Equilibration of the Oxidative Addition Product of Tetrakis(triphenylphosphine)palladium and Electron-Rich Aryl Halides Leads to Product Scrambling in the Stille Reaction

B. E. Segelstein, T. W. Butler, and B. L. Chenard*

Central Research Division, Pfizer Inc.,
Groton, Connecticut 06340

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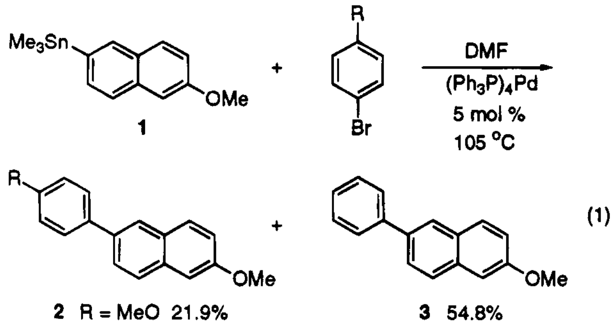
Palladium-catalyzed coupling reactions of organostannanes with aryl or alkenyl halides or triflates (collectively known as the Stille reaction[1]) and the corresponding reactions of boronic acid derivatives (Suzuki reaction[2]) have been embraced by the synthetic organic community as powerful tools for the construction of carbon–carbon bonds. Studies defining the scope, limitations, and mechanistic aspects of these reactions have led to a very good understanding of the overall process, and recent modifications of the phosphine ligands have further enhanced the utility of this chemistry.[3] In spite of this considerable knowledge base, there are times when the Stille reaction provides less than satisfactory results. These situations generally involve at least one electron-rich component in the reaction.[4,5] We report here that the initially formed intermediate in the Stille reaction (oxidative addition of Pd^0 into the aryl halide) may undergo aryl–phenyl exchange with the triphenylphosphine ligand yielding a mixture of biaryl products which may be difficult to separate. In addition, we find that the Stille catalytic cycle may be entered independently via oxidative addition of palladium into the tetraphenylphosphonium ion. These observations suggest that an equilibrium may exist between tetraarylphosphonium ion and the initially formed Pd^{2+} intermediate.

The reaction of 6-methoxy-2-(trimethylstannyl)naphthalene (**1**) and a series of aryl halides was studied. All experiments were run under a nitrogen atmosphere at 105 °C with 0.1 M **1**, 0.12 M aryl halide, and 5 mol % of catalyst. Product mixtures were quantitated by HPLC using authentic samples of **1**–**3** for reference.[6] In the initial experiment (eq 1), reaction of **1** and anisyl bromide with catalytic tetrakis(triphenylphosphine)palladium(0) produced two majorproducts, the anticipated methoxy-substituted biaryl **2** and phenyl adduct **3**. Solvent polarity had a relatively small effect on the product mixture (Table 1, entries 1–3). In DMF, dichloroethane, or dioxane, **3** remained the major product although the overall efficiency of the reaction was decreased in the less polar solvents. Substituents on the aryl halide greatly effected the outcome of the reaction (Table 1, entries 1, and 4–6). Electron-withdrawing groups reduced the amount of **3** formed in the reaction. The yield of **3** showed a significant correlation with σ_p (equation of the line: $\log(\%\ \text{yield}) = -1.7(\sigma_p) + 1.28$; $r^2 = 0.997$). While this data set is small, formation of the undesired phenyl substituted product **3** correlates in a predictable fashion with the electronic nature of the aryl halide. The choice of aryl bromide or iodide was relatively inconsequential to the overall product distribution.



(1)

The observation of **3** in the product mixture suggests that an exchange occurs between the phenyl groups on the phosphine ligand with the oxidative addition intermediate of the aryl halide and the Pd^0 catalyst. This is supported by the observations of Kong and Cheng who observed scrambling of aryl groups in Pd^{2+} complexes with the phosphine ligand in an NMR experiment.[7] In addition, group 8 transition metal-catalyzed scrambling of aryl groups in triarylphosphines has been reported [including tetrakis(triphenylphosphine)palladium(0) catalysis].[8] In the related Heck reaction, it has been noted that with electron rich aryl halides, the desired olefination reaction competed with a side reaction, where a tetraarylphosphonium salt formed with concomitant precipitation of Pd^0 as the solubilizing phosphine ligand was consumed.[9] The implication from this experiment was that the formation of the phosphonium salt was an irreversible process which prevented the reaction from proceeding to completion. In light of the above observations, we suspected that tetraarylphosphonium ions might undergo oxidative addition to palladium and enter into the Stille catalytic cycle. To test this possibility, we treated stannane **1** with tetraphenylphosphonium bromide under our standard conditions using bis(acetonitrile)palladium(II) chloride as the catalyst (eq 2).[10] We observed efficient formation of **3** (37% after 4 h, 52% after 24 h) clearly demonstrating that phosphonium salts, if generated under the reaction conditions, could enter into

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[1] For reviews of the Stille reaction and related transformations see: (a) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508–524. (b) Mitchell, T. N. *Synthesis* **1992**, 803–815.

[2] For the Suzuki reaction with arylboronic acids see: (a) Miyaura, N.; Yanagi, T.; Suzuki, A. *Synth. Commun.* **1981**, *11*, 513–519. (b) Watanabe, T.; Miyaura, N.; Suzuki, A. *Synlett.* **1992**, 207–210. See also: (c) Oh-e., T.; Miyaura, N.; Suzuki, A. *Synlett.* **1990**, 221–223. (d) Oh-e, T.; Miyaura, N.; Suzuki, A. *J. Org. Chem.* **1993**, *58*, 2201–2208. (e) Huth, A.; Beez, I.; Schumann, I. *Tetrahedron* **1989**, *45*, 6679–6682. (f) Shieh, W.-C.; Carlson, J. A. *J. Org. Chem.* **1992**, *57*, 379–381.

[3] (a) Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585–9595. (b) Farina, V.; Roth, G. P. *Tetrahedron Lett.* **1991**, *34*, 4243–4246. (c) Farina, V.; Krishnan, B.; Marshall, D. R.; Roth, G. P. *J. Org. Chem.* **1993**, *58*, 5434–5444.

[4] (a) Saa, J. M.; Martorell, G.; Garcia-Raso, A. *J. Org. Chem.* **1992**, *57*, 678–685. For an example with Suzuki coupling see ref 2e.

[5] For a creative solution to this problem involving the use of a chromium tricarbonyl complex to modulate the electronics of aryl triflates see: Gilbert, A. M.; Wulff, W. D. *J. Am. Chem. Soc.* **1994**, *116*, 7449–50.

[6] Reversed-phase HPLC conditions: column, Zorbax Rx C8 (4.6 mm × 15 cm); solvent system, 70% acetonitrile/30% water; flow rate, 1 mL/min; UV detection, 254 nM; approximate retention times, **1** (9.37 min); **2** (5.32 min); **3** (6.04 min).

[7] Kong, K.-C.; Cheng, C.-H. *J. Am. Chem. Soc.* **1991**, *113*, 6313–6315. It should be noted that an electron-donating group (methoxy) facilitated the exchange process.

[8] Abatjoglou, A. G.; Bryant, D. R. *Organometallics* **1984**, *3*, 932–934.

[9] (a) Heck, R. F. *Acc. Chem. Res.* **1979**, *12*, 146–151. (b) Ziegler, C. B., Jr.; Heck, R. F. *J. Org. Chem.* **1978**, *43*, 2941–2946.

[10] It should be noted that alkenyl(phenyl)iodonium salts and tetraarylboronates can also react under Stille or Suzuki conditions, respectively. See: (a) Moriarty, R. M.; Epa, W. R. *Tetrahedron Lett.* **1992**, *33*, 4095–4098. (b) Ciattini, P. G.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1992**, *33*, 4815–4818.

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Table 1. Reaction Conditions and Product Distribution

entry	aryl halide	solvent (dielectric constant)	catalyst	yield of **2** (%)	yield of **3** (%)
1	*p*-anisyl bromide	DMF (37)	$(Ph_3P)_4Pd$	21.9	54.8
2	*p*-anisyl bromide	DCE[a] (10.4)	$(Ph_3P)_4Pd$	17.9	34.3
3	*p*-anisyl bromide	Dioxane (2.21)	$(Ph_3P)_4Pd$	28.2	38.8
4	*p*-tolyl bromide	DMF	$(Ph_3P)_4Pd$	36.2[b]	22.0
5	*p*-(trifluoromethyl)phenyl iodide	DMF	$(Ph_3P)_4Pd$	49.3[b]	1.8
6	*p*-nitrophenyliodide	DMF	$(Ph_3P)_4Pd$	ND[a]	0
7	*p*-anisyl bromide	DMF	$(Ph_3P)_2PdCl_2$	10.9	22.2
8	*p*-anisyl bromide	DMF	$(CH_3CN)_2PdCl_2$ (Furyl)$_3$P	6.0	not observed[c]
9	*p*-anisyl bromide	DMF	$(CH_3CN)_2PdCl_2$ (Ph)$_3$As	25.9	49.2

[a] DCE = 1,2-dichloroethane, ND = not determined. [b] Estimated assuming an extinction coefficient similar to **3**. [c] The furyl adduct was the major product (60% crude, 30% recrystallized from hexane).

$$\mathrm{Ph_4P^+\ Br^-} \quad + \quad \mathbf{1} \quad \xrightarrow[\substack{(\mathrm{CH_3CN})_2\mathrm{PdCl_2} \\ 105\ ^\circ\mathrm{C}}]{\mathrm{DMF}} \quad \mathbf{3} \quad 52\% \qquad (2)$$

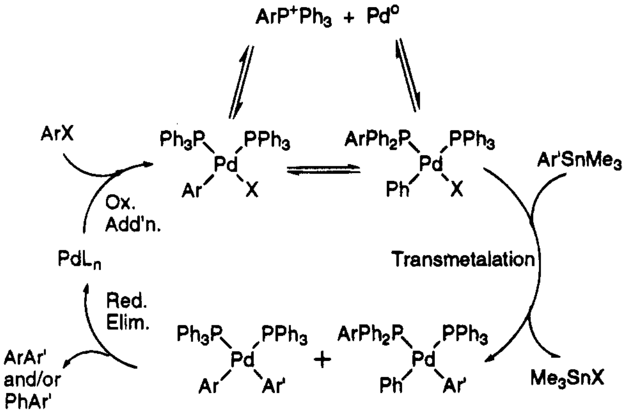
the Stille reaction without necessarily shutting down the catalytic cycle (as seen with the Heck reaction as noted above).

In order to account for the scrambling of the aryl group with the phenyl substituents of the phosphine ligand, we suggest that the Stille catalytic cycle be modified, at least for biaryl coupling reactions (Scheme 1). It must include the equilibration observed by Kong and Cheng[6] and allow for tetraarylphosphonium ion to enter the catalytic cycle. This scrambling process can be highly efficient. In the original example above (eq 1), the yield of **3** represents 78% transfer of all the available phenyl groups from the phosphine ligand. Consistent with the above observations, there are at least two factors which can facilitate the formation of **3**. First, electron-donating substituents on the aryl halide should stabilize the developing positive charge as the phosphonium salt is generated. Second, it has been suggested that electron rich arylstannanes further slow the rate-determining transmetalation step[11] which would facilitate the equilibration process.

Alternative catalyst systems were probed in an attempt to minimize or eliminate the equilibration reaction (Table 1, entries 1 and 7−9); however, none proved satisfactory. Bis(triphenylphosphine)palladium(II) chloride reduced the yield of **3** to 22.2%; this represented 74% transfer of the available phenyl groups. The preferred ligands for Stille coupling reactions recently described by Farina[3] were also ineffective at minimizing the scrambling reaction. When the phosphine ligand was replaced with triphenylarsine, essentially quantitative transfer of the phenyl groups was observed. With trifurylphosphine as the ligand, furyl group transfer was the major product from the reaction.[12]

The Suzuki reaction is an important alternative procedure for biaryl synthesis.[2] However, in the case of coupling two electron rich components, boronic acid coupling is also subject to aryl−phenyl scrambling.[13] Since the catalytic cycle is similar and the same factors favoring the equilibrium process are present in the Suzuki reaction with electron rich components, the Suzuki biaryl coupling reaction mechanism must be similarly modified to allow for equilibration of the Pd^{2+} intermediate prior to the rate-determining transmetalation step.[14] Finally, we attempted the biaryl coupling reaction with a palladium-catalyzed organozinc method.[15] While the production of **3** was not observed, the yield of **2** was poor (25−30%).

Scheme 1. Modified Stille Catalytic Cycle



In spite of extensive research, there remains much to be learned concerning metal-catalyzed coupling reactions. The biaryl coupling reaction with electron rich components described herein demonstrates that aryl−phenyl exchange of the Pd^{2+} adduct may overwhelm the desired coupling reaction leading to product mixtures which limit the utility of the reaction. The scrambling problem cannot be resolved by switching from Stille to Suzuki reaction conditions and suggests that the general mechanism for both of these biaryl coupling reactions should be modified to allow for aryl−phenyl equilibration prior to transmetalation. The discovery that tetraphenylphosphonium ion may enter into the catalytic cycle further supports the case for equilibration within the biaryl coupling catalytic cycle.

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(11) Transmetalation is generally accepted as the rate-determining step for palladium-catalyzed cross-coupling reactions although relatively few studies have been carried out. For Pd-catalyzed organostannane couplings see ref 1a. For the effect of electron-donating groups on the transmetalation step see ref 3a. For Pd-catalyzed organozinc couplings see: Negishi, E.; Takahashi, T.; Baba, S.; Van Horn, D. E.; Okukado, N. *J. Am. Chem. Soc.* **1987**, *109*, 2392−2401.

(12) 2-(2-Furyl)-6-methoxynaphthalene had mp 111.5−112.5 °C (from hexane). Anal. Calcd for $C_{15}H_{12}O_2$: C, 80.34; H, 5.39. Found: C, 80.33; H, 5.68.

(13) Unpublished results from our laboratory, but also see: O'Keefe, D. F.; Dannock, M. C.; Marcuccio, S. M. *Tetrahedron Lett.* **1992**, *33*, 6679−6680. Also note that coupling of (4-carbethoxyphenyl)boronic acid has been observed to produce high yields of 4-carbethoxybiphenyl in coupling reactions with electron rich aryl halides (Dr. Jotham Coe, unpublished results).

(14) It is interesting to note that Suzuki finds highly oxygenated triarylphosphines to be among the most effective ligands for organoboronic acid coupling reaction due to their ability to facilitate oxidative addition of the Pd^0 species to the aryl halide (ref 2d). We suggest that these oxygenated arylphosphines may also minimize the equilibration process described herein.

(15) Pelter, A.; Rowlands, M.; Clements, G. *Synthesis* **1987**, 51−3.