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Palladium-catalysed cross-coupling of 2-trimethylsilylpyridine with aryl halides

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ABSTRACT

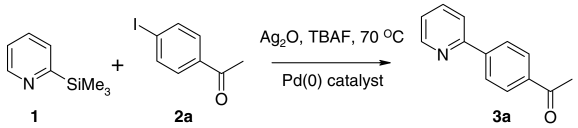
Palladium-catalysed cross-coupling of 2-trimethylsilylpyridine with aryl halides in the presence of stoichiometric silver(I) oxide, and catalytic TBAF allows the rapid preparation of the corresponding pyridin-2-ylaryl compounds in moderate to good yields under mild thermal conditions.

Effective cross-coupling of 2-pyridyl compounds with aryl derivatives is desirable for the synthesis of pharmacologically active molecules[1] and functional materials.[2] There is a need to find alternative methods to the Stille cross-coupling using 2-trialkylstannylpyridine and the Suzuki–Miyaura cross-coupling of 2-pyridylboron reagents because of the difficulty of purifying the coupled product from by-product tin salts, and since the boronates are difficult to prepare and handle due to their susceptibility to hydrolytic protodeboronation.[3] Although *N*-phenyldiethanolamine 2-pyridylboronate[4] and its polymer supported-analogue[5] have been reported as stable 2-pyridyl boronates, they give rise to formation of by-product 2-phenylpyridine in cross-coupling reactions due to aryl-phenyl exchange when triphenylphosphine is used as the ligand.[4] In an alternative approach to introducing the 2-pyridyl group by a cross-coupling reaction, Gros and co-workers[6] have shown that substituted 2-trimethylsilylpyridines possessing electron-withdrawing substituents undergo palladium(0)-catalysed Hiyama-type cross-coupling[7] with aryl and heteroaryl halides in the presence of stoichiometric copper(I) and excess tetra-*n*-butylammonium fluoride (TBAF). However, no cross-coupling was observed for the parent unsubstituted 2-trimethylsilylpyridine (**1**).[6] Herein, we report copper(I)-free conditions for the reaction of 2-trimethylsilylpyridine (**1**) with aryl iodides and aryl bromides to provide the cross-coupled products in moderate to good yields.

The starting point for our studies was the conditions that we had found to be effective for the rapid preparation of biaryls in palladium-catalysed Hiyama-type couplings of arylsiloxanes and disiloxanes with aryl halides.[8] These involve the use of palladium(0) tetrakistriphenylphosphine catalyst, stoichiometric silver(I) oxide, substoichiometric TBAF and heat. Under these conditions, 2-trimethylsilylpyridine (**1**) was found to couple with 4-iodoacetophenone (**2a**) to provide the corresponding 4-pyridin-2-ylacetophenone (**3a**) in low conversion (Table 1, entry 1).

Whilst we were encouraged by the successful formation of the desired coupled compound, the conversion was not as good as we had achieved for cross-couplings of arylsiloxanes and disiloxanes with aryl iodides under similar conditions. Therefore, we screened the effect of solvent and catalyst on reaction conversion. No conversion was observed when tetrabutylammonium triphenyl-silyldifluorosilicate (TBAT) was used as the fluoride source or when dibutyl ether or toluene were employed as solvents. NMP and DMF were found to be solvents that gave the best conversion when using palladium(0) tetrakis-triphenylphosphine as catalyst (entries

Table 1
Solvent and catalyst screen for cross-coupling of 2-trimethylsilylpyridine with 4-iodoacetophenone[a]



Entry	Solvent	Catalyst	Fluoride source	Conv.[b] (%)
1	THF	$Pd(PPh_3)_4$	TBAF	18
2	THF	$Pd(PPh_3)_4$	TBAT	0
3	Bu_2O	$Pd(PPh_3)_4$	TBAF	0
4	1,4-Dioxane	$Pd(PPh_3)_4$	TBAF	4
5	Toluene	$Pd(PPh_3)_4$	TBAF	0
6	DCM	$Pd(PPh_3)_4$	TBAF	7
7	MeCN	$Pd(PPh_3)_4$	TBAF	4
8	NMP	$Pd(PPh_3)_4$	TBAF	43
9	DMF	$Pd(PPh_3)_4$	TBAF	42
10	DMF	$PdCl_2(PPh_3)_2$	TBAF	15
11	DMF	$PdSO_4(PPh_3)_2$	TBAF	17
12	DMF	Allyl-$PdCl(PPh_3)_2$	TBAF	48
13	DMF	$Pd(dba)_2(PPh_3)_2$	TBAF	43
14	DMF	$Pd(OAc)_2(PPh_3)_2$	TBAF	46

[a] Reactions were carried out on 0.2 mmol scale with 5 mol % catalyst, 0.12 equiv TBAF (1 M in THF) or 0.12 equiv TBAT, 1 equiv Ag_2O and 1.2 equiv 2-TMS-pyridine for 30 min.

[b] Conversion was calculated from the product peak versus the 4-iodoacetophenone peak in the LCMS UV trace.

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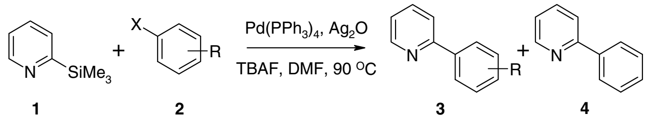
Table 2

Cross-coupling of 2-trimethylsilylpyridine with aryl iodides and aryl bromides[a]



Entry	R	X	**3** Yield[b] (%)	**4** Conv.[c] (%)
1	4-COMe	I	47 (36)[d]	<1
2	4-OMe	I	45	<1
3	4-CF_3	I	50	<1
4	4-NO_2	I	75	<1
5	4-CO_2Me	I	47	<1
6	3-COMe	I	61	<1
7	3-CN	I	65	<1
8	2-COMe	I	48	<1
9	2-Me	I	21	<1
10	4-COMe	Br	40	<1
11	4-OMe	Br	6[e]	3
12	4-Me	Br	9[e]	3
13	4-NO_2	Br	67	<1

[a] Reactions were carried out on 1 mmol scale with 5 mol % catalyst, 0.1 equiv TBAF (1 M in THF), 1 equiv Ag_2O and 3 equvi 2-TMS-pyridine.

[b] Isolated yield.

[c] Estimated by LCMS prior to isolation of the desired product.

[d] 1.2 equiv was of 2-TMS-pyridine was used. In brackets; yield with 3 equiv Ag_2O.

[e] Product was not isolated; conversion (%) was estimated by LCMS.

8 and 9). DMF was selected as the preferred solvent and different palladium(0) catalysts were screened, and it was found that a modest improvement in conversion was obtained with allyl-$PdCl(PPh_3)_2$ (entry 12) and $Pd(OAc)_2(PPh_3)_2$ (entry 14).

Next, the cross-coupling of 2-trimethylsilylpyridine (**1**) was explored with a range of substituted aryl halides **2**, using DMF as solvent and palladium(0) tetrakistriphenylphosphine as catalyst. The reaction temperature was increased from 70 °C as used in the initial investigations reported in Table 1 to 90 °C on the basis of a separate Design of Experiments (DoE) study. The coupled products **3** were obtained in moderate to good yields (Table 2).[9] The aryl iodides gave higher yields in comparison to the corresponding aryl bromides. We had anticipated that the aryl bromides might be less reactive and chose to increase the number of equivalents of 2-trimethylsilylpyridine (**1**) from 1.2 equiv to 3 equiv to drive the reactions to high conversion. However, for the more reactive aryl iodides, the use of 3 equiv of 2-trimethylsilylpyridine (**1**) may not confer a significant benefit (Table 2, entry 1) since, although not seen by LCMS analysis of the crude reaction mixtures, varying amounts of 2,2′-bipyridine were observed during purification by column chromatography of the products of reactions performed with 3 equivalents of silane **1**. A potential side reaction is desilylation to give pyridine but this, if formed, would be lost in the reaction work-up procedure. Whilst no by-product formation due to aryl-phenyl exchange with the triphenylphosphine could be detected for the reaction with aryl iodides, minor amounts of the by-product 2-phenylpyridine (**4**) were obtained with certain aryl bromides (Table 2, entries 11 and 12) but other minor side products were not isolated and characterised from these low yielding reactions. The best yields of the coupled product **3** were obtained with electron-withdrawing groups in the 4-position of the aryl halide (Table 2, entries 4 and 13). Silver(I) oxide is reported to accelerate certain Suzuki–Miyaura cross-couplings,[10] and was found here to be a crucial additive with no reaction occurring in its absence (data not shown) but increasing the number of equivalents from 1 to 3 conferred no additional benefit (Table 2, entry 1). We have not investigated the mechanistic role of the combination of TBAF and silver(I) oxide but we speculate that the reaction involves formation of a silicate (by reaction of 2-trimethylsilylpyridine with TBAF) in a catalytic amount, followed by formation of a pyridylsilver intermediate and subsequent transmetallation with palladium leading to cross-coupling with the aryl halide.

In conclusion, the cross-coupling between 2-trimethylsilylpyridine (**1**) and aryl halides reported herein overcomes the reported lack of reactivity of unsubstituted 2-trimethylsilylpyridine (**1**), and is an attractive alternative to the use of 2-pyridylboronates.

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9. *Representative procedure*: To 1 mmol of aryl iodide and 1 mmol of silver(I) oxide in 7.5 ml of DMF was added 3 mmol of 2-trimethylsilylpyridine (**1**),[11] 0.05 mmol of tetrakis(triphenylphosphine)palladium(0) and 0.1 mmol of tetrabutylammonium fluoride (1 M in THF). The resulting suspension was stirred in a pressure tube at 90 °C for 18 h. The reaction was then filtered, the retained residue was washed with EtOAc and the combined filtrates were diluted with heptane, washed with water and the organics were dried over anhydrous Na_2SO_4, filtered and added to 1.5 g of silica, and concentrated to give the adsorbed crude product which was then purified by column chromatography heptane + 0–30% EtOAc). All compounds **3** reported in Table 2 are known in the literature and were characterised by LCMS and ^1H NMR.
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