



Palladium-Catalyzed Stille Couplings of Aryl-, Vinyl-, and Alkyltrichlorostannanes in Aqueous Solution

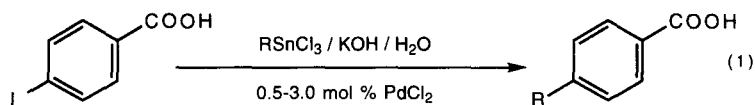
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Abstract: Stille coupling of water-soluble aryl and vinyl halides with alkyl-, aryl-, and vinyltrichlorostannane derivatives (RSnCl_3) are effected in aqueous solution using a catalyst generated *in situ* from PdCl_2 and KOH both with and without added $\text{PhP}(m\text{-C}_6\text{H}_4\text{SO}_3\text{Na})_2$. The yields are generally good to excellent, although some limitations of the protocol are described.

The health and environmental hazard posed by organic solvents makes their storage, handling and disposal an expensive process. This has heightened interest in methods for carrying out organic reactions in aqueous media with a particular emphasis on homogeneous catalysis.¹ For example, the palladium-catalyzed coupling of aryl and vinyl halides with boronic acids (Suzuki coupling^{2,3}) and unsaturated esters (Heck coupling^{3,4}) have been imported into aqueous media. While Pd-catalyzed Stille couplings⁵ using R_4Sn derivatives in aqueous acetonitrile and aqueous THF have been reported,⁶ a fully aqueous variant of the Stille coupling could possibly be the most versatile aryl and vinyl halide coupling protocol. Problems stem, at least in part, from the low water solubility of the lipophilic $n\text{-Bu}_3\text{SnR}$ reagents. During studies of tin-catalyzed aqueous radical reactions,⁷ we were alerted to the hydrolytic lability and resulting high water solubility of alkyltrichlorostannanes.⁸ In this manuscript, we describe a simple protocol for effecting Stille couplings using RSnCl_3 derivatives in aqueous media.⁹ We note that during the processing of this manuscript a closely related study was reported by Bumagin and coworkers which mirrors many of our observations.¹⁰



We examined the coupling reaction of 4-iodobenzoic acid (**1**) with PhSnCl_3 (equation 1). Heating a solution of **1**, PhSnCl_3 , and the palladium catalyst (0.5-3.0 mole %) in degassed 10% aqueous KOH at 90°C for 3 h afforded the coupled product in 95% yield after a standard organic workup and purification. The scope of the coupling was evaluated by coupling a variety of RSnCl_3 derivatives¹¹ with 4-iodobenzoic acid (Table I). In addition, a variety of aqueous soluble aryl and vinyl halides¹² were coupled with PhSnCl_3 (Table II). In some

cases we found that addition of $\text{PhP}(m\text{-C}_6\text{H}_4\text{SO}_3\text{Na})_2^{13}$ (4 equiv) dramatically improved the yield *and* reproducibility while in others there was little effect.¹⁴ In general, alkyl-, vinyl- and aryltrichlorostannanes afford coupled products in good to excellent yields.¹⁵ Notable successes include coupling with retention of olefin geometries and the successful coupling of *n*-BuSnCl₃. Attempted couplings of allyltin trichloride afford ArI homocoupling¹⁶ and reduced products as well as varying quantities of recovered ArI. Successful coupling of 3-bromophenol and the failure of 4-bromophenol are consistent with strong electronic influences on the arylhalide oxidative addition.¹⁷

Table I. Coupling of 4-iodobenzoic acid with RSnCl₃ in aqueous base (equation 1).^a

entry	RSnCl ₃	Yield (w/ PAr ₃) ^b	entry	RSnCl ₃	Yield (w/ PAr ₃) ^b
1	PhSnCl ₃	81% (95%)	4	CH ₂ =CHSnCl ₃	77% (97%)
2	<i>n</i> -BuSnCl ₃	74% (78%)	5	<i>cis</i> -HO ₂ CCH=CHSnCl ₃	72% (76%)
3	CH ₃ SnCl ₃	82% (76%)	6	(CH ₃) ₂ CHSnCl ₃	<5% (<5%)

^aReaction conditions as described in the text. ^bYields correspond to samples prepared under ligand-free conditions (see text), isolated by normal extractive workup, and purified by flash chromatography. Yields in parentheses correspond to reactions with 4.0 equiv of $\text{PhP}(m\text{-C}_6\text{H}_4\text{SO}_3\text{Na})_2$.

The aqueous palladium-catalyzed Stille coupling shows much of the versatility found for the original version using the lipophilic *n*-Bu₃SnR in organic solvents with some notable advantages. Unlike the normal Stille coupling conditions where the *n*-Bu₃SnR reagent transfers vinyl and aryl groups preferentially over the *n*-Bu groups, the aqueous variant does not require group-selective transfer (although it is disappointing that 2° alkyl groups do not transfer successfully). Furthermore, halogen substituents on the tin dramatically retard the Stille coupling in organic media.⁵ Indeed, heating a toluene solution of methyl 4-iodobenzoate and phenyltin trichloride in presence of 3 mole % Pd(PPh₃)₄ for 24 h affords no (<5%) coupling product. It would appear that hydrolysis of the RSnCl₃ reagent⁸ facilitates both solubilization *and* C-Sn bond activation. Lastly, in addition to expanding the arsenal of methods available for carrying out reactions in aqueous media, the inorganic tin by-products are considerably less toxic than alkylated tin derivatives.¹⁸

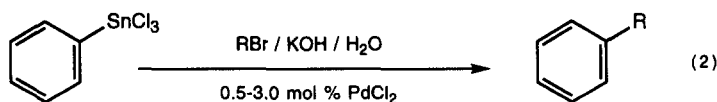
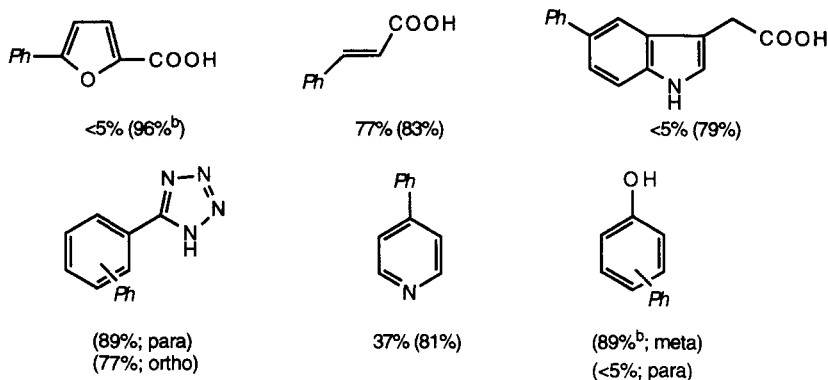


Chart 1: Coupling products of PhSnCl₃ with aryl and vinyl bromides in aqueous base (equation 2).^a



^a Yields in parentheses correspond to couplings in the presence of PhP(*m*-C₆H₄SO₃Na)₂.

^b See reference 14.

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