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Synthesis of Pyridylstannanes from Halopyridines and Hexamethyldistannane with Catalytic Palladium.

Maurizio Benaglia, Shinji Toyota, Craig R. Woods, and Jay S. Siegel*

Department of Chemistry, University of California, San Diego, La Jolla, California, 92093-0358,

Abstract: An easy method for direct stannylation of halopyridines and bipyridines by hexamethyldistannane is accomplished by Pd catalysis. © 1997 Elsevier Science Ltd.

The Stille coupling of aromatic rings[1] requires the formation of an arylstannane. Arylstannanes can be synthesized by various reactions including nucleophilic aromatic substitution of an aryl halide with trimethylstannyl sodium,[2] or very recently a sonochemical Barbier reaction involving the use of bis(tributyltin)oxide;[3] however, the most common procedure is probably the transformation of an aryl halide to the lithium derivative which is then quenched with trimethylstannyl chloride.[4] In some cases, the aromatic compound will not tolerate the strongly basic conditions of lithiation or the stannylation of the lithiate is unsuccessful. Such is our experience for various pyridine and bipyridine derivatives.

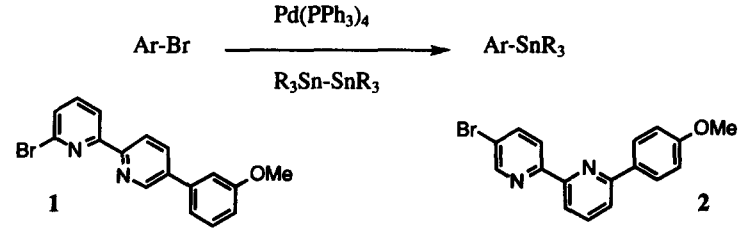
In the related Suzuki reaction,[5] which employs an aryl boronate instead of a stannane, the aryl halide can be directly converted to the boronate by pinacol ester of diboronic acid and a palladium catalyst.[6] A similar procedure using hexamethyldistannane has been reported,[7] but with the caveat that extreme electronic substituents inhibit the reaction or often homo-coupling side reactions ensue.[7-8] In contrast to the problems reported for simple arenes, we have found that halopyridines and bipyridines of importance in the construction of supramolecular scaffoldings can be conveniently stannylated by direct reaction with hexamethyldistannane and catalytic Pd.[9] This methodology may also be well suited for use in solid support based chemical synthesis of ligands for metal binding.

Our first explorations of the direct stannylation reaction came about when we were unable to stannylate **1** and **2** through formation of the lithium salt (cf. Table 1). Thus, the stannylation of these compounds became our model system to study and optimize the reaction conditions.[10] In our first experiments Bu_3Sn-$SnBu_3$ was used, but this reagent was not very successful; the product was obtained only in poor yields even upon varying solvents and temperature conditions (entries 1-3). We found hexamethyldistannane to be more reactive than hexabutyldistannane (compare entries 3 and 5), so the former was used for the optimization experiments.

The direct stannylation of **1** with hexamethyldistannane and 1.3% palladium seems to proceed faster in a polar solvent such as DME (dimethoxyethane) than in toluene. Indeed, the palladium catalyzed reaction of **1** with hexamethyldistannane in toluene yielded no product after 1 hour, and after 3 hours the trimethyltin derivative was obtained in only 15% of yield, whereas in DME after 3 hours the yield was 81% (entries 4-5). A slightly higher yield is obtained by using 5% catalyst and refluxing the reaction mixture for 15 hours (entry 6).

It is noteworthy that in none of our experiments could we detect the bis-heteroaryl compound, as the result of the homocoupling, a side reaction which represents a major problem in the stannylation of haloaromatics .[6-7]

Table 1. Experimental conditions for the stannylation of bromobipyridine **1** and **2**.



Entry	Comp.#	R	Solvent	Time/hrs	T/°C	eq. Pd[0]	Y%[a)]
1	1	Bu	Toluene	14	115°	1.3%	33%
2	1	Bu	Toluene	48	80°	1.3%	/
3	1	Bu	DME	3	80°	1.3%	9%
4	1	Me	Toluene	3	80°	1.3%	15%
5	1	Me	DME	3	80°	1.3%	81%
6	1	Me	DME	15	80°	5%	90%
7	2	Me	DME	3	80°	1.3%	/
8	2	Me	Toluene	14	115°	1.3%	/
9	2	Me	DME	15	80°	1.3%	/
10	2	Me	DME	15	80°	5%	85%
11	2	Me	DME	20	80°	5%	91%

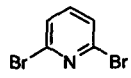
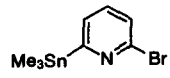
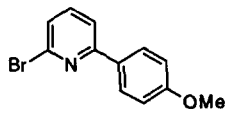
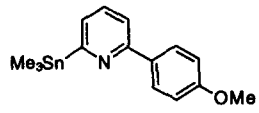
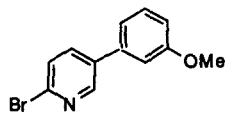
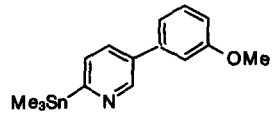
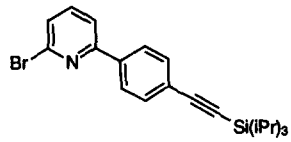
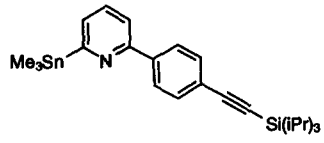
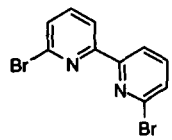
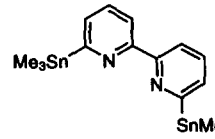
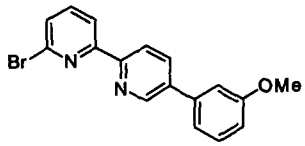
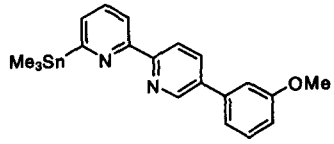
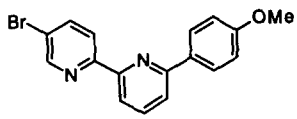
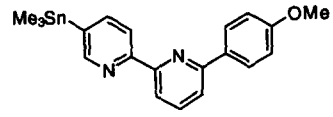
a) Yields determined after chromatographic purification

When conditions of toluene or DME and 1.3% of catalyst were used to try and stannylate **2** only unreacted starting material was recovered (entries 7-9). Increasing the amount of catalyst from 1.3% to 5% was enough to afford the desired stannyl derivative in 85% after 15 hours (entry 10). Our typical reaction conditions thus became, a 1:1 mixture of haloheterocycle and hexamethyldistannane in DME with 5% palladium catalyst at 80° for 15 h. Once optimized, these conditions were applied to a number of related pyridine and bipyridine derivatives to extend the generality of the method (table 2).[10]

Substituted 2-bromopyridines, give the expected organostannane, in almost quantitative yield (entries 2-4), and always with better yield than the procedure via lithiation followed by quenching the pyridyllithium salt with trimethylstannyl chloride. This procedure works very well, even for compounds with no substituents in the position α to the nitrogen of the pyridine; such products very often give problems in the lithiation process, causing low yields (compare entries 2-3) or no reaction at all. This method gives even more interesting results

with the bipyridines. For compounds **7**, **1**, and **2** we found it impossible to synthesize the stannyl compound by lithiation of the bromobipyridine, but we were able to obtain the desired organotin derivative in very good yields by palladium catalyzed stannylation (entries 5-7).[11]

Table 2. Comparison of direct stannylation Pd catalyzed vs. stannylation through the pyridyllithium salt.

Entry	Comp #	Compound	Product	A[a, c]	B[b, c]
1	**3**			25%	90%
2	**4**			97%	85%
3	**5**			97%	77%
4	**6**			95%	67%
5	**7**			63%	/
6	**1**			90%	/
7	**2**			85%	/

a) Method a : $Me_3Sn\text{-}SnMe_3$, 5% $Pd(Ph_3)_4$, DME , 15 hours, 80° b) Method b : 1) BuLi, THF 2) Me_3SnCl c) Yields determined after chromatographic purification

In general, we find the direct stannylation of halopyridines and bipyridines an extremely facile procedure with great potential for use in the synthesis of complex metal-coordinating ligands with sensitive functionality. We assume that the reaction works so well for pyridines because the coupling of the pyridylstannane with a second halopyridine is slow compared to the initial stannylation. If indeed, the rate of aryl coupling reaction is the major drawback for this reaction with simple arenes, then we speculate that use of this method for

stannylation of haloarenes on solid supports and polymers (compounds where exhaustive lithiation could be quite problematic) should be as easy and efficient as for the pyridines.

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10. All compounds were fully characterized by ^1H NMR, ^{13}C NMR and mass spectroscopy.
11. Preliminary experiments on some phenanthrolines were not successful; in the reaction of 8-bromo-2-iodophenanthroline and 3-bromophenanthroline (experimental conditions as in method a) only unreacted starting material was recovered.

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