Synthesis of Mono-, Di-, and Tri- Phenyl Arenes by Sequential Photostimulated $S_{RN}1$ and Pd(0)-Catalyzed Cross Coupling Reactions on Aryl Halides

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Abstract: The photostimulated reaction of Me_3Sn^- ion with mono-, di-, and trichloro- arenes in liquid ammonia gave very good yields of stannanes by the $S_{RN}1$ mechanism. These products reacted by a palladium-catalyzed cross coupling reaction with halobenzenes to give phenylated products also in very good yields. Similar yields can be obtained in one-pot reactions.

Key words: Stille, $S_{RN}1$ reactions, cross coupling, photostimulation

For more than a decade, the palladium-catalyzed coupling of organotin compounds with carbon electrophiles, known as the Stille reaction,[1] has been shown to be a very important tool in organic synthesis.[2]

There are several methods of synthesis for trialkylarylstannanes, typically by the reaction of aryl lithium or organomagnesium derivatives with trialkyltin halides. These reactions have the drawback that many substituents on the aromatic ring are incompatible with the formation of aryl lithium or organomagnesium derivatives.[3] Another approach is the Stille reaction of aryl halides[4] or aryl triflates[5] with hexamethyl- and hexabutyldistannanes. Bis(trimethylstannyl)arenes can also be synthesized using palladium catalysis. Thus, the reaction of 3,5-dibromobiphenyl with hexamethydistannane gave 90% yield of the ditin product; other examples yielded 40-60% yield of disubstitution.[6]

There are few examples of the reactions of bis(trimethylstannyl)arenes and heteroarenes with aryl halides which afford a double arylation by the palladium cross coupling reaction. Thus, the palladium catalyzed reaction of 3,4-bis(tributylstannyl)furan with bromo or iodoarenes gave 45-85% of diarylation[7] and the reaction of 3-bromopyridine with 2,4-bis(trimethylstannyl)pyridine gave 48% yield of diheteroarylated product.[8] Other examples gave low yields (6-13% yield) of double arylation.[9] As far as we know there is no report of triphenylation on tris(trimethylstannyl) arenes.[2]

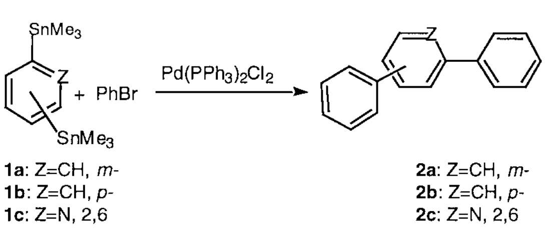
We have previously described the photostimulated reactions of trimethylstannyl anions which gave very good to excellent yields of substitution products with a number of chloro or dichloro arenes and heteroarenes by the $S_{RN}1$ mechanism in liquid ammonia.[10]

Many substituents are compatible with the $S_{RN}1$ mechanism, such as CO_2^-, CO_2R, $CONR_2$, RO^-, -CN, R, aryl, NH_2, NR_2, and SO_2R. Substituents such as $-O^-$ or $-NO_2$ are not suitable, except when arylazo phenyl sulfide are used as substrates.[11] When the substrate has two or three chlorines as leaving groups, it is possible to obtain di and tri substitution products in high yields.[12]

We thought that the photostimulated reaction of mono-, di- and trichloroarenes with Me_3Sn^- ions in liquid ammonia to synthesize the trimethylarylstannanes followed by the Pd(0) cross coupling reaction with haloarenes would be an important approach for the synthesis of arylated or polyarylated compounds. Thus, we undertook the study of the palladium catalyzed reaction of trimethylarylstannanes, synthesized by the $S_{RN}1$ mechanism, with mono-, di- and trichloroarenes as a model reaction for this methodology. Also we performed both reactions in one-pot procedures.

The reaction of *p*-cyanophenyltrimethylstannane[13] with PhI and $Pd(PPh_3)_2Cl_2$ (6 mol%) as catalyst in DMF (80 °C, 3 h), afforded the coupled product 4-biphenycarbonitrile in 81% yield.[14]

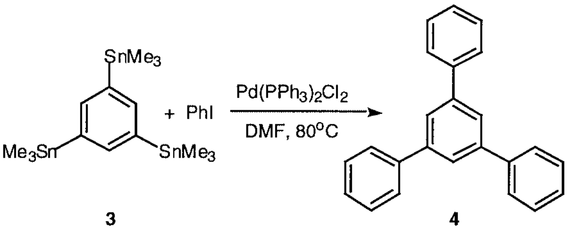
When the distannane **1a** (0.547 g, 1.35 mmol) was heated at 80 °C during 24 h in the presence of PhBr (0.424 g, 2.70 mmol) and $Pd(PPh_3)_2Cl_2$ (3 mol%) in DMF as solvent, *m*-terphenyl **2a** was obtained (0.302 gr, 97% isolated yield) (Scheme 1).



Scheme 1

Under the same reaction conditions, the distannane **1b** (0.609 g, 1.50 mmol) reacted with PhBr (0.477 g, 3.0 mmol) and $Pd(PPh_3)_2Cl_2$ (3 mol%) to yield 0.310 g (90% isolated yield) of *p*-terphenyl **2b**. The reaction of 2,6-di(trimethylstannyl)pyridine **1c** (0.560 gr, 1.38 mmol) with PhI (0.571 gr, 2.80 mmol) (xylene, 140 °C, 24 h) and $Pd(PPh_3)_2Cl_2$ (5 mol%), afforded the diphenylated pyridine **2c** (72%), together with 25% yield of 2-phenylpyridine.

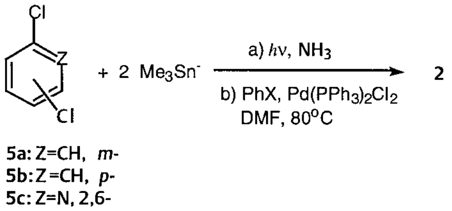
We studied the possibility of performing a triphenylation reaction. Thus, the reaction of the tristannane **3** (0.283 gr, 0.5 mmol) with PhI (0.306 gr, 1.50 mmol) and $Pd(PPh_3)_2Cl_2$ (5 mol%) gave the triphenylated product **4** in 89% yield (Scheme 2).



Scheme 2

We also studied the possibility of performing the synthesis of the distannane and the Stille reaction in a one-pot procedure. A solution of *p*-chlorobenzonitrile (0.137 g, 1.00 mmol) in 250 mL of dry liquid ammonia and Me_3SnNa (1.2 mmol) was irradiated (two 250-W UV lamps) during 1 h. The reaction was quenched by adding methyl iodide (0.030 g, 0.2 mmol).[15] Then the ammonia was allowed to evaporate, and the residue was redissolved in DMF. To this solution, PhI (0.242 g, 1.19 mmol) and $Pd(PPh_3)_2Cl_2$ (5.5 mol%) were added and heated at 80 °C for 3 h, and the product 4-biphenycarbonitrile was obtained in 63%.

A solution of *m*-dichlorobenzene (**5a**) (0.441 g, 3.00 mmol) in 250 mL of dry liquid ammonia and Me_3SnNa (1.315 g, 6.6 mmol) was irradiated during 90 min. The reaction was quenched by adding methyl iodide (0.085 g, 0.60 mmol). Then the ammonia was allowed to evaporate. The residue was redissolved in DMF. To this solution PhBr (0.942 g, 6.0 mmol) and $Pd(PPh_3)_2Cl_2$ (3 mol%) were added, and reacted as described above. The product **2a** was obtained in 76% yield (duplicated run) (Scheme 3).



Scheme 3

We studied the photostimulated reaction (90 min) of *p*-dichlorobenzene (**5b**) (0.441 g, 3.0 mmol) with Me_3SnNa (1.315 g, 6.6 mmol) in liquid ammonia followed by addition of methyl iodide. After evaporation of the ammonia, the residue was dissolved in DMF. PhBr (0.942 g, 6.0 mmol) and $Pd(PPh_3)_2Cl_2$ (3 mol%) were then added, and the rest of the procedure was similar to the previous reactions. Product **2b** was obtained in 71% yield (Scheme 3). In the same manner, **5c** (1.40 mmol) was irradiated (90 min) with Me_3Sn^- ions (3.20 mmol), and after evaporation of the solvent, xylene was added followed by PhI (0.571 g, 2.80 mmol) and $Pd(PPh_3)_2Cl_2$ (5 mol%) (140 °C, 24 h), affording **2c** (60%), together with 27% of 2-phenylpyridine.

We studied the one-pot reaction with 1,3,5-trichlorobenzene as substrate. The photostimulated reaction (105 min) of 1,3,5-trichlorobenzene (0.091 g, 0.5 mmol) with Me_3SnNa (0.984 g, 5 mmol) in liquid ammonia was followed by addition of methyl iodide. After evaporation of the ammonia, the residue was redissolved in DMF. PhI (0.306 g, 1.5 mmol) and $Pd(PPh_3)_2Cl_2$ (5 mol%) were then added, and the rest of the procedure was similar to the previous reactions. Product **4** was obtained in 61% isolated yield together with 27% of **2a**. This decrease in the overall yield for product **4** when comparing the step-wise reaction (89%) and the one pot-process (61%) can be accounted for the presence of **1a** in the starting mixture is due that the photostimulated reaction of 1,3,5-trichlorobenzene with Me_3Sn^- ions affords 70% of **3** and 20% of **1a**.

All these results indicated that the $S_{RN}1$ mechanism is an excellent method to obtain stannanes by the photostimulated reactions of mono-, di- and trichloroarenes with Me_3Sn^- in liquid ammonia. The stannanes thus obtained can be arylated by further reaction with bromo- or iodoarenes through the palladium catalyzed reactions (or to perform other palladium-catalyzed reactions). Further work is in progress to examine the reaction conditions and to extend its scope by using different mono- and dichloroarenes and heteroarenes in reactions with Me_3Sn^- ions followed by a palladium-catalyzed reaction with aryl halides and other catalyzed reactions in a stepwise or one-pot conditions.

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(13) Prepared by the photostimulated reaction of *p*-chlorobenzonitrile and Me_3Sn^- ion in liquid ammonia in 85% yield, see ref. 12.

(14) The following procedure is representative of all the reactions. Into a three-necked, 50-mL, round-bottomed flask equipped with a condenser, a nitrogen inlet, and a magnetic stirrer were added 20 mL of DMF, and afterwards the stannane **1** (0.425 g, 1.6 mmol), PhI (0.347 g, 1.7 mmol) and the catalyst $Pd(PPh_3)_2Cl_2$ (0.056 g, 0.080 mmol, 5%) and the solution was heated to 80 °C during 3 h. The solution was filtered and water (50 mL) was added and then extracted three times with diethyl ether. The product was quantified by GLC using the internal standard method compared with authentic samples. Products were isolated by column chromatography and their spectroscopic data agreed with those reported in the literature, see *Properties of Organic Compounds,* Version 5.0, CRC Press Data Base, CRC Press: Boca Raton, 1996.

(15) The excess of Me_3SnNa would react with methyl iodide to form Me_4Sn. It is more difficult to transfer a methyl group than a phenyl ring, see ref. 2. No toluene was found in all these reactions.

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