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## Optimized Stille Coupling Reactions Catalyzed by Palladium on Carbon with CuI as Cocatalyst

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**Summary:** The coupling reaction of aryl and vinyl iodides, bromides, and triflates with organostannanes can be effectively conducted using palladium on carbon as a source of  $Pa^0$ . The yield and rate of reaction are significantly affected by the addition of copper iodide as co-catalyst and triphenylarsine as ligand.

The palladium catalyzed cross-coupling reaction between aryl or vinyl halides and triflates with organostannanes, well known as the Stille reaction,<sup>1</sup> has developed in the past few years into an extremely popular synthetic tool for the construction of carbon-carbon bonds. Recent studies of the Stille cross-coupling process have led to two key improvements: the realization of a ligand effect<sup>2</sup> and significant co-catalysis by copper(I) salts.<sup>3</sup> Under certain conditions, copper iodide reacts with organostannanes to produce transient organocopper intermediates which are presumably more reactive than organostannanes towards transmetalation to palladium, a key step of the cross-coupling reaction. It stands to reason that, if intermediate organocopper species are generated from organostannanes and copper iodide, then copper iodide alone may be sufficient to induce a cross-coupling reaction.<sup>4</sup>

During studies of copper mediated cross-couplings,<sup>5</sup> inconsistent results with a 'copper only' protocol were obtained. The inconsistency was traced to the presence of minute amounts of metallic palladium on the porous surface of the teflon stirbar (deposited during a previous homogeneous reaction) which served to catalyze the reaction. Once the nature of the sporadic results was discovered, a more detailed examination of the use of inexpensive palladium on carbon as a heterogeneous catalyst for the Stille cross-coupling reaction was evaluated. A related study, describing the use of Pd/C as a catalyst for the coupling of aryl halides with phenylboronic acids was recently reported by Buchecker and coworkers.<sup>6</sup>

As a model reaction, the coupling of *p*-methoxyphenyl iodide (1) with 1.1 equivalents of tri-*n*-butylstannylbenzene (2) in the presence of 0.5 mole% of palladium on carbon produced a modest yield of the cross-coupling product and a significant amount of biphenyl (Eq. 1). The process using Pd/C alone was plagued by short catalyst activity (slow reaction after an initial burst), and incomplete conversion (< 50%).



An optimization of the model reaction was carried out using 1.1 equivalents of the organostannane for each experiment (Table 1). Addition of CuI as a cocatalyst significantly improved the heterogeneous coupling compared to the use of Pd/C alone, and subsequent addition of triphenylarsine further enhanced the rate and overall yield of coupling. In comparison, the corresponding homogeneous reaction using Pd<sub>2</sub>dba<sub>3</sub>, although faster, provided a slightly lower yield and a similar amount of homocoupled side product. The addition of triphenylphosphine was deleterious, essentially shutting down the coupling and providing biphenyl as the major product. These data are consistent with earlier studies which showed a facile transmetalation from phenyltri-nbutylstannane to CuI giving phenyl copper, which is probably a more reactive species towards transmetalation to palladium than the stannane.<sup>3</sup> In addition, it is suggested that the phenylcopper species is complexed with triphenylarsine (PhCu•Ph<sub>3</sub>As) and this may be more reactive than 'PhCu' alone in the heterogeneous transmetalation step. These data also agree with observations that transmetalation from tin to copper is blocked by addition of triphenylphosphine, but is not affected by triphenylarsine.<sup>3</sup>

Catalyst	t <sub>1/2</sub>	% Yield of <b>3</b> (48h)	% Biphenyl
Pd/C (0.5 mole%)	>24h	46	25
Pd/C (0.5%)/ 10% Cul	120 min	75	12
Pd/C (0.5%)/ 10% Cul/ 20% AsPh <sub>3</sub>	21 min	88	10
Pd <sub>2</sub> dba <sub>3</sub> (0.25%)/10% Cul/ 20% AsPh <sub>3</sub>	6 min	78	14
Pd/C (0.5%)/10% Cul/ 20% PPh <sub>3</sub>	N/A	<2	90

Table 1		Optimization	of the	Heterogeneous	Coupling of 1	and 2 to	Furnish 3	ł
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The examples collected in Table 2 demonstrate the generality of the Stille reaction under the optimized conditions using Pd/C as a heterogeneous catalyst.<sup>7</sup> The use of vinyl halides and triflates as well as aryl halides is well tolerated. Aryl fluorosulfonates and aryl triflates performed poorly under these conditions (20-30% conversion), due to competing triflate hydrolysis.

In summary, we have presented additional data demonstrating that the Stille reaction can be conducted in an apparent heterogeneous manner<sup>8</sup> using inexpensive palladium on carbon as catalyst. The protocol has been optimized by the addition of co-catalytic copper iodide and the ligand triphenylarsine to allow the reaction to occur at a reasonable rate with a variety of substrates.

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R-X +	R'SnBu <sub>3</sub> <sup>Pd/0</sup>	C, Cul, AsPh <sub>3</sub> R-R'		
Substrate	Stannane	Product	Rxn Time <sup>b</sup>	Yield <sup>c</sup>
0 <sub>2</sub> N	CH <sub>3</sub> S SnBu <sub>3</sub>	O <sub>2</sub> N CH <sub>3</sub>	24h	85% <sup>d</sup>
$\sqrt{s}$	€ SnBu <sub>3</sub>	S C	16h	77%
Me	∕∕ SnBu₃	Me	16h	79%
сн₃о	(95% trans)	CH <sub>3</sub> O (100% trans)	16h	82%
(85% trans)	SnBu <sub>3</sub> N BOC	BOC (3:1 trans/cis	12h )	86%
t-Bu	(95% trans)	t-Bu (100% trans)	16h	80%
	O SnBu₃ O Me		24h	67%
Me	SnBu₃	S G Me	24h	60%°

## Table 2. Examples of Stille Cross-Coupled Products using Pd/C-Cul as Catalyst<sup>a</sup>

a. All reactions were conducted using 0.5 mole % Pd (10% Pd/C), 10 mole% Cul, and 20 mole% AsPh<sub>3</sub>.

b. Most reactions were >1/2 complete after 40 min, but were allowed to run 16 or 24h for convenience.

c. Isolated yield of pure product.

d. 5 mole % Pd was used.

e. For a representative experimental procedure see reference 7.

## References

- 1. Stille, J. K. Angew. Chem. Int. Ed. Engl. 1986, 25, 508.
- 2. Farina, V.; Krishnan, B.; Marshall, D. R.; Roth, G. P. J. Org. Chem. 1993, 58, 5434.
- 3. Farina, V.; Kapadia, S.; Krishnan, B.; Wang, C.; Liebeskind, L.S. J. Org. Chem. 1994, 59, 5905 and references cited therein.
- 4. For an example of an intramolecular cross coupling of this type using excess (> 2 equiv.) copper chloride see: Piers, E.; Wong, T. J. Org. Chem. 1993, 58, 3609. For a review on the chemistry of organocopper compounds and similar species see: Lipshutz, B. H.; Sengupta, S. Organic Reactions 1992, 41, 135.
- 5. All CuI used in this report was purified according to the following procedure: Kauffman, G. B.; Teter, L. A. *Inorg. Syn.* **1963**, *7*, 9.
- Marck, G.; Villiger, A.; Buchecker, R. Tetrahedron Lett. 1994, 35, 3277. For the use of Pd black in the coupling of Grignard reagents see: Sekiya, A.; Ishikawa, N. J. Organomet. Chem. 1977, 125, 281. It is not unlikely that the so-called 'ligandless' protocol involves heterogeneous catalysis, given the short lifespan of Pd(0) without stabilizing ligands; see: Beletskaya, I. P. J. Organomet. Chem. 1983, 250, 551.
- 7. Typical experimental procedure: 2-(4-acetylphenyl)benzothiophene. A solution consisting of N-methyl-2-pyrrolidinone (5 mL), 4-iodoacetophenone (121 mg, 0.5 mmol), triphenylarsine (30 mg, 0.1 mmol), and CuI (10 mg, 0.05 mmol) was degassed by sparging with nitrogen. 2-Tri-n-butylstannylthiophene (310 mg, 0.7 mmol) was added by syringe and the reaction was placed in an oil bath set at 80 °C. Under positive nitrogen pressure, Pd/C (10%, 3 mg, 0.003 mmol) was added and the mixture was allowed to stir at 80 °C for 24 h. The reaction was cooled, treated with a saturated KF solution and allowed to stir for 30 min. The mixture was passed through a pad of Celite and rinsed with ether. The filtrate was washed with water, then dried (MgSO<sub>4</sub>) and concentrated to give a crude yellow solid. Chromatography (hexanes/ethyl acetate (10%), silica gel) furnished the desired product as white flakes (74 mg, 60%). m.p. 207-208 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.10-7.70 (m, 6H); 7.64 (s, 1H); 7.34 (m, 2H); 2.60 (s, 3H). Anal. Calcd. for C<sub>16</sub>H<sub>12</sub>OS: C, 76.16; H, 4.79; O, 6.34; S, 12.71. Found: C, 76.27; H, 4.86; S, 12.71.
- 8. The studies outlined in reference 6 have led the authors to conclude that Pd(0) is acting in a heterogeneous manner. It is worth noting that Guzman and coworkers, in the coupling of monosubstituted acetylenes with aryl halides using Pd/C have also presented evidence that the reaction may be homogeneous in nature, presumably due to leaching of Pd(0) from the catalyst. See: De laRosa, M. A.; Velarde, E.; Guzman, A. Synthetic Commun. 1990, 20, 2059.

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