

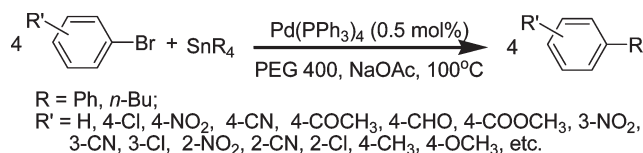
Pd(PPh₃)₄-PEG 400 Catalyzed Protocol for the Atom-Efficient Stille Cross-Coupling Reaction of Organotin with Aryl Bromides

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Aryl bromides (4 equiv) were coupled efficiently with organotin (1 equiv) in an atom-efficient way using the tetra(triphenylphosphine)palladium/polyethylene glycol 400 (Pd(PPh₃)₄/PEG 400) catalytic system in the presence of sodium acetate (NaOAc) as base at 100 °C, providing excellent yields of the corresponding functionalized biaryls in short reaction times.

The cross-coupling reactions of organometallic reagents with electrophilic reagents are an important route for carbon–carbon bond formation.¹ The Stille reaction, known as palladium-catalyzed cross-coupling of organostannanes with organic halides and triflates, has proven to be one of the most important, powerful, and versatile tools for the formation of carbon–carbon bonds.² This coupling reaction has been widely applied in organic synthesis,³ especially in the synthesis of biaryls compounds, which

are important structural substructures in numerous natural products, polymers, agrochemicals, and pharmaceutical mediators.⁴ During the past decades, numerous efforts have been made to develop an efficient catalyst protocol for Stille cross-coupling reactions.⁵ However, most of these reactions were carried out in organic solvents under inert and anhydrous conditions due to the instability of most catalysts and coupling reagents.

The advantage of tetraphenyltin is that it can react with 4 equiv of electrophilic reagents.⁶ Despite this obvious advantage, only a few reactions involving tetraphenyltin for C–C bond formation have been reported.^{7–9} Furthermore, almost all of these reactions suffer from drawbacks such as atom inefficiency, long reaction times, and harsh reaction conditions. In our recent investigations, luckily, we found that tetraphenyltin can react with 4 equiv of aryl bromides in the Stille cross-coupling reaction, which has attracted our attention as a viable atom-efficient organometallic coupling partner for C–C bond formations. Hence, to expand the scope and reactivity of tetraphenyltin, the development of new and efficient catalytic protocols is in demand.

As environmentally friendly “green” synthesis is becoming more and more important, it is desirable to avoid any use of hazardous and expensive organic solvents. To satisfy these concerns, polyethylene glycol (PEG) represents a very attractive medium for organic reactions.¹⁰ PEG as an environmentally benign protocol proved to have many applications, particularly in coupling,¹¹ oxidation,¹² substitution,¹³

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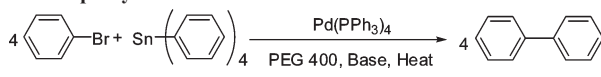
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TABLE 1. Optimized Conditions via the Coupling of Bromobenzene with Tetraphenyltin^a


entry	base (mmol)	T (°C)	time (h)	yield ^b (%)
1	K ₂ CO ₃ (3.0)	100	1	56
2	Na ₂ CO ₃ (3.0)	100	1	52
3	K ₃ PO ₄ (3.0)	100	1	66
4	KF/Al ₂ O ₃ (3.0)	100	1	66
5	NaHCO ₃ (3.0)	100	1	72
6	KF (3.0)	100	1	70
7	KOH (3.0)	100	1	83
8	NaOH (3.0)	100	1	78
9	Et ₃ N (3.0)	100	1	20
10	NaOAc (3.0)	100	1	97
11	NaOAc (4.0)	100	1	96
12	NaOAc (3.5)	100	1	95
13	NaOAc (2.5)	100	1	95
14	NaOAc (2.0)	100	1	90
15	NaOAc (3.0)	80	1	89
16	NaOAc (3.0)	90	1	93
17	NaOAc (3.0)	95	1	96
18	NaOAc (3.0)	105	1	92
19	NaOAc (3.0)	110	1	91
20	NaOAc (3.0)	120	1	92
21	NaOAc (3.0)	100	0.5	97 ^c

^aReaction conditions: bromobenzene (1.0 mmol), Ph₄Sn (0.28 mmol), PEG 400 (3 mL), base, Pd(PPh₃)₄ (0.005 mmol), stirring for at an appropriate temperature. ^bIsolated yield based on bromobenzene. ^c0.01 mmol Pd(PPh₃)₄ was used.

addition,¹⁴ and reduction reactions¹⁵ and so on.¹⁶ To the best of our knowledge, the atom-efficient Stille cross-coupling reaction catalyzed by palladium catalyst in PEG 400 has not been reported thus far. In continuation of our interest on the transition-metal-catalyzed organic transformations,¹⁷ we now report a new and novel palladium-catalyzed protocol for the atom-efficient cross-coupling of tetraphenyltin with aryl bromides in PEG-400.

In order to explore an atom-economic reaction in PEG-400, we screened the Stille cross-coupling reaction of bromobenzene as a representative example reacting with tetraphenyltin using Pd(PPh₃)₄ catalyst by optimizing the conditions in terms of bases, reaction time, and temperatures. As shown in Table 1, it was found that K₂CO₃, Na₂CO₃, K₃PO₄, and KF/Al₂O₃ (mol ratio of 1:1) were ineffective in providing the desired coupled product (Table 1, entries 1–4). A comparative reactivity study of bases in the reaction showed that NaHCO₃, KF, KOH, and NaOH proved to be more effective for this coupling (Table 1, entries 5–8). When Et₃N was used as base, 20% of biphenyl was obtained (Table 1, entry 9). The reaction carried out in the

presence of different bases in PEG-400 revealed that NaOAc as a suitable base provided the highest yield (Table 1, entry 10). Further study with varying NaOAc equivalents revealed that 3.0 equiv of base is necessary to obtain a high yield of the coupled product (Table 1, entries 11–14). Finally, the effect of temperature was also evaluated, and the results indicated that 100 °C was the appropriate temperature for the atom-efficient Stille cross-coupling reaction (Table 1, entries 10, 15–20). It is interesting to note that the reaction can be carried out efficiently under higher Pd loading in a short reaction time (entry 21).

Strikingly, the Stille reaction carried out in the presence of NaOAc in PEG-400 with Pd(PPh₃)₄ catalyst at 100 °C provided the highest conversion (Table 1, entry 10). Furthermore, the atom-efficient reaction of tetraphenyltin in which all four phenyls were efficiently coupled with 4 equiv of their electrophilic coupling partner was thoroughly established.

Thus, we investigated the Stille cross-coupling reaction of tetraphenyltin with a variety of electronically diverse aryl bromides (Table 2). The reactivity and substrate scope provided by the aryl bromides under the present conditions are excellent, giving good to high yields of the cross-coupled products, and biphenyl was obtained as byproduct. As shown in Table 2, all of the reactions of electron-withdrawing aryl bromides occurred efficiently with tetraphenyltin (Table 2, entries 1–17). We can discern that chloro, nitro, cyano, and acetyl substituents at the *meta* or *para* positions of the aromatic ring did not exert a strong influence upon the Stille cross-coupling reaction (Table 2, entries 2, 3, 5, 6, 8, 9, 11, 12, and 14–17), except for the *ortho* position of the aromatic ring, which gave the product of in lower yield (Table 2, entries 4, 7, 10, and 13). Furthermore, 1-bromonaphthalene and 2-bromonaphthalene were remarkable, furnishing the corresponding coupling products in excellent yields (Table 2, entries 18 and 19). Amazingly, heterocyclic bromides also provided the cross-coupling products in high yields, except for 3-bromopyridine where a moderate yield was observed (Table 2, entries 20–23). A possible problem for 3-bromopyridine is that the pyridine nitrogen coordinates to Pd strongly and slows the turnovers. Further study revealed that the Stille cross-coupling reactions of electron-rich functional groups such as methyl and methoxy groups in aryl bromides at the *para* position furnished moderate yields of the desired products of 48% and 50% (Table 2, entries 24 and 25), respectively.

We next examined the Stille cross-coupling reaction of tetra-*n*-butyltin with electronically diverse aryl bromides; the results are summarized in Table 3. We find out that carboxaldehyde, acetyl, nitro, and cyano substituents at the *para* position of the aromatic ring give the desired products in moderate yields (Table 3, entries 1–4). When 3-bromobenzonitrile was used, a lower yield was obtained even after prolonged reaction times (Table 3, entry 5).

To evaluate the activity of the Pd catalyst, we also investigated the influence of simple catalyst on the representative reaction under the applied conditions (Table 1, entry 10), and the results are summarized in Table 3. It can be gathered that Ni and Co pieces were not efficient for the cross-coupling reaction even after a prolonged stirring time (Table 3, entries 1–3). Both reactions catalyzed by PdCl₂ and Pd/C provided moderate yields of biphenyl

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TABLE 2. Pd-Catalyzed Cross Coupling of Aryl Bromides (1) with Tetraphenyltin (2)^a

Entry	R	Products	Time [h]	Yield [%] ^b 3(4)	Entry	R	Products	Time [h]	Yield [%] ^b 3(4)
1	H		0.5	97	13	2-NO ₂		2	90(5)
2	4-Cl		0.5	96	14	4-F		1	76(12)
3	3-Cl		1	94	15	4-CHO		1	94
4	2-Cl		2	91(6)	16	4-CO ₂ CH ₃		1	88(10)
5	4-CN		0.5	93(3)	17	4-CO ₂ C ₂ H ₅		2	90(6)
6	3-CN		1	92(5)	18			0.5	91(2)
7	2-CN		2	90(8)	19			0.5	90(2)
8	4-COCH ₃		0.5	91	20			1	76(15)
9	3-COCH ₃		1	90(5)	21			1	77(12)
10	2-COCH ₃		2	89(9)	22			1	93(1)
11	4-NO ₂		0.5	95	23	3-Py		3	58(12)
12	3-NO ₂		1	94(3)	24	4-OCH ₃		5	48(43)
					25	4-CH ₃		5	50(38)

^aReaction conditions: **1** (1.0 mmol), **2** (0.28 mmol), PEG 400 (3 mL), NaOAc (3.0 mmol), Pd(PPh₃)₄ (0.005 mmol), stirring at 100 °C for an appropriate time.

TABLE 3. Pd-Catalyzed Cross Coupling of Aryl Bromides with Tetra-*n*-butyltin^a

Entry	R	Products	Time [h]	Yield [%] ^b
1	4-CHO		3	66
2	4-COCH ₃		3	62
3	4-NO ₂		3	58
4	4-CN		3	61
5	3-CN		8	42

^aReaction conditions: aryl bromides (1.0 mmol), tetra-*n*-butyltin (0.30 mmol), PEG 400 (3 mL), NaOAc (3.0 mmol), Pd(PPh₃)₄ (0.01 mmol), stirring at 100 °C for an appropriate time.

(Table 4, entries 4 and 5). When PdCl₂(PPh₃)₂ was used, the cross-coupling reaction proceeded smoothly, and satisfactory yields were obtained (Table 4, entry 6). It can be seen that Pd(PPh₃)₄ was the most effective catalyst for the atom-efficient Stille cross-coupling reaction (Table 4, entry 7). The control reaction carried out without catalyst delivered no cross-coupling product, indicating that the catalyst is necessary to the cross-coupling reaction (Table 4, entry 8).

To conclude, in the present study we reported a palladium-catalyzed protocol for the Stille cross-coupling reaction of organotin with aryl bromides using the catalytic system employs Pd(PPh₃)₄ along with NaOAc as base in PEG-400 media. It is noteworthy that the present protocol is highly efficient as 4 equiv of aryl bromides reacted with 1 equiv of tetraphenyltin cleanly to provide high yield of the cross-coupling products in short reaction time. This process has significant features: (i) atom-efficient coupling under mild conditions in environmentally friendly media in air,

TABLE 4. Comparative Experiments with Simple Catalysts on the Representative Reaction^a

entry	catalyst	time (h)	yield ^b (%)
1	Nano Ni	24	0
2	Ni(PPh ₃) ₂ Cl ₂	24	0
3	Co(PPh ₃) ₃ Cl	24	0
4	PdCl ₂	2	63
5	Pd/C	2	44
6	Pd(PPh ₃) ₂ Cl ₂	1	94
7	Pd(PPh ₃) ₄	1	98
8	none	24	0

^aReaction conditions: bromobenzene (1.0 mmol), Ph₄Sn (0.28 mmol), PEG 400 (3 mL), NaOAc (3.0 mmol), catalyst (0.01 mmol), stirring at 100 °C for an appropriate time. ^bIsolated yield based on bromobenzene.

(ii) short reaction time, (iii) easy isolation of the product, and (iv) broad substrate scopes. Further research is in progress in our laboratory to utilize these catalytic systems in wide synthetic applications.

Experimental Section

Typical Procedure for the Stille Cross-Coupling Reactions.

A glass flask was charged with aryl bromides (1.0 mmol)

followed by tetraphenyltin (0.28 mmol) or tetra-*n*-butyltin (0.30 mmol), NaOAc (3.0 mmol), Pd (PPh₃)₄ (0.005 mmol), and PEG 400 (3 mL). Then the mixture was stirred at 100 °C for an appropriate time. After being cooled to room temperature, the mixture was directly extracted with diethyl ether (5 × 10 mL). The upper layers were decanted, combined, and washed with water and brine. PEG 400 was recovered by a short flash column chromatography and reused several times. The organic phase was then dried over anhydrous MgSO₄ and concentrated under vacuo, and the crude product was purified by flash column chromatography to provide the corresponding product.

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Supporting Information Available: Experimental details, characterization data, ¹H NMR and ¹³C NMR spectra for all compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.