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Palladium-Catalyzed Direct Arylation of 2-Pyridylmethyl Silanes with Aryl Bromides

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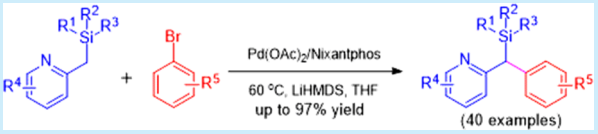
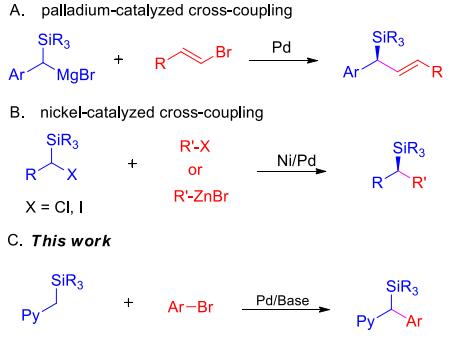
ABSTRACT: The first palladium-catalyzed direct arylation of 2-pyridylmethyl silanes with aryl bromides to generate a diverse array of aryl(2-pyridyl)-methyl silane derivatives has been developed. This protocol facilitates access to various kinds of heterocycle-containing silanes in good to excellent yields (40 examples, 66−97% yield) with good functional group tolerance. The scalability of this transformation is demonstrated.



Organosilanes are important structures that have found broad applications ranging from silicon materials to pharmaceuticals.[1] They are also useful precursors in many cross-coupling reactions[2] and are used as ligands in transition-metal coordination chemistry.[3] Furthermore, the rapid functionalization of heterocycles continues to attract much attention in medicinal chemistry. Taken together, the demand for a more general and straightforward synthesis of heterocycle-containing silanes remains high,[4] where the direct α-functionalization of azaarylmethyl silanes represents one of the ideal strategies.

The methods for α-functionalization of the existing organosilanes include (1) the transition-metal-catalyzed cross-coupling of silylated Grignard reagents with organo halides[5] (Scheme 1A) and (2) the nickel-catalyzed cross-coupling process between α-silylated alkyl halides and vinyl bromides[6] or alkylzinc reagents[7] (Scheme 1B). These methods require prefunctionalization of the corresponding silanes. Driven by the desire to simplify the starting materials, we turned our attention to the deprotonative functionalization of azaarylmethyl silanes.

Scheme 1. Transition-Metal-Catalyzed Functionalization of Silanes



In recent years, a variety of functionalizations of weakly acidic C_{sp^3}−H bonds via deprotonative cross-coupling processes were reported with substrates including diarylmethanes,[8] sulfoxides,[9] and amines,[10] among others.[11] However, the direct deprotonative cross-coupling of silanes has not been explored. Herein we provide a methodology to generate a variety of aryl(2-pyridyl)-methyl silane derivatives via a deprotonative cross-coupling process with 2-pyridine silane derivatives under mild conditions. This protocol avoids using Grignard reagents, and the starting materials are easily prepared and air-stable. Also, the products generated here could be easily transferred to an aryl(2-pyridyl)methanol core and are commonly found in drug candidates.[12] Compared with the existing methods for constructing organosilanes, such as the hydrosilylation of terminal olefin,[13] the transition-metal-catalyzed cross-coupling of silicon electrophiles or nucleophiles,[4a,14] and transition-metal-catalyzed C−H silylation,[15] our strategy provides an alternative synthesis of heterocycle containing silanes (Scheme 1C).

We commenced our research by choosing $Pd(OAc)_2$/Nixantphos as the catalyst and 2-((trimethylsilyl)methyl)-pyridine **1a** and bromobenzene **2a** as model starting materials (Table 1). Initially, we screened different bases ($LiN(SiMe_3)_2$, $NaN(SiMe_3)_2$, $KN(SiMe_3)_2$, LiO^{t}Bu, NaO^{t}Bu, and KO^{t}Bu) by using THF (tetrahydrofuran) as the solvent at 40 °C for 12 h (Table 1, entries 1−6). After the six bases were screened, we

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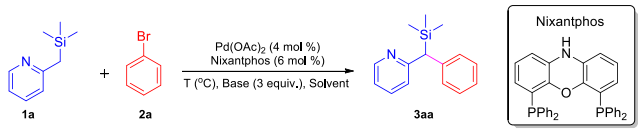
Table 1. Optimization of the Reaction Conditions[a]



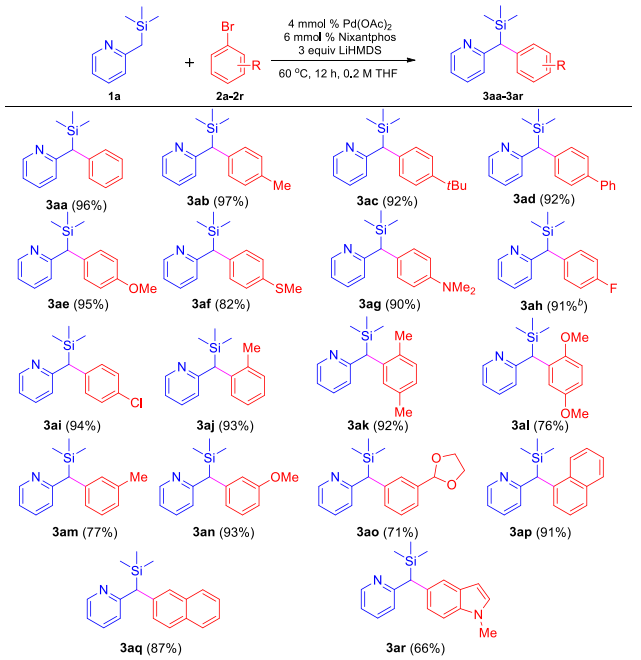
entry	base	solvent	temp (°C)	yield (%)[b]
1	$LiN(SiMe_3)_2$	THF	40	76
2	$NaN(SiMe_3)_2$	THF	40	68
3	$KN(SiMe_3)_2$	THF	40	71
4	LiO^tBu	THF	40	57
5	NaO^tBu	THF	40	53
6	KO^tBu	THF	40	52
7	Et_3N	THF	40	trace
8	DBU	THF	40	trace
9	$LiN(SiMe_3)_2$	toluene	40	0
10	$LiN(SiMe_3)_2$	dioxane	40	39
11	$LiN(SiMe_3)_2$	CPME	40	60
12	$LiN(SiMe_3)_2$	TBME	40	63
13	$LiN(SiMe_3)_2$	THF	60	96
14	$LiN(SiMe_3)_2$	THF	80	89

[a]Reactions were conducted on a 0.1 mmol scale using **1a** (1 equiv), **2a** (2 equiv), $Pd(OAc)_2$ (4 mol %), and Nixantphos (6 mol %), base (3 equiv), and solvent (0.2 M). [b]Yield determined by ^1H NMR spectroscopy of the crude reaction.

observed that $LiN(SiMe_3)_2$ provided the best yield of the desired cross-coupling product **3aa** in 76% yield (Table 1, entry 1). Other silylamide bases such as $NaN(SiMe_3)_2$ and $KN(SiMe_3)_2$ proved less effective for this reaction, affording the product in 68 and 71% yields, respectively (Table 1, entries 2 and 3). In contrast, MO^tBu (M = Li, Na, K) exhibited low efficiency (Table 1, entries 4–6). We also screened Et_3N and DBU as the base for this transformation; however, only a trace cross-coupling product was found (Table 1, entries 7 and 8). Next, $LiN(SiMe_3)_2$ was used going forward to study the effect of solvents on the reactivity of this transformation (Table 1, entries 9–12). This screen exhibited that non-chelation solvent toluene did not afford the desired cross-coupling product at all (Table 1, entry 9), and THF outperformed other ether solvents (Table 1, entry 1 vs entries 10–12). To increase the yield of **3aa**, we next examined the impacts of temperature. Increasing the temperature from 40 to 60 °C had a good effect on the yield, affording the desired product in 96% isolated yield (Table 1, entry 13); further increasing the temperature from 60 to 80 °C decreased the yield to 89% (Table 1, entry 14). Ultimately, the best conditions for this transformation were 2-((trimethylsilyl)methyl)pyridine (**1a**, 1.0 equiv), bromobenzene (**2a**, 2.0 equiv), $LiN(SiMe_3)_2$ (3 equiv), $Pd(OAc)_2$ (4 mol %), Nixantphos (6 mol %), and THF (0.2 M) at 60 °C for 12 h.

With the optimized reaction conditions in hand, we next explored the scope of aryl bromides with 2-((trimethylsilyl)-methyl)pyridine **1a** under the standard conditions (Scheme 2). In general, it was proved that our conditions tolerated a variety of functional groups, affording a wide range of aryl(2-pyridyl)-methyl silane derivatives **3aa**–**3ar** in good to excellent yields (66–97%). The parent bromobenzene **2a** reacted to give the cross-coupling product **3aa** in 96% isolated yield. Aryl bromides containing electron-neutral and -donating groups, such as 4-Me, 4-*t*Bu, 4-Ph, 4-OMe, 4-SMe, and 4-NMe_2 exhibited good to excellent reactivities, affording **3ab**–**3ag** in

Scheme 2. Substrate Scope of Aryl Bromides[a]



[a]Reactions performed on a 0.2 mmol scale. [b]3.0 equiv of aryl bromide was used.

82–97% yields. In addition, substrates bearing electron-withdrawing groups, such as 4-fluorobromobenzene **2h** and 4-chlorobromobenzene **2i**, proved to be suitable nucleophiles as well, affording the corresponding products **3ah** and **3ai** with excellent chemoselectivity. Then, sterically hindered aryl bromides were applied in this transformation, such as 2-bromotoluene **2j** and 2,5-dimethylbromobenzene **2k** as well as 2,5-dimethoxybromobenzene **2l**, forming **3aj**–**3al** in 76–93% yields. We also found that meta-substituted reagents could be utilized in this transformation, providing the desired products **3am**–**3ao** in 71–93% yields. π-Extended substrates **2p** and **2q** successfully underwent this transformation to afford **3ap** and **3aq** in 87–91% yields. In addition, heterocyclic *N*-methyl-5-bromoindole **2r** was compatible under our standard conditions, generating the desired products **3ar** in 66% yield.

Next, we turned our attention to different silanes (Scheme 3). In this part, we chose bromobenzene and 4-methylbromobenzene as electrophiles to couple to different silanes. In general, these transformations proceeded well to produce the corresponding products in moderate yields when triethylsilane was used in this coupling process (**3ba** and **3bb**, 88–90% yields). Compared with triethylsilane **1b**, triisopropylsilane **1c** exhibited slightly decreased reactivity, providing the desired product **3cb** in 79% isolated yield. Similarly, dimethyl(*n*-propyl)silane **1d** and dimethyl(*n*-butyl)silane **1e** underwent the desired deprotonative cross-coupling processes, providing the corresponding products in good yields (**3da**, **3db**, **3ea**, and **3eb**, 83–85% yields). Dimethyl(*t*-butyl)silane **1f** was an excellent substrate under our conditions, giving the corresponding products **3fa** and **3fb** in >90% yield. It should be noted that more sterically hindered silanes such as dimethyl-(2,3-dimethylbutan-2-yl)silane **1g** led to a slightly diminished yield, providing the desired product **3gb** in 77% yield. Next, we extended one of the carbon chains of silanes (dimethyl(*n*-octyl)silane **1h**) to react with bromobenzene and 4-

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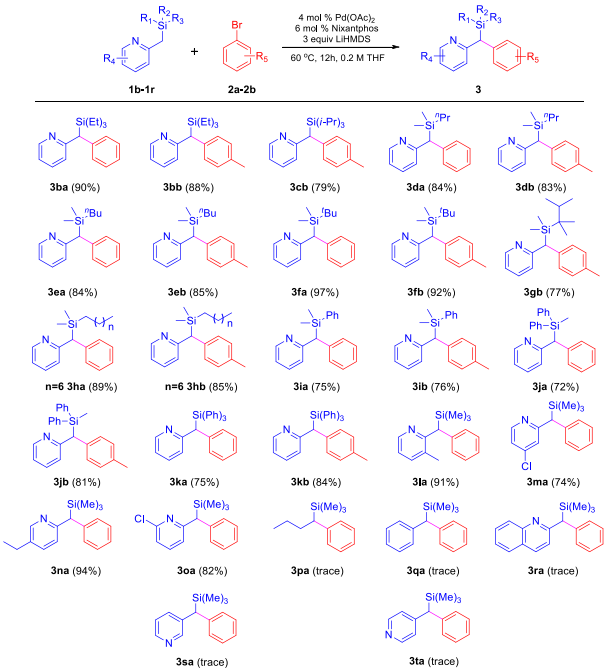
Scheme 3. Substrate Scope of 2-Pyridylmethyl Silanes[a]

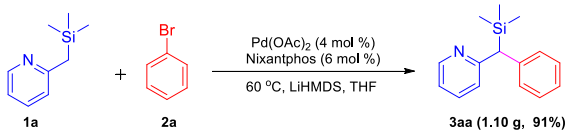


[a]Reactions performed on a 0.2 mmol scale.

methylbromobenzene under standard conditions, giving **3ha** and **3hb** in 89 and 85% yields, respectively. We were delighted to observe that various aryl-substituted silanes were suitable partners, generating the corresponding products **3ia**, **3ib**, **3ja**, **3jb**, **3ka**, and 3**kb** in 72−84% yields. We continued to explore the nature of the pyridine group. It was found that substituted 2-pyridines could provide the corresponding products in good yields (**3la**−**3oa**, 74−94% yields). Unfortunately, alkyl group (**1p**), simple phenyl group (**1q**), and other heterocycle groups such as **1r** and 3- and 4-pyridyl (**1s** and **1t**) gave only trace target products under the standard conditions. These findings implied that 2-pyridyl-substituted silanes, which can coordinate with the main group metal of the base, are needed in this transformation.

To test the scalability of this transformation, 5.0 mmol of 2-((trimethylsilyl)methyl)pyridine **1a** was coupled to bromobenzene **2a** under the standard conditions (Scheme 4). The desired cross-coupling product **3aa** was isolated in 91% yield (1.10 g).

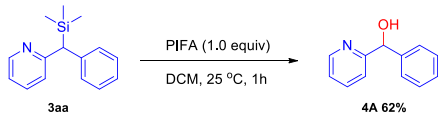
Scheme 4. Scale-up the Transformation on 5.0 mmol Scale



In addition, the aryl(2-pyridyl)methanol core is an important building block that is widely utilized in drug candidates;[16] therefore, we tried to explore the transformation of the C−Si bond to the C−O bond (Scheme 5). To our delight, the C−O bond could be formed by using PIFA as the oxidant, affording the desired product **4A** in 62% yield.[12]

In summary, we have shown here that a broad array of aryl(2-pyridyl)-methyl silane derivatives can be prepared by the palladium-catalyzed cross-coupling of 2-pyridylmethyl

Scheme 5. Transformations of the 2-Pyridylmethyl Silane



silanes with aryl bromides. Both electron-donating and electron-withdrawing aryl bromides can undergo the cross-coupling process with good to excellent reactivity. Furthermore, a diverse array of tetraorganosilanes are suitable for this transformation. To the best of our knowledge, this method represents the first palladium-catalyzed direct deprotonative functionalization of silanes, although a reactive pyridine group is needed in the current stage. Because of the significance of these aryl(2-pyridyl)-methyl silane derivatives, we anticipate that this methodology will find applications in medicinal chemistry. Studies toward the functionalization of simple silanes are ongoing in our laboratories

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00677.

Experimental details, characterization data, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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