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# Atom-Efficient, Palladium-Catalyzed Stille Coupling Reactions of Tetraphenylstannane with Aryl Iodides or Aryl Bromides in Polyethylene Glycol 400 (PEG-400)

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**Abstract:** The Stille coupling of tetraphenylstannane with aryl iodides or aryl bromides using the bis(triphenylphosphine)palladium dichloride/sodium acetate/polyethylene glycol 400 [$PdCl_2(PPh_3)_2$/NaOAc/PEG-400] catalytic system at 100 °C has been developed. The reactions were carried out in an atom-efficient way, as 4 equivalents of aryl iodides or aryl bromides coupled effectively with 1 equivalent of tetraphenylstannane to furnish 4 equivalents of the corresponding functionalized biaryls in high yields.

**Keywords:** aryl bromides; aryl iodides; atom efficiency; polyethylene glycol 400 (PEG-400); Stille coupling; tetraphenylstannane

## Introduction

The palladium-catalyzed cross-coupling of organostannanes with organic halides and triflates, known as Stille reaction, is an important, powerful, and versatile tool for the formation of carbon-carbon bonds.[1] This coupling reaction has been widely applied in organic synthesis[2] since a variety of functionalities can be tolerated in either partner. The yields of coupled products are often high, and the organotin reagents can be readily synthesized, purified, and stored. The importance of this method led to the development of numerous new catalytic protocols.[3] However, most of these reactions are carried out in organic solvents associated with the protection of a nitrogen atmosphere to improve the yields. In addition, the lack of atom efficiency is another drawback of these methods.

Since tetraphenylstannane is known to be an important organometallic reagent, it is a potentially useful candidate for Stille cross-coupling reactions. Up to the present, a few reactions involving tetraphenylstannane for C−C bond formation have been reported.[4–6] Furthermore, the known reactions of tetraphenylstannane with electrophilic reagents always suffer from disadvantages such as atom inefficiency, long reaction times, and harsh reaction conditions. Thus, the development of atom-efficient organometallic reagents to react with more than 1 equivalent of the electrophilic coupling reagents in order to reduce the organometallic loadings for industrial scale preparations is needed.[7] In the course of our continuing investigations, we found that tetraphenylstannane, unlike with other organotin reagents, can react with 4 equivalents of electrophilic reagents, which has attracted our attention as a viable atom-efficient organometallic coupling partner for C−C bond formation. Hence, to expand the scope and reactivity of tetraphenylstannane, the development of new and efficient catalytic protocols is in demand.

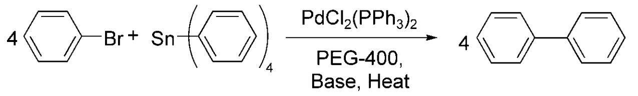
Recently, polyethylene glycol (PEG) was found to be an interesting solvent system.[8] PEG as an environmentally benign protocol proved to have many particular applications, such as in coupling,[9] substitution,[10] oxidation,[11] addition,[12] and reduction reactions.[13] To the best of our knowledge, the palladium-catalyzed atom-efficienct Stille cross-coupling reaction of tetraphenylstannane in PEG-400 has not so far been reported. In our search for developing new processes for cross-coupling reactions,[14] in this paper, we wish to report a highly efficient palladium-catalyzed protocol for an atom-efficient coupling of tetraphenylstannane with aryl iodides or aryl bromides in PEG-400. The methodology reported here has the following advantages: atom economy, short reaction time, and broad substrate scope.

## Results and Discussion

As a starting point for the development of the atom-economic reaction in PEG-400, we initially studied the Stille coupling of bromobenzene with tetraphenylstannane for optimizing the reaction conditions, and the effects of base, reaction time, temperature on the yield of the coupling reaction are summarized in Table 1.

It was found that bases such as $K_2CO_3$, $Na_2CO_3$, NaOH, and KOH were ineffective in providing the corresponding cross-coupling product (Table 1, entries 1–4). However, an increase in the cross-coupling reactivity was observed with $NaHCO_3$ or $KF/Al_2O_3$ (mol ratio of 1:1) under similar conditions (Table 1, entries 5 and 6). A comparative reactivity study of bases in the reaction showed that KF or $K_3PO_4$ proved to be more effective for this coupling (Table 1, entries 7 and 8). As shown in Table 1, the reactions carried out in the presence of different bases in PEG-400 revealed NaOAc as a suitable base giving a 94% cross-coupling yield (Table 1, entry 9) and 3.5 equivalents of base are necessary to obtain a high yield of the cross-coupling product (Table 1, entries 11–14). Furthermore, lowering or elevating the reaction temperature had no positive effect, and 100 °C is the best temperature for the Stille cross-coupling reaction (Table 1, entries 15–21). Control reactions carried out without base delivered only 38% cross-coupling conversion indicating that the role of the base is to activate tetraphenylstannane for the cross-coupling reaction (Table 1, entry 22). From this study, it was clear that NaOAc (3.5 equiv.) in PEG-400 with $PdCl_2(PPh_3)_2$ (0.01 equiv.) at 100 °C are the optimized conditions for high cross-coupling conversion.

**Table 1.** Optimized conditions for the coupling of bromobenzene with $Ph_4Sn$.[a]



| Entry | Base (mmol) | $T$ [°C] | $t$ [h] | Yield [%][b] |
|---|---|---|---|---|
| 1 | $K_2CO_3$ (3.5) | 100 | 1 | 45 |
| 2 | $Na_2CO_3$ (3.5) | 100 | 1 | 36 |
| 3 | KOH (3.5) | 100 | 1 | 40 |
| 4 | NaOH (3.5) | 100 | 1 | 32 |
| 5 | $NaHCO_3$ (3.5) | 100 | 1 | 63 |
| 6 | $KF/Al_2O_3$ (3.5) | 100 | 1 | 56 |
| 7 | KF (3.5) | 100 | 1 | 72 |
| 8 | $K_3PO_4$ (3.5) | 100 | 1 | 79 |
| 9 | NaOAc (3.5) | 100 | 1 | 94 |
| 10 | $Et_3N$ (3.5) | 100 | 1 | 10 |
| 11 | NaOAc (4.0) | 100 | 1 | 90 |
| 12 | NaOAc (3.0) | 100 | 1 | 91 |
| 13 | NaOAc (2.5) | 100 | 1 | 90 |
| 14 | NaOAc (2.0) | 100 | 1 | 83 |
| 15 | NaOAc (3.5) | 80 | 1 | 85 |
| 16 | NaOAc (3.5) | 90 | 1 | 90 |
| 17 | NaOAc (3.5) | 95 | 1 | 92 |
| 18 | NaOAc (3.5) | 105 | 1 | 92 |
| 19 | NaOAc (3.5) | 110 | 1 | 88 |
| 20 | NaOAc (3.5) | 115 | 1 | 89 |
| 21 | NaOAc (3.5) | 120 | 1 | 89 |
| 22 | none | 100 | 24 | 38[c] |

[a] *Reaction conditions:* bromobenzene (1.0 mmol), $Ph_4Sn$ (0.28 mmol), PEG-400 (3 mL), base, $PdCl_2(PPh_3)_2$ (0.01 mmol), stirring for the appropriate temperature.

[b] Isolated yield based on bromobenzene.

[c] Homocoupling product was obtained.

In previous reports on the coupling reaction of aryl halides with tetraphenylstannane,[4–6] usually only one or two phenyl groups could be transferred. In order to explore the possibility for further efficient transfer of the phenyl groups in tetraphenylstannane, we examined the reaction of bromobenzene with 0.25, 0.28 or 0.33 equiv. of tetraphenylstannane again under the optimized conditions. As summarized in Table 2, either increasing the reaction temperature or prolonging the reaction time could not promote the reaction when 0.25 equiv. of tetraphenylstannane was used, and we only detected a trace of bromobenzene by TLC (Table 2, entries 1 and 2). A satisfactory result could be achieved when the reaction was performed at 100 °C for 1 h with 0.28 equiv. of tetraphenylstannane (Table 2, entries 3 and 4). There is no significant difference in yield when 0.33 equiv. of tetraphenylstannane were reacted with bromobenzene (Table 2, entry 5). These results indicate that all four phenyl groups of tetraphenylstannane could be efficiently utilized in the Stille cross-coupling reactions.

Subsequently, we investigated the cross-coupling reaction of various aryl bromides with tetraphenylstannane, and the results are given in Table 3.

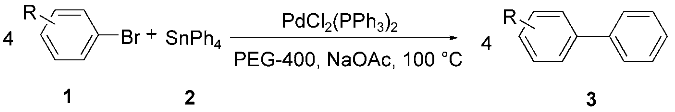
**Table 2.** Reaction of bromobenzene with $Ph_4Sn$.[a]

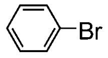
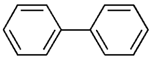
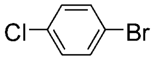
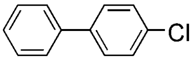
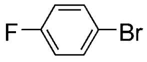
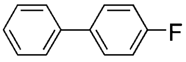
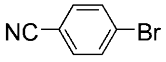
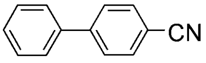
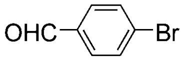
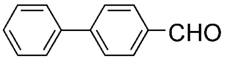
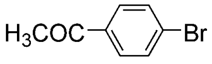
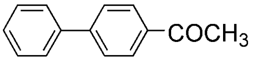
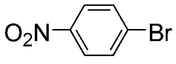
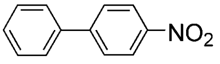
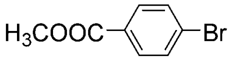
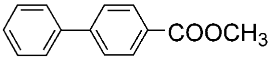
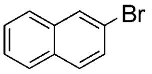
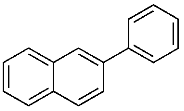
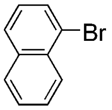
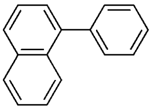
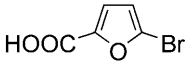
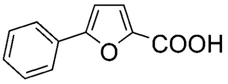
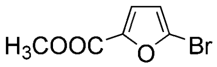
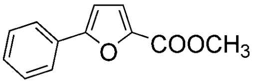
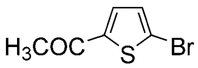
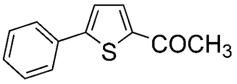
| Entry | Amount of $Ph_4Sn$ [equiv. to bromobenzene] | $T$ [°C] | $t$ [h] | Yield [%][b] |
|---|---|---|---|---|
| 1 | 0.25 | 120 | 1 | 87 |
| 2 | 0.25 | 100 | 6 | 88 |
| 3 | 0.28 | 100 | 0.5 | 86 |
| 4 | 0.28 | 100 | 1 | 94 |
| 5 | 0.33 | 100 | 1 | 94 |

[a] Reactions were carried out using bromobenzene (1.0 mmol), $Ph_4Sn$ as indicated in the table, NaOAc (3.5 mmol), and $Pd(PPh_3)_2Cl_2$ (0.01 mmol) in PEG-400 (3 mL), stirring at the appropriate temperature for the indicated time.

[b] Isolated yield based on bromobenzene.

**Table 3.** Pd(II)-catalyzed cross coupling of aryl bromides (**1**) with $Ph_4Sn$ (**2**).[a]



| Entry | Ar-Br | Products[b] | *t* [h] | Yield [%][c] |
|---|---|---|---|---|
| 1 |  |  | 1 | 94 |
| 2 |  |  | 1 | 95 |
| 3 |  |  | 1 | 85 |
| 4 |  |  | 1 | 93 |
| 5 |  |  | 1 | 93 |
| 6 |  |  | 1 | 94 |
| 7 |  |  | 1 | 95 |
| 8 |  |  | 3 | 75 |
| 9 |  |  | 1 | 90 |
| 10 |  |  | 1 | 93 |
| 11 |  |  | 1 | 88 |
| 12 |  |  | 1 | 75 |
| 13 |  |  | 1 | 92 |

[a] *Reaction conditions:* **1** (1.0 mmol), **2** (0.28 mmol), PEG-400 (3 mL), NaOAc (3.5 mmol), $Pd(PPh_3)_2Cl_2$ (0.01 mmol), stirring at 100 °C for the appropriate time.

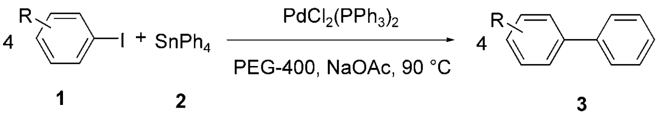
[b] All products were characterized by melting point, IR, $^1H$ NMR and MS.

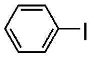
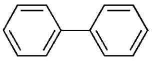
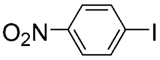
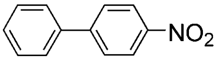
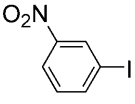
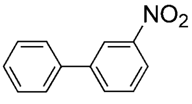
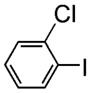
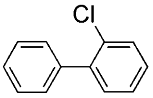
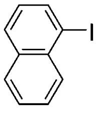
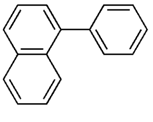
[c] The yields are based on **1**.

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. As shown in Table 3, the cross-coupling reaction of various functionalized aryl bromides occurred efficiently with tetraphenylstannane. For example, the reaction of a variety of functionalized electron-poor aryl bromides reacted very well with tetraphenylstannane leading to good to high yields of the functionalized biaryls (Table 2, entries 2–8). Further, bromobenzene, 1-bromonaphthalene and 2-bromonaphthalene were remarkable, furnishing the corresponding coupling products in excellent yields (Table 2, entries 1, 9 and 10). Similarly, the reactivity of heterocyclic bromides also provided the cross coupling products in high yields (Table 2, entries 11–13). Further study revealed that cross-coupling reactions of electron-rich functional groups such as methyl, methoxyl, ethoxyl, amino, and acetamido groups in aryl bromides at the *para*-position furnished moderate yields of cross-coupled biphenyls: 48%, 45%, 41%, 45% and 39%, respectively. Notably, the aryl bromides with electron-withdrawing groups studied showed good to high cross-coupling reactivity with tetraphenylstannane. On the other hand, electron-rich substrates, which are otherwise known to show poor reactivity in this type of reaction showed moderate reactivity.

The reactions of substituted aryl iodides with tetraphenylstannane were found to be faster and efficient in furnishing good to high yields of the cross-coupled biphenyls in a short period of 0.5 h. The cross-coupling reactivity with aryl iodides was found to be efficient even with a lower temperature when compared to the corresponding reactivity with aryl bromides. As shown in Table 4, the reactions of electron-deficient aryl iodides afforded high yields of cross-coupling products (Table 4, entries 1–4). The reaction of 1-iodonaphthalene gave 93% of the corresponding coupled product (Table 4, entry 5). The reactions of electron-rich substituted phenyl iodides, such as *p*-methoxy- and *m*-methylphenyl iodides, furnished 49% or 50% yields of the products.

**Table 4.** Pd(II)-catalyzed cross coupling of aryl iodides (**1**) with $Ph_4Sn$ (**2**).[a]



| Entry | Ar-I | Products[b] | *t* [h] | Yield [%][c] |
|---|---|---|---|---|
| 1 |  |  | 0.5 | 98 |
| 2 |  |  | 0.5 | 96 |
| 3 |  |  | 0.5 | 95 |
| 4 |  |  | 1 | 90 |
| 5 |  |  | 0.5 | 93 |

[a] *Reaction conditions:* **1** (1.0 mmol), **2** (0.25 mmol), PEG 400 (3 mL), NaOAc (3.5 mmol), $Pd(PPh_3)_2Cl_2$ (0.01 mmol), stirring at 90 °C for the appropriate time.

[b] All products were characterized by melting point, IR, $^1$HNMR and MS.

[c] The yields are based on **1**.

## Conclusions

In conclusion, we have disclosed a palladium-catalyzed protocol for the Stille cross-coupling reaction of tetraphenylstannane with aryl iodides or aryl bromides using a catalytic system that employs $PdCl_2(PPh_3)_2$ along with NaOAc as base in PEG-400. The high atom-efficiency of tetraphenylstannane as demonstrated by reacting with 4 equivalents of electrophilic coupling partners further defines its breadth and versatility, which is not known with similar reagents. Thus, the present study and the established new palladium protocol is expected to exploit the advantages associated with tetraphenylstannane as an atom-efficient reagent for application in organic synthesis.

## Experimental Section

### General Procedure

A hot, oven-dried Schlenk tube was charged with aryl bromides (1.0 mmol) followed by tetraphenylstannane (0.28 mmol), NaOAc (3.5 mmol), $PdCl_2(PPh_3)_2$ (0.01 mmol), and PEG-400 (3 mL). Then the mixture was stirred at 100 °C for 1 h. After cooling to room temperature, the mixture was directly extracted four times with diethyl ether. The upper layers were decanted, combined, washed with water and brine, dried over anhydrous $MgSO_4$ and concentrated under vacuum. Silica gel column chromatography using ethyl acetate in petroleum ether as eleunt afforded the pure products.

## Acknowledgements

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