacted with a variety of tributyl organotin compounds (1.5 equiv) to give the corresponding cross-coupled products in good to excellent yields (Table 4, entries 1–11) under the optimized conditions using 10% Pd/C (5 mol %) and LiF (1.5 equiv) in heated NMP. It is noteworthy that heteroaryltributyltin, such as 2-furyl and

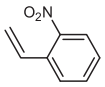
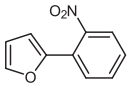
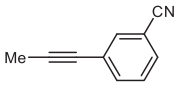
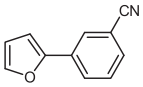
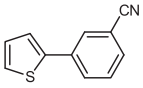
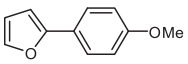
Table 4
Cross-coupling of aryl iodides with tributyltin derivatives[a]



Entry	R	R′	Temp [°C]	Product	Yield [%][b]
1	4-COMe	Vinyl	90		83
2	4-COMe	1-Phenylethynyl	90		90
3	4-COMe	1-Propynyl	50		90
4	4-COMe	2-Furyl	120		89[c]
5	4-COMe	2-Thienyl	120		75[c]

(*continued on next page*)

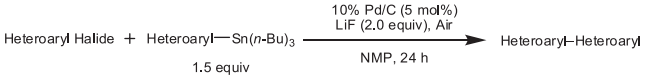
Table 4 (*continued*)

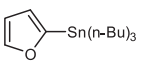
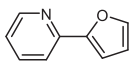
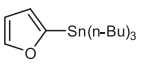
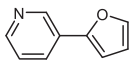
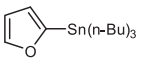
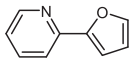
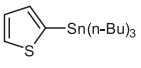
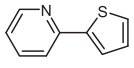
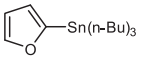
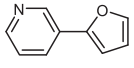
Entry	R	R′	Temp [°C]	Product	Yield [%][b]
6	2-NO_2	Vinyl	90		63
7	2-NO_2	2-Furyl	120		83[c]
8	3-CN	1-Propynyl	70		63
9	3-CN	2-Furyl	120		74[c]
10	3-CN	2-Thienyl	120		67[c]
11	4-OMe	2-Furyl	140		96[c]

[a] All reactions were performed once.
[b] Isolated yield.
[c] LiF (2 equiv) was used.

2-thienyltributyltins, are also good substrates for the cross-coupling, while heterogeneous palladium-catalyzed cross-coupling reactions are usually hard to apply to the heterocycles in the absence of ligands. Then, the cross-coupling reactions between heteroaryl halides and heteroaryltributyltin derivatives were investigated. Pyridines bearing an iodine or bromine atom at the 2 or 3 position reacted with 2-tributylstannylfuran and -thiophen to give the corresponding furyl- and thienylpyridines in moderate yields (Table 5, entries 1–4). To the best of our knowledge, this is the first example of the Stille coupling between heteroaryl halides and heteroaryltin reagents using heterogeneous palladium catalyst under ligand-free conditions.

Table 5
Cross-coupling of heteroaryl halides with heteroaryltributyltin derivatives[a]

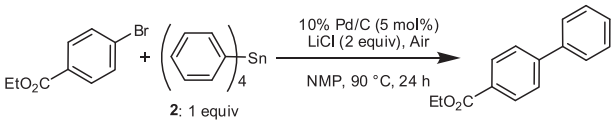


Entry	Heteroaryl halide	Heteroaryl–$Sn(n\text{-}Bu)_3$	Temp [°C]	Heteroaryl–heteroaryl	Yield[b] [%]
1			120		62
2			140		60
3			140		50
4			140		55
5			140		50

[a] All reactions were performed twice.
[b] Isolated yield.

The catalyst activity of Pd/C basically depends on the supplier or even manufacturing lot numbers of the same product since charcoal is obtained from natural resources, such as peat or sawdust and contaminated with a small amount of impurities, such as metals. During the course of the study on chemoselective hydrogenation, we previously reported a significant supplier-dependent disparity in the catalyst activity of commercial Pd/Cs in the hydrogenolysis of triethylsilyl ether.[21] The present Pd/C-catalyzed Stille reaction between ethyl 4-bromobenzoate and tetraphenyltin was not affected by either catalyst suppliers (Table 6, entries 1 and 4–7), lot numbers of the same product (entry 2) or product numbers from the same supplier (entry 3) to give the corresponding biphenyl in high yield in each case.

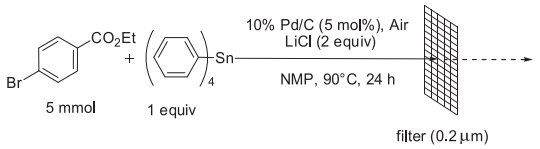
Table 6
Evaluation suppliers, lot and product numbers of 10% Pd/C on the Stille Coupling reaction[a]



Entry	10% Pd/C	Yield[b]
1	N.E. Chemcat (K type, Lot21A-050759)	99
2	N.E. Chemcat (K type, Lot217-075941)	92
3	N.E. Chemcat (NX type, Lot 21A-70169)	92
4	Nacalai	99
5	Aldrich	89
6	Acros	91
7	Kishida	99

[a] All reactions were preformed once.
[b] Isolated yield.

The leaching of palladium metal from Pd/C into the reaction media is an important issue for the practical application. No leached palladium was detected within the limits of the assay (<1 ppm) by inductively coupled plasma atomic emission spectrometry (ICP-AES) in the filtrate of the Pd/C-catalyzed Stille reaction of ethyl 4-bromobenzoate with tetraphenyltin using LiCl in heated NMP (Scheme 1). This result suggests that the Pd/C-catalyzed Stille reaction involves no risk of the elution of Pd species into the desired product, although the process of 'release and capture' of the Pd metal on the activated carbon might take place during the reaction.[7i,22]



Scheme 1. Leaching palladium species free Stille cross-coupling reaction.

3. Conclusions

In conclusion, we have developed two kinds of protocols for the ligand- and copper-free heterogeneous Pd/C-catalyzed Stille coupling reaction under atmospheric conditions. When tetraphenyltin was used as a coupling partner, the efficient reaction progress was achieved by the addition of LiCl, and even aryl chlorides could also be employed as a substrate. The reaction of tributyl organotin compounds afforded the corresponding coupled products in good to high yields in the presence of LiF. The distinctive future of these

methods is that the cross-coupling reactions of a wide range of substrates efficiently proceed without ligands. No leached palladium was detected in the reaction mixture. The present protocols will be in practical use for the syntheses of functional and bioactive materials.

4. Experimental section

4.1. General

All reagents and solvents were obtained from commercial sources and used without further purification. The 10% Pd/C was obtained from N.E. Chemcat Corporation (Japan).

The ^{1}H and ^{13}C NMR spectra were recorded on a JEOL JNM EX-400 or JEOL JNM AL-400 spectrometer (400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR). Chemical shifts (δ) are expressed in parts per million and internally referenced [0.00 ppm for tetramethylsilane (TMS)/$CDCl_3$ for ^{1}H NMR and 77.0 ppm for $CDCl_3$ for ^{13}C NMR]. The EI mass spectra were taken on a JEOL JMS-SX102A instrument. Flash column chromatography was performed using silica gel 60 N [spherical neutral (63–210 μm)] from Kanto Chemical Co., Inc.

4.2. Typical procedure for the Stille cross-coupling reaction using tetraphenyltin (Table 2)

A mixture of LiCl (21.2 mg, 500 μmol), the aryl halide (250 μmol), tetraphenyltin (107 mg, 250 μmol), and 10% Pd/C (13.3 mg, 12.5 μmol) in NMP (1 mL) in a test tube was stirred at the given temperature for 24 h. To the mixture at room temperature was added a saturated aqueous KF solution (10 mL), and the mixture was stirred overnight, diluted with H_2O (20 mL) and EtOAc (20 mL), and passed through a Celite pad. The filtrate was separated into two layers and the aqueous layer was extracted with EtOAc (2×10 mL). The combined organic layers were washed with another saturated KF solution (2×10 mL), dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (*n*-hexane/EtOAc, 80:1) or preparative TLC on silica gel (*n*-hexane/EtOAc, 100:1) to give the corresponding biaryl.

4.2.1. 4-Acetylbiphenyl[23]. For entry 1: 88% (43.1 mg) as a colorless solid obtained from 4-iodoacetophenone (61.5 mg, 250 μmol) at 50 °C.

^{1}H NMR δ 8.02 (d, 2H, J=8.3 Hz), 7.67 (d, 2H, J=8.3 Hz), 7.62 (dt, 2H, J=8.1, 2.2 Hz), 7.46 (t, 2H, J=8.1, 7.1 Hz), 7.40 (tt, 1H, J=7.1, 2.2 Hz), 2.62 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 197.7, 145.8, 139.9, 135.9, 129.0, 128.9, 128.2, 127.7, 127.2, 26.7; MS (EI) m/z (%) 196 (M^+, 48), 181 (100), 152 (38), 76 (10); HRMS (EI) calcd for $C_{14}H_{12}O$ (M^+) 196.08882. Found 196.08915.

4.2.2. 4-Nitrobiphenyl[23,24]. For entry 2: 63% (31.4 mg) as a colorless solid obtained from 4-iodonitorobenzen (62.2 mg, 250 μmol) at 50 °C.

For entry 15: 62% (30.9 mg) as a colorless solid obtained from 4-chloronitorobenzen (39.4 mg, 250 μmol) at 120 °C.

^{1}H NMR δ 8.29 (d, 2H, J=0 8.8 Hz), 7.73 (d, 2H, J=8.8 Hz), 7.62 (d, 2H, J=6.8 Hz), 7.52–7.42 (m, 3H); ^{13}C NMR δ 147.6, 147.1, 138.8, 129.2, 128.9, 127.8, 127.4, 124.1; MS (EI) m/z (%) 199 (M^+, 72), 169 (40), 152 (100), 141 (46), 127 (12), 115 (20), 102 (10), 84 (6), 76 (16), 63 (14), 51 (16); HRMS (EI) calcd for $C_{12}H_9NO$ (M^+) 199.06333. Found 196.06260.

4.2.3. 3-Nitrobiphenyl[24]. For entry 3: 90% (45.0 mg) as a yellow solid obtained from 3-iodonitrobenzen (62.2 mg, 250 μmol) at 50 °C.

For entry 11: 86% (42.9 mg) as a yellow solid obtained from 3-bromonitrobenzen (56.5 mg, 250 μmol) at 70 °C.

^{1}H NMR δ 8.44 (t, 1H, J=2.2 Hz), 8.19 (ddd, 1H, J=8.3, 2.2, 1.2 Hz), 7.91 (dt, 1H, J=7.8, 1.2 Hz), 7.63–7.57 (m, 3H), 7.49 (t, 2H, J=7.3, 7.3 Hz), 7.43 (t, 1H, J=7.3 Hz); ^{13}C NMR δ 148.7, 142.8, 138.6, 133.0, 129.7, 129.1, 128.5, 127.1, 122.0, 121.9; MS (EI) m/z (%) 199 (M^+, 100), 152 (80), 141 (12), 115 (6), 77 (12), 61 (8), 44 (8); HRMS (EI) calcd for $C_{12}H_9NO_2$ (M^+) 199.06333. Found 199.06396.

4.2.4. 2-Nitrobiphenyl[24]. For entry 4: 60% (29.9 mg) as a yellow solid obtained from 2-iodonitorobenzen (62.2 mg, 250 μmol) at 50 °C.

^{1}H NMR ($CDCl_3$) δ 7.84 (dd, 1H, J=8.0, 1.2 Hz), 7.60 (dd, 1H, J=7.5, 7.5, 1.2 Hz), 7.49–7.38 (m, 5H), 7.33–7.30 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 149.3, 137.4, 136.3, 132.2, 131.9, 128.6, 128.2, 128.1, 127.9, 124.0; MS (EI) m/z (%) 199 (M^+, 68), 182 (44), 171 (48), 152 (100), 115 (52), 76 (24); HRMS (EI) calcd for $C_{12}H_9NO$ (M^+) 199.06333. Found 196.06394.

4.2.5. Biphenyl-4-carbonitrile[25]. For entry 5: 88% (39.4 mg) as a colorless solid obtained from 4-iodobenzonitrile (57.3 mg, 250 μmol) at 90 °C.

For entry 16: 65% (28.9 mg) as a colorless solid obtained from 4-chlorobenzonitrile (34.3 mg, 250 μmol) at 90 °C.

^{1}H NMR δ 7.74–7.67 (m, 4H), 7.60–7.58 (m, 2H), 7.50–7.42 (m, 3H); ^{13}C NMR δ 146.1, 139.6, 133.0, 129.5, 129.0, 128.1, 127.6, 119.3, 111.3; MS (EI) m/z (%) 179 (100), 151 (12), 132 (10), 104 (10), 76 (10); HRMS (EI) calcd for $C_{13}H_9N$ (M^+) 179.07350. Found 179.07264.

4.2.6. Biphenyl-3-carbonitrile[25]. For entry 6: 85% (37.9 mg) as a colorless solid obtained from 3-iodobenzonitrile (57.3 mg, 250 μmol) at 50 °C.

^{1}H NMR ($CDCl_3$) δ 7.85 (t, 1H, J=3.0 Hz), 7.81 (dd, 1H, J=7.8, 3.0, 1.8 Hz), 7.62 (dd, 1H, J=7.6, 1.8 Hz), 7.57–7.51 (m, 3H), 7.47 (t, 2H, J=8.0, 7.2 Hz), 7.41 (t, 1H, J=7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 142.2, 138.6, 132.24, 130.4, 129.4, 128.9, 128.1, 126.8, 118.6, 112.7; MS (EI) m/z (%) 179 (M^+, 100), 151 (12), 76 (6); HRMS (EI) calcd for $C_{13}H_9N$ (M^+) 179.07350. Found 179.07275.

4.2.7. 4-Methoxybiphenyl[23,25]. For entry 7: 79% (36.4 mg) as a colorless solid obtained from 4-iodoanisole (58.5 mg, 250 μmol) at 120 °C.

For entry 13: 68% (31.4 mg) as a colorless solid obtained from 4-bromoanisole (31.3 μL, 250 μmol) at 110 °C.

^{1}H NMR δ 7.56–7.51 (m, 4H), 7.41 (t, 2H, J=7.6 Hz), 7.31 (t, 2H, J=7.6 Hz), 6.98 (d, 2H, J=8.8 Hz), 3.84 (s, 3H); ^{13}C NMR δ 159.1, 140.8, 133.8, 128.7, 126.7, 126.6, 114.2, 55.3; MS (EI) m/z (%) 184 (M^+, 100), 169 (36), 141 (24), 115 (18), 44 (7); HRMS (EI) calcd for $C_{13}H_{12}O$ (M^+) 184.08882. Found 184.08816.

4.2.8. 3-Methoxybiphenyl[23]. For entry 8: 90% (42.6 mg) as a colorless solid obtained from 3-iodoanisole (29.8 μL, 250 μmol) at 110 °C.

^{1}H NMR δ 7.58 (d, 2H, J=8.2 Hz), 7.42 (t, 2H, J=8.2, 7.8 Hz), 7.34 (m, 2H), 7.17 (ddd, 1H, J=7.6, 1.7, 1.7 Hz), 7.12 (t, 1H, J=2.4, 1.7 Hz), 6.89 (ddd, 1H, J=8.3, 2.4,1.7 Hz), 3.84 (s, 3H); ^{13}C NMR δ 159.9, 142.7, 141.1, 129.7, 128.7, 127.4, 127.2, 119.6, 112.9, 112.6, 55.2; MS (EI) m/z (%) 184 (M^+, 100), 154 (20), 141 (24), 115 (20), 44 (16); HRMS (EI) calcd for $C_{13}H_{12}O$ (M^+) 184.08882. Found 184.08798.

4.2.9. 2-Methoxybiphenyl[23]. For entry 9: 86% (39.8 mg) as a colorless solid obtained from 2-iodoanisole (32.6 μL, 250 μmol) at 110 °C.

^{1}H NMR δ 7.52 (d, 2H, J=87.6 Hz), 7.40 (t, 2H, J=7.6, 7.3 Hz), 7.33–7.29 (m, 3H), 7.02 (t, 1H, J=7.6 Hz), 6.97 (d, 1H, J=8.5 Hz), 3.79 (s, 3H); ^{13}C NMR δ 156.4, 138.5, 130.9, 130.7, 129.5, 128.6, 127.9, 126.9, 120.8, 111.2, 55.5; MS (EI) m/z (%) 184 (M^+, 100), 169 (46), 141 (36), 115 (32), 91 (8), 44 (6); HRMS (EI) calcd for $C_{13}H_{12}O$ (M^+) 184.08882. Found 184.08828.

4.2.10. Ethyl biphenyl-4-carboxylate[25,26]. For entry 10: 99% (56.0 mg) as a colorless solid obtained from ethyl 4-bromobenzoate (40.8 μL, 250 μmol) at 90 °C.

^{1}H NMR δ 8.11 (d, 2H, *J*=8.3 Hz), 7.64 (d, 2H, *J*=8.3 Hz), 7.62 (dd, 2H, *J*=7.1, 1.2 Hz), 7.46 (dd, 2H, *J*=7.1, 7.3 Hz), 7.39 (dd, 1H, *J*=7.3, 1.2 Hz), 4.40 (q, 2H, *J*=7.2 Hz), 1.41 (t, 3H, *J*=7.2 Hz); ^{13}C NMR δ 166.2, 145.2, 139.8, 129.8, 129.7, 129.0, 128.6, 127.8, 127.0, 126.7, 60.7, 14.0; MS (EI) *m*/*z* (%) 226 (M^+, 62%), 198 (26), 181 (100), 152 (44), 90 (6), 76 (10); HRMS (EI) calcd for $C_{15}H_{14}O_2$ (M^+) 226.10022. Found 226.09938.

4.2.11. Biphenyl-2-carbonitrile[23,25]. For entry 12: 74% (33.2 mg) as a yellow solid obtained from 2-bromobenzonitrile (45.5 mg, 250 μmol) at 70 °C.

^{1}H NMR δ 7.76 (d, 1H, *J*=7.8 Hz), 7.63 (t, 1H, *J*=7.7 Hz), 7.57–7.41 (m, 7H); ^{13}C NMR δ 145.5, 138.1, 133.7, 132.8, 130.0, 128.7, 128.7, 127.5, 118.7, 111.3; MS (EI) *m*/*z* (%) 179 (M^+, 100), 152 (12), 76 (6); HRMS (EI) calcd for $C_{13}H_9N$ (M^+) 179.07275. Found 179.07350.

4.2.12. 2, 4-Dinitrobiphenyl[24]. For entry 14: 47% (28.9 mg) as a yellow solid obtained from 1-chloro 2,4-dinitorobenzene (50.6 mg, 250 μmol) at 110 °C.

^{1}H NMR δ 8.71 (d, 1H, *J*=2.2 Hz), 8.47 (dd, 1H, *J*=8.5, 2.2 Hz), 7.68 (d, 1H, *J*=8.5 Hz), 7.50–7.47 (m, 3H), 7.36–7.33 (m, 2H); ^{13}C NMR δ 149.1, 146.9, 142.3, 135.2, 133.2, 129.6, 129.1, 127.7, 126.4, 119.7; MS (EI) *m*/*z* (%) 244 (M^+, 50), 227 (36), 216 (100), 168 (36), 151 (84), 139 (88), 115 (44), 102 (24), 102 (24), 63 (32), 51 (20); HRMS (EI) calcd for $C_{12}H_9N_2O_4$ (M^+) 244.04908. Found 244.04841.

4.3. Typical procedure for the Stille cross-coupling reaction using tributyl organotin compounds (Table 4)

A mixture of LiF (9.8 mg, 375 μmol), the aryl halide (250 μmol), tributyl organotin compound (375 μmol), and 10% Pd/C (13.3 mg, 12.5 μmol) in NMP (1 mL) in a test tube was stirred at the given temperature for 24 h. To the mixture at room temperature was added saturated aqueous KF solution (10 mL), and the mixture was stirred overnight, diluted with H_2O (20 mL) and EtOAc (20 mL), and passed through a Celite pad. The filtrate was separated into two layers and the aqueous layer was extracted with EtOAc (2×10 mL). The combined organic layers were washed with another saturated KF solution (2×10 mL), dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (*n*-hexane/EtOAc, 80:1) or preparative TLC on silica gel (*n*-hexane/EtOAc, 100:1) to give the corresponding biaryl.

4.3.1. 1-(4-Ethenylphenyl)ethanone[27]. For entry 1: 83% (30.2 mg) as a colorless solid obtained from 4-iodoacetophenone (61.5 mg, 250 μmol) at 90 °C.

^{1}H NMR δ 7.92 (d, 2H, *J*=8.5 Hz), 7.48 (d, 2H, *J*=8.5 Hz), 6.76 (dd, 1H, *J*=17.6, 10.9 Hz), 5.88 (d, 1H, *J*=17.6 Hz), 5.40 (d, 1H, *J*=10.9 Hz), 2.60 (s, 3H); ^{13}C NMR δ 197.6, 142.1, 136.3, 136.0, 128.7, 126.3, 116.7, 26.6; MS (EI) *m*/*z* (%) 146 (44), 131 (100), 103 (52), 77 (42), 57 (20); HRMS (EI) calcd for $C_{10}H_{10}O$ (M^+) 146.07317. Found 146.07380.

4.3.2. 1-(4-Phenylethynylphenyl)ethanone[28]. For entry 2: 90% (49.6 mg) as a colorless solid obtained from 4-iodoacetophenone (61.5 mg, 250 μmol) at 90 °C.

^{1}H NMR δ 7.94 (d, 2H, *J*=8.8 Hz), 7.61 (d, 2H, *J*=8.8 Hz), 7.55 (m, 2H), 7.37 (m, 3H), 2.61 (s, 3H); ^{13}C NMR δ 197.3, 136.1, 131.7, 131.7, 128.8, 128.4, 128.2, 128.2, 122.6, 92.7, 88.6, 26.6; MS (EI) *m*/*z* (%) 220 (72), 205 (100), 176 (36), 151 (16), 102 (6), 88 (8), 43 (6); HRMS (EI) calcd for $C_{16}H_{12}O$ (M^+) 220.08882. Found 220.08935.

4.3.3. 1-[4-(1-Propyn-1-yl)phenyl]ethanone[29]. For entry 3: 90% (35.4 mg) as a colorless solid obtained from 4-iodoacetophenone (61.5 mg, 250 μmol) at 50 °C.

^{1}H NMR δ 7.87 (d, 2H, *J*=8.5 Hz), 7.45 (d, 2H, *J*=8.5 Hz), 2.58 (s, 3H), 2.08 (s, 3H); ^{13}C NMR δ 197.4, 135.8, 131.6, 129.1, 128.2, 89.8, 79.3, 26.6, 4.5; MS (EI) *m*/*z* (%) 158 (56), 143 (100), 115 (72), 89 (20), 63 (16), 43(10); HRMS (EI) calcd for $C_{11}H_{10}O$ (M^+) 158.07317. Found 158.07369.

4.3.4. 1-[4-(Furan-2-yl)phenyl]ethanone[30]. For entry 4: 89% (41.3 mg) as a colorless solid obtained from 4-iodoacetophenone (61.5 mg, 250 μmol) at 120 °C.

^{1}H NMR δ 7.97 (d, 2H, *J*=8.4 Hz), 7.74 (d, 2H, *J*=8.4 Hz), 7.53 (d, 1H, *J*=1.7 Hz), 6.80 (d, 1H, *J*=3.4 Hz), 6.51 (dd, 1H, *J*=1.7, 3.4 Hz), 2.60 (3H, s); ^{13}C NMR δ 197.3, 152.8, 143.2, 135.5, 134.8, 128.9, 123.5, 112.0, 107.4, 26.5; MS (EI) *m*/*z* (%) 186 (60), 171 (100), 143 (12), 115 (36), 63 (6); HRMS (EI) calcd for $C_{12}H_{10}O_2$ (M^+) 186.06808. Found 186.06753.

4.3.5. 1-(4-Thiophen-2-yl-phenyl)ethanone[31]. For entry 5: 75% (38.0 mg) as a colorless solid obtained from 4-iodoacetophenone (61.5 mg, 250 μmol) at 120 °C.

^{1}H NMR δ 7.96 (d, 2H, *J*=8.3 Hz), 7.69 (d, 2H, *J*=8.3 Hz), 7.42 (d, 1H, *J*=3.6 Hz), 7.37 (d, 1H, *J*=4.8 Hz), 7.12 (dd, 1H, *J*=4.8, 3.6 Hz), 2.60 (3H, s); ^{13}C NMR δ 197.2, 142.9, 138.7, 135.7, 129.1, 128.3, 126.4, 125.6, 124.6, 26.51; MS (EI) *m*/*z* (%) 202 (64), 187 (100), 159 (20), 115 (52), 89 (8), 79 (6), 63 (6), 43 (6); HRMS (EI) calcd for $C_{12}H_{10}O$ (M^+) 202.04524. Found 202.04626.

4.3.6. 1-Ethenyl-2-nitrobenzene[27]. For entry 6: 63% (23.5 mg) as a yellow oil obtained from 2-iodonitrobenzen (62.2 mg, 250 μmol) at 90 °C.

^{1}H NMR δ 7.92 (dd, 1H, *J*=8.2, 1.1 Hz), 7.63 (dd, 1H, *J*=7.8, 1.6 Hz), 7.58 (ddd, 1H, *J*=8.0, 7.8, 1.1 Hz), 7.41 (d, 1H *J*=8.2, 8.0, 1.6 Hz), 7.17 (dd, 1H, 17.3, 11.0 Hz), 5.75 (dd, 1H, *J*=17.3, 1.0 Hz), 5.48 (dd, 1H, *J*=11.0, 1.0 Hz); ^{13}C NMR δ 147.4, 132.9, 132.6, 132.0, 128.0, 127.9, 123.9, 118.5; MS (EI) *m*/*z* (%) 149 (M^+, 40), 132 (26), 120 (32), 105 (70), 91 (64), 77 (100), 65 (40), 51 (48); HRMS (EI) calcd for $C_8H_7NO_2$ (M^+) 149.04768. Found 149.04822.

4.3.7. 2-(2-Nitrophenyl)furan[32]. For entry 7: 83% (39.1 mg) as a brown solid obtained from 2-iodonitorobenzene (62.2 mg, 250 μmol) at 120 °C.

^{1}H NMR δ 7.71 (dd, 1H, *J*=7.8, 1.3 Hz), 7.68 (dd, 1H, *J*=8.1, 1.0 Hz), 7.57 (ddd, 1H, *J*=7.8, 7.6, 1.0 Hz), 7.51 (d, 1H, *J*=1.8 Hz), 7.41 (ddd, 1H, *J*=8.1, 7.6, 1.3 Hz), 6.67 (d, 1H, *J*=3.4 Hz), 6.50 (dd, 1H, *J*=3.4, 1.3 Hz); ^{13}C NMR δ 148.0, 143.4, 131.5, 128.5, 127.9, 123.8, 123.4, 111.5, 109.3; MS (EI) *m*/*z* (%) 189 (M^+, 36), 172 (8), 161 (14), 144 (38), 131 (22), 117 (82), 103 (24), 89 (84), 77 (100), 63 (56), 50 (24); HRMS (EI) calcd for $C_{10}H_7NO_3$ (M^+) 189.04260. Found 189.04162.

4.3.8. 3-(1-Propyn-1-yl)benzonitrile. For entry 8: 63% (31.4 mg) as a colorless oil obtained from 3-iodobenzonitrile (57.3 mg, 250 μmol) at 70 °C.

^{1}H NMR δ 7.65 (s, 1H), 7.58 (dd, 1H, *J*=7.8, 1.3 Hz), 7.53 (dd, 1H, *J*=7.8, 1.3 Hz), 7.38 (t, 1H, *J*=7.8 Hz), 2.06 (s, 3H); ^{13}C NMR δ 135.7, 134.9, 130.8, 129.1, 125.7, 118.3, 112.7, 88.9; MS (EI) *m*/*z* (%) 141 (M^+, 92), 140 (100), 114 (36), 88 (6), 63 (8), 44 (8); HRMS (EI) calcd for $C_{10}H_7N$ (M^+) 141.05785. Found 141.05730.

4.3.9. 3-(2-Furanyl)benzonitrile[33]. For entry 9: 74% (31.3 mg) as a yellow oil obtained from 3-iodobenzonitrile (57.3 mg, 250 μmol) at 120 °C.

^{1}H NMR δ 7.93 (s, 1H), 7.86 (dt, 1H, *J*=7.6, 1.7 Hz), 7.53–7.45 (m, 3H), 6.74 (d, 1H, *J*=3.4 Hz), 6.51 (dd, 1H, *J*=3.4, 2.0 Hz); ^{13}C NMR δ 151.5, 143.1, 131.9, 130.3, 129.5, 127.6, 127.1, 118.6, 112.9, 112.0,

106.8; MS (EI) *m*/*z* (%) 169 (M^+, 100), 140 (70), 130 (8), 114 (20), 102 (8), 75 (6), 63 (8), 51 (6); HRMS (EI) calcd for $C_{11}H_7NO$ (M^+) 169.05277. Found 169.05213.

4.3.10. 3-(2-Thienyl)benzonitrile[34]. For entry 10: 67% (31.0 mg) as a colorless solid obtained from 3-iodobenzonitrile (57.3 mg, 250 μmol) at 120 °C.

^{1}H NMR δ 7.87 (t, 1H, *J*=1.5, 1.5 Hz), 7.81 (dt, 1H, *J*=7.8, 1.5, 1.2 Hz), 7.55 (dt, 1H, *J*=7.8, 1.5, 1.2 Hz), 7.48 (t, 1H, *J*=7.8, 7.8 Hz), 7.36 (dd, 1H, *J*=4.9, 1.2 Hz), 7.36 (dd, 1H, *J*=3.7, 1.2 Hz), 7.12 (dd, 1H, *J*=4.9, 3.7 Hz); ^{13}C NMR δ 141.6, 135.7, 130.6, 130.0, 129.8, 129.2, 129.2, 128.4, 126.4, 124.5, 118.6, 113.2; MS (EI) *m*/*z* (%) 185 (M^+, 100), 140 (12), 58 (4); HRMS (EI) calcd for $C_{10}H_7N$ (M^+) 185.02992. Found 185.03034.

4.3.11. 2-(4-Methoxyphenyl)furan[30]. For entry 11: 96% (42.0 mg) as a yellow solid obtained from 4-iodoanisole (58.5 mg, 250 μmol) at 140 °C.

^{1}H NMR δ 7.60 (d, 2H, *J*=9.0 Hz), 7.42 (d, 1H, *J*=1.8 Hz), 6.92 (d, 2H, *J*=9.0 Hz), 6.51 (d, 1H, *J*=3.2 Hz), 6.44 (dd, 1H, *J*=3.2, 1.8 Hz), 3.83 (s, 3H); ^{13}C NMR δ 159.8, 154.9, 142.2, 126.0, 124.9, 114.9, 112.3, 104.2, 56.1; MS (EI) *m*/*z* (%) 174 (M^+, 100), 159 (68), 131 (30), 115 (8), 102 (16), 77 (20), 57 (8), 43 (8); HRMS (EI) calcd for $C_{10}H_7NO_3$ (M^+) 174.06808. Found 174.06745.

4.4. Typical procedure for the cross-coupling reaction using between heteroaryl halide and heteroaryltributyltin (Table 5)

A mixture of LiF (13.0 mg, 500 μmol), the aryl halide (250 μmol), tributyl organotin compound (375 μmol), and 10% Pd/C (13.3 mg, 12.5 μmol) in NMP (1 mL) in a test tube was stirred at the given temperature for 24 h. To the mixture at room temperature was added saturated aqueous KF solution (10 mL), and the mixture was stirred overnight, diluted with H_2O (20 mL) and EtOAc (20 mL), and passed through a Celite pad. The filtrate was separated into two layers and the aqueous layer was extracted with EtOAc (2×10 mL). The combined organic layers were washed with another saturated KF solution (2×10 mL), dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (*n*-hexane/EtOAc, 80:1) or preparative TLC on silica gel (*n*-hexane/EtOAc, 100:1) to give the corresponding heterobiaryl.

4.4.1. 2-Furan-2-ylpyridine[30]. For entry 1: 62% (25.2 mg) as a colorless oil obtained from 2-iodopyridine (26.6 μL, 250 μmol) at 120 °C.

For entry 3: 50% (18.2 mg) as a colorless oil obtained from 2-bromopyridine (23.9 μL, 250 μmol) at 140 °C.

^{1}H NMR δ 8.60 (d, 2H, *J*=4.8 Hz), 7.73–7.64 (m, 2H), 7.54 (m, 1H), 7.15 (m, 1H), 7.06 (d, 1H, *J*=3.4 Hz), 6.54 (m, 1H); ^{13}C NMR δ 153.7, 149.6, 149.5, 143.3, 136.7, 121.9, 118.6, 112.1, 108.6; MS (EI) *m*/*z* (%) 145 (100), 117 (48), 89 (32), 78 (20), 63 (30), 51 (24); HRMS (EI) calcd for C_9H_7NO (M^+) 145.05277. Found 145.05347.

4.4.2. 3-Furan-2-ylpryidine[35]. For entry 2: 60% (21.8 mg) as a colorless oil obtained from 3-iodopyridine (51.3 mg, 250 μmol) at 140 °C.

For entry 5: 50% (18.2 mg) as a colorless oil obtained from 3-bromopyridine (24.1 μL, 250 μmol) at 140 °C.

^{1}H NMR δ 8.94 (d, 1H, *J*=1.5 Hz), 8.50 (dd, 1H, *J*=4.9, 1.5 Hz), 7.95 (ddd, 1H, *J*=8.0, 2.2, 1.9 Hz), 7.53 (d, 1H, *J*=1.9, 0.7 Hz), 7.31 (ddd, 1H, *J*=8.0, 4.9, 0.8 Hz), 6.76 (dd, *J*=3.4, 0.7 Hz), 6.52–6.50 (m, 1H); ^{13}C NMR δ 147.9, 145.2, 143.1, 130.9, 127.0, 123.6, 111.8, 106.5; MS (EI) *m*/*z* (%) 145 (100), 116 (50), 89 (44), 63 (60), 50 (20); HRMS (EI) calcd for C_9H_7NO (M^+) 145.05277. Found 145.05306.

4.4.3. 2-(2-Thienyl)pyridine[36]. For entry 3: 50% (17.3 mg) as a colorless solid obtained from 2-bromopyridine (23.9 μL, 250 μmol) at 140 °C.

^{1}H NMR δ 8.58 (dt, 1H, *J*=4.5, 1.3 Hz), 7.68–7.62 (m, 2H), 7.58 (dd, 1H, *J*=3.8, 1.2 Hz), 2.08 (s, 3H), 7.39 (dd, 1H, *J*=5.0, 1.2 Hz), 7.16–7.10 (m, 2H); ^{13}C NMR δ 125.6, 149.5, 144.8, 136.6, 128.0, 127.5, 124.5, 121.9, 118.8.

4.5. Five mmol-scale synthesis of ethyl biphenyl-4-carboxylate

A mixture of LiCl (424 mg, 10 mmol), ethyl 4-bromobenzoate (816 μL, 5 mmol), tetraphenyltin (2.14 g, 5 mmol), and 10% Pd/C (266 mg, 250 μmol) in NMP (20 mL) in a 200 mL-flask was stirred at 90 °C for 24 h. To the mixture at room temperature was added a saturated aqueous KF solution (10 mL), and the mixture was stirred overnight, diluted with H_2O (20 mL) and EtOAc (20 mL), and passed through a Celite pad. The filtrate was separated into two layers, and the aqueous layer was extracted with EtOAc (2×10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (*n*-hexane/EtOAc, 100:1→50:1) to give ethyl biphenyl-4-carboxylate (939 mg, 83%).

4.6. Procedure for the detection of the leached palladium in the reaction media (Scheme 1)

A mixture of LiCl (424 mg, 10 mmol), ethyl 4-bromobenzoate (816 μL, 5 mmol), tetraphenyltin (2.14 g, 5 mmol), and 10% Pd/C (266 mg, 250 μmol) in NMP (20 mL) in a 200 mL-flask was stirred at 90 °C for 24 h. To the mixture at room temperature was added a saturated aqueous KF solution (10 mL), and the mixture was stirred overnight, diluted with H_2O (20 mL) and EtOAc (20 mL), and passed through a Celite pad. The filtrate was separated into two layers, and the aqueous layer was extracted with EtOAc (2×10 mL). The organic layer was filtrated through two membrane filters (Millipore Corporation, Billerica, MA, USA; Millex-LH, 0.45 μm and 0.25 μm). The filtrate was diluted with EtOAc to 50 mL of total volume, and the residual palladium was assayed using a Varian 730-ES (Varian Inc. Corp., Palo Alto, CA, USA) by the inductively coupled plasma-optical emission spectroscopy.

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Supplementary data

Electronic Supplementary data available: ^{1}H and ^{13}C NMR spectra of new compounds. Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2010.09.027. These data include MOL files and InChIKeys of the most important compounds described in this article.

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