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Mild and robust Stille reactions in water using ppm levels of a new triphenylphosphine-based palladacycle

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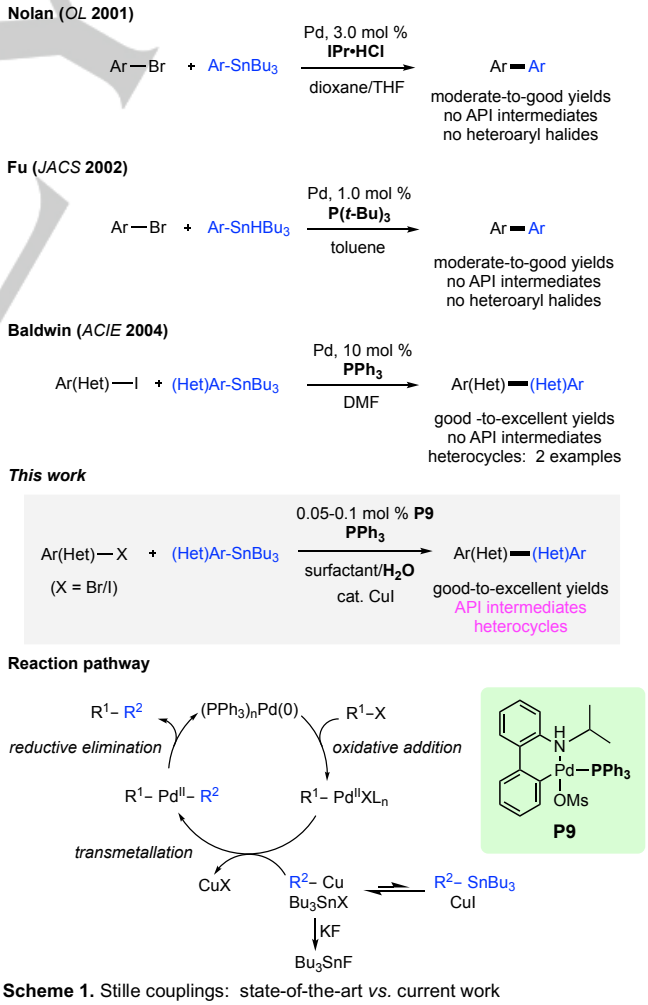
Abstract: An inexpensive and new triphenylphosphine-based palladacycle has been developed as a pre-catalyst leading to highly effective Stille cross coupling reactions in water under mild conditions. Only 500-1000 ppm of Pd suffices for couplings involving a variety of aryl/heteroaryl halides with aryl/hetaryl stannanes. Several drug intermediates can be prepared using this catalyst in aqueous nanoreactors formed by 2 wt % Brij-30 in water.

Introduction

Carbon-carbon formation via palladium-catalyzed cross coupling reactions has significantly impacted research in numerous industrial labs, providing rapid entry to a remarkable range of targeted structures.[1] Among these processes, as described in the Colacot and Sniekus review discussing the Nobel Prizes from 2010,[2] Stille reactions[3] remain among the most heavily utilized reactions within this category.[4] They have been found to be especially valuable for syntheses of natural products, pharmaceuticals, and in molecules with interesting physical properties.[5] Stille reactions tend to tolerate a wide array of functional groups, while organotin reagents are typically more forgiving towards air and moisture compared to the corresponding boron and zinc reagents.[6] Hence, they have been widely used[7] in syntheses of complex molecules, such as Pfizer's VEGFR kinase inhibitor, where after trying more than five different cross-coupling strategies, the authors conclude that a Stille coupling was "*Robust and scalable, only method which was reliable on >50 g scale.*"[8]

The first general process for Stille couplings was disclosed by Fu and Littke using 3 mol % Pd, along with *t*-Bu)$_3$P as ligand.[9] Many advances then followed; for example, Nolan's NHC-based Pd catalyst,[10] Verkade's bulky proazaphosphatrane-Pd catalyst,[11] and Buchwald's use of the XPhos ligand.[12] These ligands have proven to be highly effective for Stille cross couplings. However, none led to lower reaction temperatures or catalyst loading, presumably due to retardation of transmetalation from tin to palladium. In this context, triphenylphosphine is known be a good choice for enhancing transmetallation of organostannanes[13] while being a far less costly item of commerce. We have recently disclosed processes based on substituted biarylamine-containing palladacycles, that together with our newly designed ligands allow for ppm level catalyst loadings for use in Suzuki-Miyaura[14] and



Scheme 1. Stille couplings: state-of-the-art *vs.* current work

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Mizoroki-Heck cross coupling reactions in water.[15] In efforts to develop even more cost-effective and sustainable processes for use in organic synthesis,[16] we have prepared a new PPh_3-based palladacycle from commercially available and inexpensive materials. This pre-catalyst is very effective in Stille cross couplings run in aqueous nanoparticles derived from inexpensive and commercially available surfactant Brij-30,[17] typically only requiring loadings in the 0.05-0.1 mol % (500-1000 ppm) range.[18]

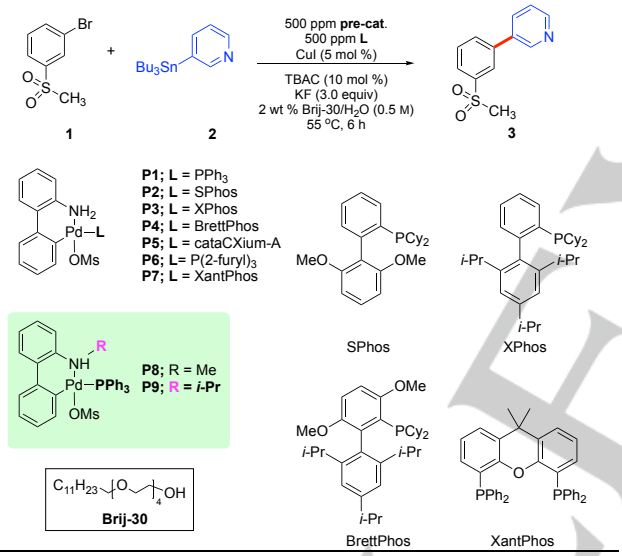
Results and Discussion

Model studies started with the synthesis of OSU 6162, a potential CNS agent from Pharmacia.[19] At first, 500 ppm (or 0.05 mol %) of palladacycle **P1** containing PPh_3 (and KF as base) was selected as pre-catalyst, although no product formation was noted (Table 1, entry 1). Baldwin[20] showed that Stille reactions that were unsuccessful using 10 mol % $Pd(PPh_3)_4$ catalyst showed dramatic improvements in the presence of catalytic CuI with CsF as base. Following a similar approach in micellar media by adding CuI, some conversion was noted (entry 2). However, given that our desired catalyst loading was 200 times lower than that used previously by others,[9-12,20] the extent of conversion and thus, yield of the desired product, was still too low. In the absence of CuI, there was no coupling (entry 3). The effect of added phase transfer catalyst (tetrabutylammonium chloride, TBAC) was surprising, leading to a jump in chemical yield (entry 4).[21] Both the co-catalyst (CuI) and additive (TBAC) could be used in catalytic amounts. Several additional known palladacycles with far more costly ligands (i.e., **P2**-**P7**) were tested under these optimized conditions and found to give roughly comparable, and somewhat better results (entries 5-11).

Recently, however, it has been shown that the carbazole by-product resulting from base-induced decomposition of the palladacycle pre-catalyst can impact cross coupling reactions, presumably by competitive ligation of nitrogen to palladium.[15] To minimize such ligation, which could be playing a critical role in these couplings given the ppm level of Pd, the corresponding *N*-alkylated analogs were prepared (**P8** and **P9**). While the *N*-methyl derivative is common,[22, 23] its preparation is cumbersome, oftentimes requiring use of *n*-BuLi, and leads to mixtures of mono-/di-methylamine products which can be quite difficult to purify.[23] On the other hand, the *N*-*i*-Pr-biphenylamine is easily prepared via reductive amination.[15] Both the *N*-Me (**P8**) and *N*-*i*-Pr (**P9**) pre-catalysts were examined, each unexpectedly leading to biaryl **3** in essentially identical yields (entries 11 and 12). This was atypical, as several additional examples confirmed the benefits of using the more hindered palladacycle (**P9**) by minimization of chelation by the newly formed carbazole (see Table 2, products **18**, **20**, and **21**). Reaction "on water" (i.e., in the absence of surfactant) led to a lower conversion (entry 13). The identical reaction run in an organic solvent such as THF led to a modest yield of the desired product (59%; entry 14). Lowering the reaction temperature, likewise, reduced the yield to 56% (entry 15).

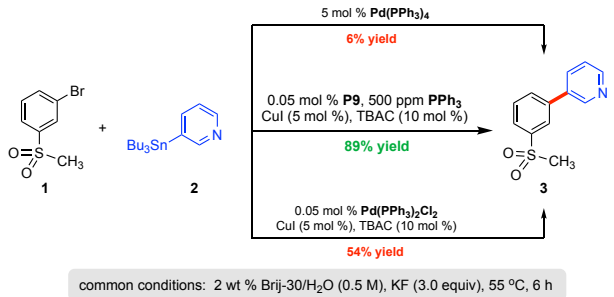
It is especially noteworthy that the alternative use of $(Ph_3P)_2PdCl_2$ in place of palladacycle **P9**, which (in principle) supplies the same catalyst components, was far less effective, highlighting the importance of pre-catalyst lipophilicity[24] in gaining entry to the inner micellar cores prior to catalyst generation (Scheme 2).

Table 1. Optimization for ppm Pd-catalyzed arylation of **1**.[a]



entry	catalyst	conversion (%)[b]
1	**P1** no additives	no reaction
2	**P1** with CuI	45
3	**P1** without CuI	trace
4	**P1** with CuI + TBAC	78
5	**P2**	85
6	**P3**	89
7	**P4**	78
8	**P5**	80
9	**P6**	78
10	**P7**	89
11	**P8**	92
12	**P9**	**91 (89)**[c]
13	**P9** no Brij-30 ("on water")	70
14	**P9** THF as solvent	59
15	**P9** 45 °C instead of 55 °C	56

[a] Reaction conditions: unless otherwise noted; 0.25 mmol of **1**, 0.55 equiv **2**, 500 ppm **Pre-cat**, 500 ppm **L**, 5 mol % CuI, 10 mol % TBAC, KF (3.0 equiv), 2 wt % Brij-30/H_2O [0.5 M], stirred at 55 °C. [b] Conversions based on GC-MS. [c] Isolated yield.



Scheme 2. Control reactions comparing pre-catalyst **P9** with alternatives.

The optimized Stille coupling conditions were applied to syntheses of a wide variety of targets, including pharmaceuticals or intermediates required en route. As demonstrated in Table 2, products **4** and **5** are intermediates associated with lead compounds for cancer treatment from Array biopharma[25a] and Johnson & Johnson,[25b] respectively, both prepared in high yields. Likewise, intermediates for anticancer agent venetoclax[25c] (AbbVie) **6**, telmisartan[25d] (for hypertension; Boehringer

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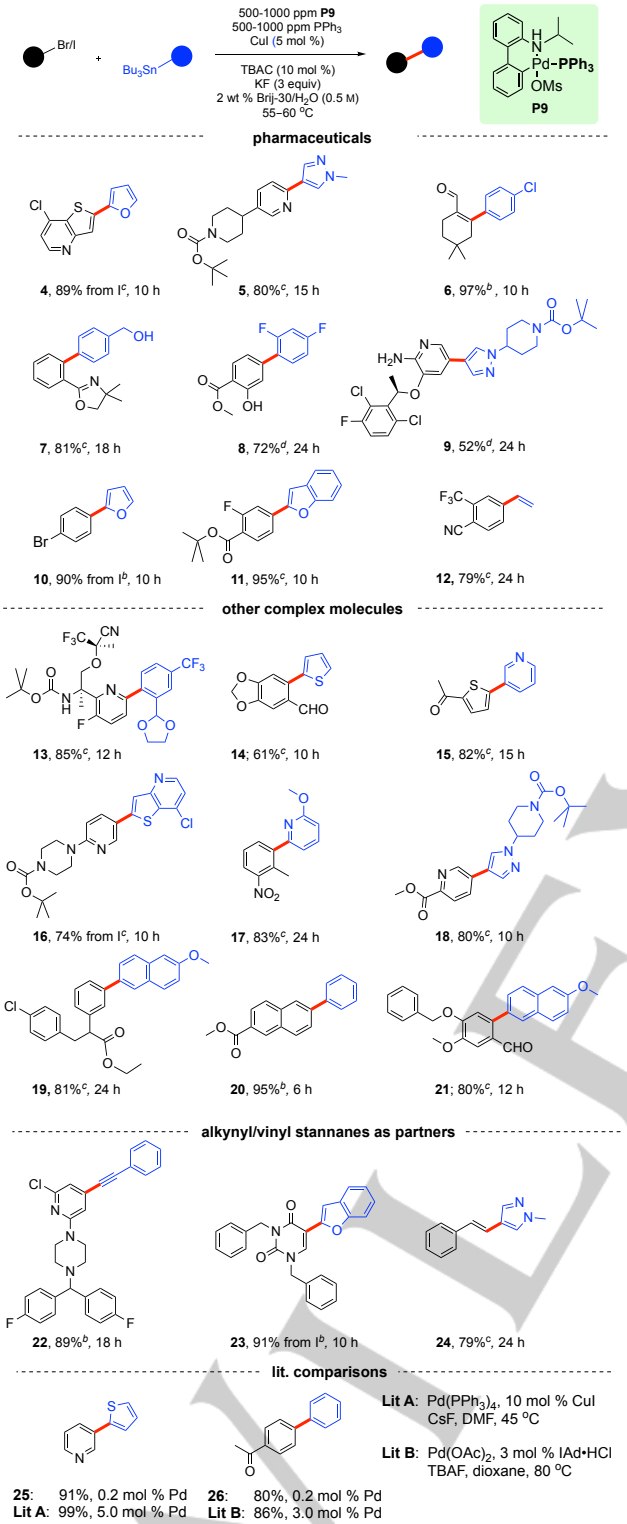
Table 2. Substrate scope for *ppm* Pd-catalyzed Stille couplings.[a]

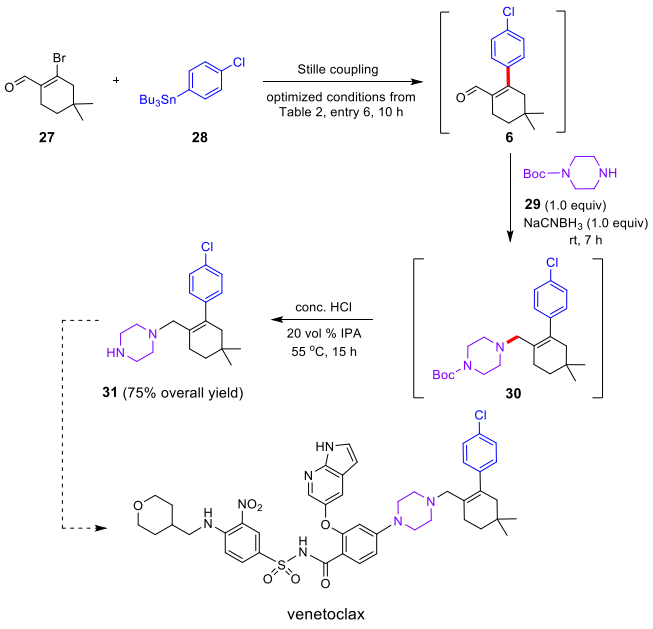


[a] Reaction conditions: unless otherwise noted; 0.25 mmol of aryl bromide (unless indicated otherwise), 1.05 equiv arylstannane, 500-1000 ppm **P9**, 5 mol % CuI, 10 mol % TBAC, KF (3.0 equiv), 2 wt % Brij-30/H_2O [0.5 M] stirred at 55-60 °C; 1.2 equiv stannane and 2 mol % CuI used for the reaction with 2-benzofuranylstannane; isolated yields are shown. [b] 500 ppm **P9** was used. [c] 1000 ppm of **P9** was used. [d] 2000 ppm of **P9** was used.

Ingelheim) **7**, the anti-inflammatory agent methylated diflunisal **8**[25e] (Merck), and anticancer agent Boc-crizotinib **9**[25f] (Pfizer) were all obtained in good-to-excellent chemical yields. Similarly, other intermediates such as **10**[25g] (J&J), **11**[25h] (Astra Zeneca), and **12**[25i] (BMS) were also prepared efficiently using 500-1000 ppm of Pd.

Highly functionalized biaryl **13** was smoothly prepared using this new process. Further generality could be established by subjecting a variety of heterocyclic halides to these Stille couplings to arrive at adducts **15, 16, 18, 20,** and **22.** Heterocyclic stannanes also readily participated, affording coupling products **14-18, 20,** and **23**. Several functional groups such as esters, amides, nitrile, nitro, ketone, aldehydes, and alcohol residues were tolerated under these conditions. Protecting groups such as Boc (see products **5, 9, 13, 16,** and **18**) and oxazoline (product **7**) were stable to these conditions as well. Selective cross coupling could also be observed with bromides (leading to products **9** and **19**), and iodides (generating adducts **4, 10,** and **22**) in the presence other potentially competitive halides. Vinyl- and alkynyl-stannanes leading to products **12** and **22**, respectively, readily underwent couplings, as did partners including vinyl halides (giving products **6, 23,** and **24**) in good chemical yields. A quick comparison using model substrates from both Nolan's[10] and Baldwin's[20] work suggested that biaryls **25** and **26** could also be effectively prepared using *over an order of magnitude less Pd* (0.1-0.2 mol % **P9**) under optimized conditions.

Given the opportunities to run a variety of reactions in aqueous micellar media,[26] sequential syntheses can be planned to make, e.g., pharmaceutical intermediates, such as the eastern subsection of venetoclax[25c, 27] (Scheme 3). Thus, **31** was prepared in a *1-pot, 3-step* fashion using an initial Stille coupling between **27** and **28** to arrive at styrene derivative **6**. Without isolation, reductive amination with secondary amine **29** led to **30**, which underwent Boc deprotection to give the desired product **31** in 75% overall yield.



Scheme 3. 1-Pot, 3-step sequence involving an initial Stille coupling, towards venetoclax.

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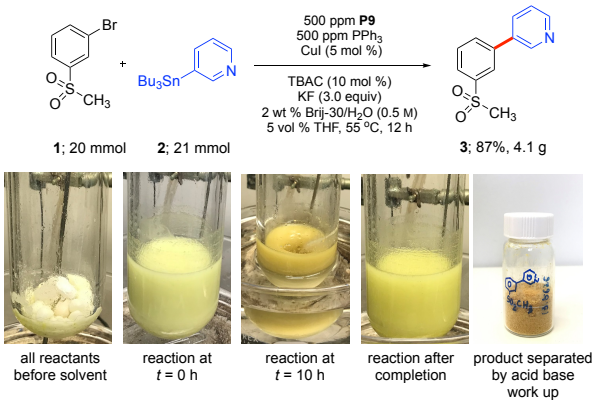
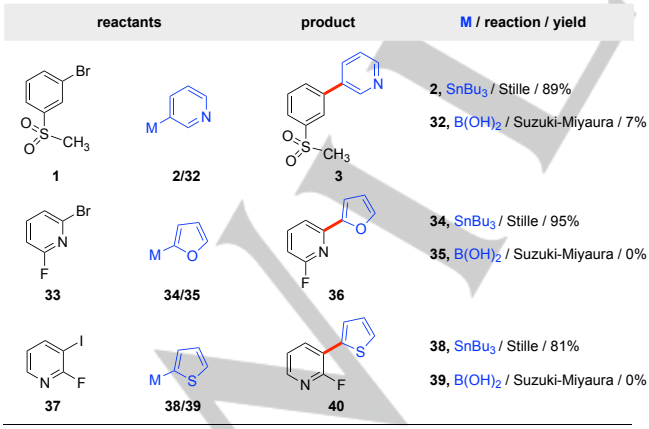
To test scalability, a multigram scale coupling between **1** and **2** led to OSU 6162 (**3**), performed on a 20 mmol scale (Scheme 4). Only 0.05 mol % Pd, or 6.4 mg catalyst, was required to produce 4.1 g of **3**, run at 55 °C over 12 hours (87% yield). The product was easily purified by an acid/base work up, effectively leading to spectroscopically pure material without further purification (see ESI).



Scheme 4. Gram scale reaction to arrive at OSU 6162 (**3**).

Although methods are available to remove tin following a Stille coupling from the desired product, the alternative Pd-catalyzed Suzuki-Miyaura (SM) coupling eliminates this potential challenge. However, heterocyclic boronic acids are oftentimes unstable, thus making SM couplings ineffective. Various derivatives of sensitive boronic acid (e.g., MIDA boronates)[6c] have been developed as a solution to this problem. Stannanes, on the other hand, are stable to air, moisture, and heat, and can be an attractive alternative especially when heterocyclics are required as reaction partners. In direct comparisons involving a pyridyl-, furanyl-, and thienyl-stannane in Stille *vs.* SM couplings using the corresponding boronic acids, as shown in Table 3, only the former led to the desired products in synthetically useful yields.

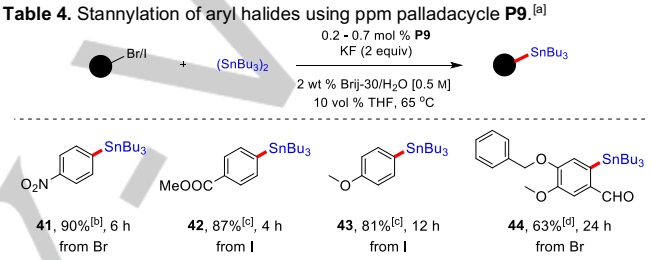
Table 3. Comparisons between Stille and Suzuki-Miyaura couplings.[a], [b]



[a] Reaction conditions: **Stille coupling**; 0.25 mmol of aryl halide, 1.05 equiv of heteroarylstannane, **P9**, 500 ppm (for **1**)/1000 ppm (**32** and **37**), 5 mol % (for **1**)/ 2.5 mol % (for **33** and **37**) CuI, 10 mol % TBAC, KF (3.0 equiv) 2 wt % Brij-30/H_2O [0.5 M], stirred at 55 °C. **Suzuki-Miyaura coupling**; 0.25 mmol of aryl halide, 1.05 equiv heteroaryl boronic acid, 1000 ppm pre-cat **P9**, 10 mol % TBAC, K_3PO_4•H_2O (3.0 equiv), 2 wt % Brij-30/H_2O [0.5 M], stirred at 55 °C. [b] Isolated yields.

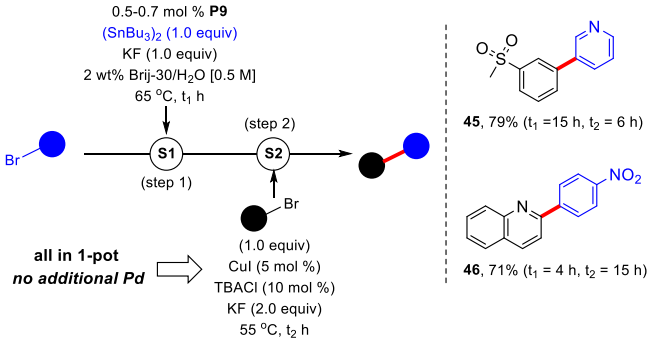
The same pre-catalyst and aqueous micellar conditions could also be used to perform direct stannylation of aryl halides (Table 4), which previously has been reported to require 10 mol % Pd catalyst at 110 °C.[28] From the examples chosen for study, encompassing both electron-rich and electron-deficient aryl iodides/bromides, the amount of Pd catalyst involved could be significantly reduced (ca. 20 times). Moreover, an important observation associated with stannylations and Stille couplings is the lack of formation of homocoupling products. This is especially important for the case of, e.g., *p*-chlorophenylstannane **28** (Scheme 2), since the homocoupled biaryl is a highly toxic PCB.[29] Noteworthy is the case of 4-bromonitrobenzene; in previous work stannylation, again using 10 mol % Pd, gave **41** in 68% yield.[28] This same reaction in water proceeded smoothly to the desired product in 90% yield in 6 h using only 0.5 mol % Pd.

Table 4. Stannylation of aryl halides using ppm palladacycle **P9**.[a]



[a] Reaction conditions: unless otherwise mentioned; 0.25 mmol of aryl halide, 0.25 mmol of $(SnBu_3)_2$, 0.2-0.7 mol % **P9**, 2 equiv. KF, 2 wt % Brij-30/H_2O [0.5 M] were stirred at 65 °C; isolated yields are shown. [b] Reaction was performed using 0.5 mol % **P9**. [c] Reaction was performed using 0.2 mol % **P9**. [d] Reaction was performed using 0.7 mol % **P9** at 70 °C

Since these stannylations take place with remarkable selectivity (i.e., no homocoupling) both processes could be combined into sequential couplings, where initial stannylation is followed by usage of the product stannane in a subsequent Stille coupling. Thus, as illustrated in Scheme 5, stannylation of an aryl/heteroaryl bromide led to adduct from step 1 (**S1**). Immediate introduction of the second aryl/heteroaryl bromide in step 2 (**S2**) led to Stille coupling *without additional Pd being added*. Two examples of this 1-pot, 2-step process affording biaryls **45** and **46** illustrate this new mode of C-C coupling using low catalyst loading (0.25-0.35 mol % Pd/step), *performed in the complete absence of organic solvents.*



Scheme 5. 1-Pot, 2-step process to make biaryls using ppm palladacycle **P9**.

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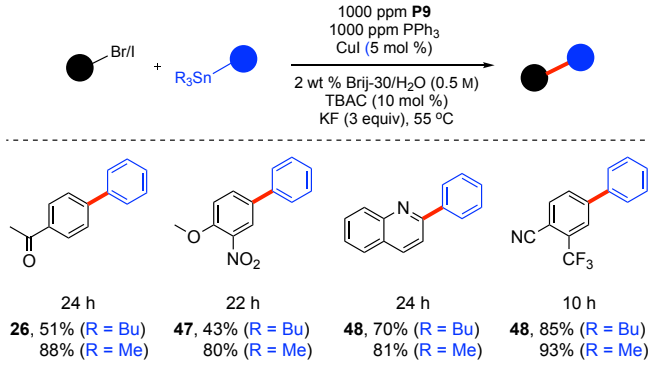
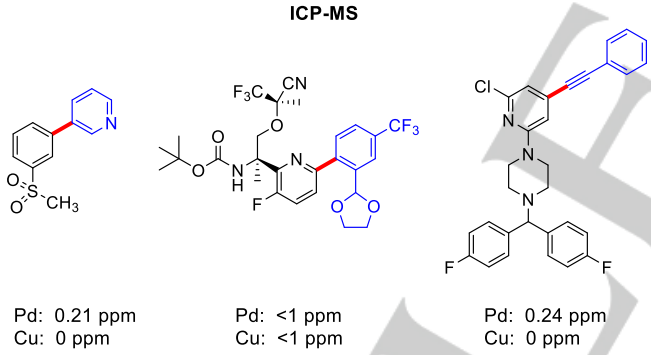
Opportunities to increase the rate of these Stille couplings in water using the corresponding *trimethyl*stannane analogs, in place of the far more typical tri-*n*-butylstannanes, led to the expected results. Thus, as shown in Scheme 6, in all cases examined, the aryltrimethylstannane coupling partner gave greater levels of conversion for the times allotted, thereby leading to higher chemical yields.



Scheme 6. Comparison reactions of trimethyl- *vs.* tri-*n*-butyl-stannanes.

In previous studies of various cross coupling reactions for which similar ppm levels of catalyst loadings were involved, isolated products tended to contain low levels of residual Pd.[14,15] Similar analyses on highly complex, multi-heteroatom-containing products via ICP-MS indicated that residual amounts of both Pd and Cu were negligible, both being well within FDA limits (Scheme 7).[30] Removal of tin from product **13** using a literature process reduced its presence to an acceptable limit.[31]



Scheme 7. Residual Pd and Cu in products from Stille couplings.

In summary, a new palladacycle (**P9**) has been developed for use as a pre-catalyst under mild and environmentally responsible aqueous micellar catalysis conditions, leading to an efficient technology for effecting valued Stille cross couplings. The combination of an inexpensive ligand (Ph_3P) and easily installed *N*-isopropyl group on the palladacycle are crucial structural features adding to the attractiveness of this process. Nanoreactors composed of commercially available and inexpensive Brij-30 surfactant play an enabling role, where couplings typically occur in the presence of only 0.05 to 0.10 mol % of endangered Pd. Several pharmaceutical targets and intermediates have been prepared documenting the potential, and generality in synthesis. The process could also be applied to a tandem 1-pot, 3-step sequence resulting in the preparation of an intermediate en route to AbbVie's venetoclax. The viability of this technology at scale was also shown via synthesis of the pharmaceutical intermediate OSU6255. Pre-catalyst **P9**, likewise, could be applied to efficient stannylations of aryl halides. Finally, recycling of the catalyst and surfactant was illustrated via a 2-step sequence involving initial stannylation followed by Stille coupling *in the same pot without additional catalyst*. Further advances using the many attributes of chemistry in water will be reported in due course.

Acknowledgements

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Keywords: cross coupling • Stille couplings • organostannanes • green chemistry • parts per million catalysis

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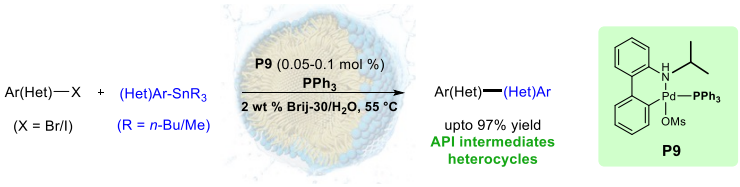

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