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Palladium-Catalyzed Silylation of Aryl Chlorides with Hexamethyldisilane

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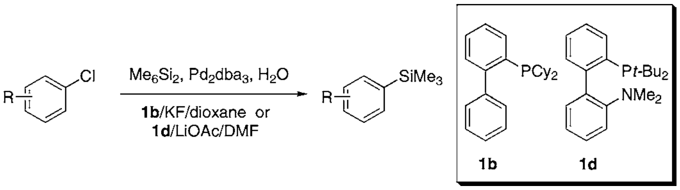
ABSTRACT



A method for the palladium-catalyzed silylation of aryl chlorides has been developed. The method affords desired product in good yield, is tolerant of a variety of functional groups, and provides access to a wide variety of aryltrimethylsilanes from commercially available aryl chlorides. Additionally, a one-pot procedure that converts aryl chlorides into aryl iodides has been developed.

Classically, arylsilanes have been synthesized from the corresponding aryl halide by lithium/halogen exchange or generation of the Grignard reagent, followed by nucleophilic attack on a silicon electrophile.[1] This method, however, is limited to arenes which lack base-sensitive functional groups. Beginning in the 1970s, a number of groups reported on the synthesis of arylsilanes by coupling aryl bromides, aryl iodides, aryl nitriles, or aroyl chlorides with disilanes or hydrosilanes using transition-metal catalysis[2−11] and electrochemical methods.[12] Notably, Goossen recently published a useful method for the synthesis of aryltrimethylsilanes via Pd catalysis with unhindered aryl bromides and hexamethyldisilane.[6] Additionally, Tsuji reported the silylation of PhCl;[13] however, this was the only aryl chloride employed. As aryl chlorides are generally less expensive and more readily available than aryl bromides, we initiated an investigation on the coupling of hexamethyldisilane with both hindered and unhindered substrates. Herein, we report a method for the palladium-catalyzed silylation of aryl chlorides with hexamethyldisilane as well as an one-pot procedure to convert aryl chlorides into aryl iodides.

Biaryl ligands (Figure 1) have shown tremendous utility in cross-coupling reactions for the formation of carbon−carbon, carbon−nitrogen, and carbon−oxygen bonds.[14] We

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(11) Hamze, A.; Provot, O.; Alami, M.; Brion, J.-D. *Org. Lett.* **2006**, *8*, 931−934.

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(14) Recent papers that utilize biaryl phosphines in C−O, C−N, and C−C bond forming processes: (a) Burgos, C. H.; Barder, T. E.; Huang, X.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2006**, *45*, 4321−4326. (b) Anderson, K. W.; Tundel, R. E.; Ikawa, T.; Altman, R. A.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2006**, *45*, 6523−6527. (c) Billingsley, K.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 3358−3366.

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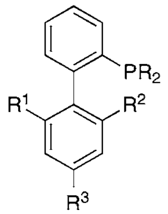
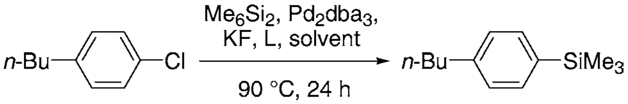


1a $R^1 = R^2 = R^3 = H$, R = *t*-Bu
1b $R^1 = R^2 = R^3 = H$, R = Cy
1c $R^1 = NMe_2$, $R^2 = R^3 = H$, R = Cy
1d $R^1 = NMe_2$, $R^2 = R^3 = H$, R = *t*-Bu
1e $R^1 = R^2 = OMe$, $R^3 = H$, R = Cy
1f $R^1 = R^2 = O$*i*-Pr, $R^3 = H$, R = Cy
1g $R^1 = R^2 = R^3 =$ *i*-Pr, R = Cy

Figure 1. Biaryl ligands tested for the cross-coupling of aryl chlorides with hexamethyldisilane.

decided to test several of these ligands for the Pd-catalyzed silylation reaction of aryl chlorides. Ligands **1a**−**g** were tested in a variety of solvents for the reaction of 4-*n*-butylchlorobenzene with hexamethyldisilane in the presence of 5 equiv of KF and 2 equiv of H_2O at 90 °C for 24 h (Table 1). It was determined that the reaction proceeded to 96% conversion and in 91% GC yield when using dioxane as the solvent in conjunction with **1b**. Upon raising the reaction temperature from 90 to 100 °C, complete conversion of the starting material was observed, and the desired product was isolated in 89% yield. After obtaining optimized conditions for the coupling of 4-*n*-butylchlorobenzene with hexamethyldisilane, we analyzed the coupling of a variety of electron-rich and electron-neutral aryl chloride substrates (Table 2).

Table 1. Optimization of Conditions for the Silylation of 4-*n*-Butylchlorobenzene with Hexamethyldisilane[a]

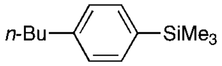
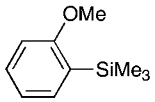
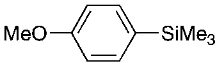
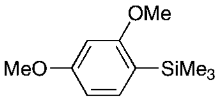
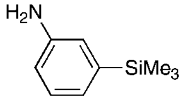
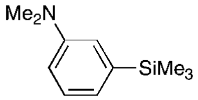
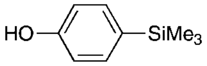
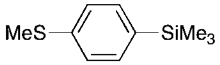
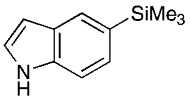
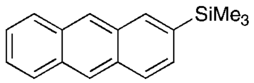


entry	ligand	solvent	conversion[b] (%)	yield[b] (%)
1	**1a**	dioxane	55	42
2	**1b**	dioxane	96[c]	91
3	**1c**	dioxane	64	58
4	**1d**	dioxane	67	22
5	**1e**	dioxane	17	17
6	**1f**	dioxane	30	<1
7	**1g**	dioxane	22	10
8	**1b**	DMPU[d]	13	<1
9	**1b**	toluene	19	5
10	**1b**	DMSO	9	<1
11	**1b**	DMF	98	5

[a] Reaction conditions: 1.0 mmol of 4-*n*-butylchlorobenzene, 1.2 mmol of Me_6Si_2, 0.015 mmol of Pd_2dba_3, 0.09 mmol of ligand, 2 mmol of H_2O, 5 mmol of KF, 3 mL of solvent, 90 °C, 24 h. [b] GC yield. [c] Increasing the reaction temperature to 100 °C led to full conversion of the substrate and 92% GC yield of product. [d] 1,3-Dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone.

The original conditions were compatible with numerous electron-rich and electron-neutral aryl chlorides and displayed broad functional group tolerance. By varying the catalyst loading and the amount of water and hexamethyldisilane present, we were able to synthesize arylsilanes bearing ethers (entries 2−4), amines (entries 5 and 6), phenols (entry 7), sulfides (entry 8), and indoles (entry 9). Disappointingly, electron-poor aryl chlorides were not efficiently converted to arylsilanes under these conditions. Instead, significant amounts of reduced arene were formed.

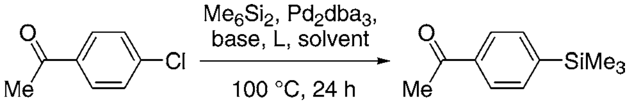
Table 2. Pd-catalyzed Silylation of Electron-Rich and -Neutral Aryl Halides[a]

entry	product	mol % Pd	equiv Me_6Si_2	yield[b] (%)
1		1.5	1.2	89
2		3	1.5	75[c]
3		2	1.2	90
4		3	1.8	89[c]
5		2	1.8	78[d]
6		2	1.2	91
7		3	1.2	74
8		3	1.8	80
9		2	1.8	86
10		3	1.2	66

[a] Reaction conditions: 1.0 mmol of aryl chloride, Pd_2dba_3 and Me_6Si_2 as listed, ligand **1b** in a 3:1 ligand/Pd ratio, 2 mmol of H_2O, 5 mmol of KF, 3 mL of dioxane, 100 °C, 24 h. [b] Isolated yields, representing the average of two runs. [c] No H_2O was added. [d] 1 equiv of H_2O was added.

There are examples in the literature of electron-rich aryl chlorides behaving differently than electron-deficient ones in catalytic silylation reactions[6,8,11] With this in mind, we again tested combinations of ligands, solvents and bases in hopes of discovering a set of conditions that would efficiently silylate electron-deficient aryl chlorides. The reaction of 4-chloroacetophenone with hexamethyldisilane was used as a test system (Table 3). It was determined that the combination of **1d** and lithium acetate in DMF afforded 4-tri-

Table 3. Optimization of Reaction Conditions for the Catalytic Silylation of 4-Chloroacetophenone with Hexamethyldisilane[a]



entry	ligand	solvent	base	yield[b] (%)
1	**1a**	DMF	KF	81
2	**1b**	DMF	KF	25
3	**1c**	DMF	KF	<1
4	**1d**	DMF	KF	84
5	**1e**	DMF	KF	<1
6	**1f**	DMF	KF	<1
7	**1g**	DMF	KF	<1
8	**1d**	DMPU	KF	34
9	**1d**	dioxane	KF	66
10	**1d**	NMP	KF	80
11	**1d**	DMF	LiF	4
12	**1d**	DMF	NaF	6
13	**1d**	DMF	K_2CO_3	62
14	**1d**	DMF	LiOAc	99[c]
15	**1d**	DMF	NaOAc	40
16	**1d**	DMF	KOAc	<1

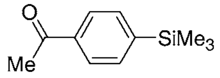
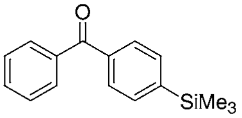
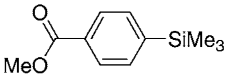
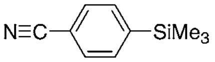
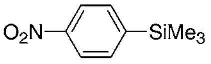
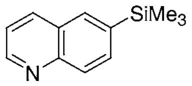
[a] Reaction conditions: 1.0 mmol of 4-chloroacetophenone, 1.2 mmol of Me_6Si_2, 0.015 mmol of Pd_2dba_3, 0.09 mmol of ligand **1d**, 2 mmol of H_2O, 5 mmol of base, 3 mL of solvent, 100 °C, 24 h. [b] GC yield. [c] Isolated yield 95%.

methylsilylacetophenone in 99% GC yield and 95% isolated yield. At present, we have no simple explanation for the superior efficiency of the protocol that uses **1d**.

Subsequent to this reaction optimization, we proceeded to examine the substrate scope with respect to electron-deficient aryl chlorides (Table 4). The method proved to be effective for a range of electron-deficient aryl chlorides bearing a variety of functional groups, including base-sensitive groups such as ketones (entries 1 and 2), esters (entry 3), nitriles (entry 4), and nitro groups (entry 5).

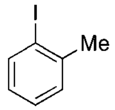
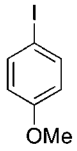
One synthetic elaboration of arylsilanes is their conversion to aryl iodides via electrophilic iodination with I_2 or ICl in the presence of stoichiometric silver salts.[15] Our group has previously investigated the conversion of aryl bromides to aryl iodides using copper catalysis.[16] However, both aryl bromides and iodides are reactive toward lithium/halogen exchange, cross-coupling reactions with commonly used Pd(PPh_3)$_4$ as catalyst, and Cu catalysis, while aryl chlorides are generally unreactive in these processes. Hence, the conversion of aryl chlorides to aryl iodides is a reaction of potential synthetic utility.[17] We attempted a one-pot procedure that converts aryl chlorides to aryl iodides via an arylsilane intermediate. It was found that when 1.5 equiv of ICl were added to the crude reaction mixture resulting from the reaction of 2-chlorotoluene with hexamethyldisilane under the conditions given in Table 2, 2-iodotoluene was isolated in 51% yield. Similarly, 4-iodoanisole was synthesized from 4-chloroanisole in 80% yield (Table 5). These results demonstrate that this transformation is feasible for electron-rich or electron-neutral aryl chlorides in one pot and without the use of stoichiometric silver salts.

Table 4. Pd-catalyzed Silylation of Electron-Deficient Aryl Halides[a]

entry	product	yield[b] (%)
1		89
2		87
3		66
4		82
5		77
6		82

[a] Reaction conditions: 1.0 mmol of aryl chloride, 0.015 mmol of Pd_2dba_3, 1.2 mmol of Me_6Si_2, 0.09 mmol of ligand **1d**, 2 mmol of H_2O, 5 mmol of LiOAc, 3 mL of DMF, 100 °C, 24 h. [b] Isolated yields, representing the average of two runs.

Table 5. One-Pot Sequential Silylation/Iodination of Aryl Chlorides[a]

entry	product	yield[b] (%)	entry	product	yield[b] (%)
1		51	2		80

[a] Conditions: (1) 1.0 mmol of aryl chloride, 1.2 mmol of Me_6Si_2, 1.5 mol % of Pd_2dba_3, 9 mol % of ligand **1b**, 2 mmol of H_2O, 5 mmol of KF, 3 mL of dioxane, 100 °C, 24 h. (2) 1.5 mmol of ICl, rt, 4 h. [b] Isolated yields, representing the average of two runs.

In conclusion, we have developed methods for the catalytic silylation of both electron-rich, -neutral, and -deficient aryl chlorides. The conditions are mild and the reaction displays wide functional group tolerance while affording product in good yield. In addition, we have shown that electron-rich and electron-neutral aryl chlorides can be converted to aryl

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[15] (a) Wilson, S. R.; Jacob, L. A. *J. Org. Chem.* **1986**, *51*, 4833−4836. (b) Jacob, L. A.; Chen, B.-L.; Stec, D. *Synthesis* **1993**, 611−614.

[16] Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 14844−14845.

[17] For a direct conversion of aryl chlorides to aryl iodides using a solid-supported copper(I) catalyst, see: Clark, J. H.; Jones, C. W. *J. Chem. Soc., Chem. Commun.* **1987**, 1409−1410.

iodides in a one-pot, two-step procedure. We believe this method is a useful complement to the existing methods for the preparation of arylsilanes.

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Supporting Information Available: Detailed experimental procedures and characterization data for each compound. This material is available free of charge via the Internet at http://pubs.acs.org.

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