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Cross-Coupling Reactions through the Intramolecular Activation of Alkyl(triorgano)silanes**

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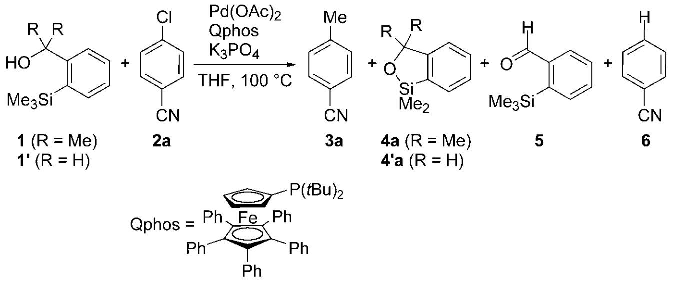
Silicon-based cross-coupling reactions have received much attention in terms of their chemoselectivity, reagent stability, and the nontoxicity associated with organosilicon reagents, and many efforts have resulted in the extensive development of cross-coupling reactions with alkenyl- and arylsilane compounds in the last decade.[1] Despite the widespread use of these alkyl cross-coupling strategies in organic synthesis,[2] the silicon-based methods have relied on the use of polyfluorinated alkylsilane reagents, which are moisture-, acid-, and base-sensitive, and require the use of a highly nucleophilic and expensive fluoride activator.[3] Herein, we report a palladium/copper-catalyzed alkyl-cross-coupling reaction using 2-(2-hydroxyprop-2-yl)phenyl-substituted alkylsilanes, which are highly stable tetraorganosilicon reagents that transfer both primary and secondary alkyl groups with the aid of K_3PO_4 as a mild base.

We have previously reported that 2-(hydroxymethyl)-phenyl-substituted alkenyl- and arylsilanes cross-couple with a range of electrophiles.[4] Therefore, we began by examining the palladium-catalyzed methylation of aryl halides using a structurally modified alkylsilane reagent, trimethyl[2-(2-hydroxyprop-2-yl)phenyl]silane (**1**; Scheme 1). The reaction of **1** (1.5 mmol) with 4-chlorobenzonitrile (**2a**, 1.0 mmol) in the presence of $Pd(OAc)_2$ (1 mol%), Qphos (2.1 mol%),[5] and K_3PO_4 (2.5 mmol) in tetrahydrofuran at 100 °C for 2 hours gave 4-methylbenzonitrile (**3a**) in 88% yield, as estimated by ^1H NMR spectroscopy. It is worth noting that the very strong Si−Me bond of the tetraorganosilicon reagent is activated exclusively over the Si−Ar bond with the aid of the metal catalysts and the mild base.[6,7] Indeed, no coupling of the aryl group was observed under these reaction conditions. Formation of cyclic silyl ether **4a** in 93% yield was calculated based on the conversion of **1** (95%), both estimated by GC analysis. Cyclic silyl ether **4a** was subsequently used as a starting material for synthesizing alkylsilanes through ring-opening reactions with alkyl lithium reagents. The presence of the benzylic methyl groups in **1** is essential: the reaction of trimethyl[2-(hydroxymethyl)phenyl]silane (**1′**) under identical conditions resulted in the oxidation of **1′** and reduction of **2a** to almost-exclusively afford **5** and **6**, respectively.



	Conv. [%][a]	Yield [%][a] 3a	4a or 4'a[b]	5	6
1 (2 h):	95	88[c]	93	—	—
1' (5 h):	76	<5	<5	70	75

[a] Estimated by GC. [b] Based on consumed **1** or **1'**. [c] Estimated by ^1H NMR spectroscopy.

Scheme 1. Cross-coupling of 2-(hydroxymethyl)phenyl-substituted methylsilanes with 4-chlorobenzonitrile (**2a**).

These results prompted us to examine the methylation of a range of aryl electrophiles (Table 1).[8] A variety of functional groups were tolerated in the reaction, including nitro, formyl, keto, and ester groups (Table 1, entries 1–5). For the methylation of some aryl halides, 1,1′-bis(diphenylphosphino)ferrocene (DPPF)[9] gave better yields (Table 1, entries 2 and 4). Use of copper(II) hexafluoroacetylacetonate hydrate $[Cu(hfacac)_2]$ as a co-catalyst was effective for the methylation of **2′d**, whilst competitive α-arylation of the acetyl group[10] was observed in its absence. Activation of the silicon reagents by a base other than fluoride allowed silyl ethers to participate in the coupling reaction, with the protecting group being completely retained (Table 1, entry 6). In most cases, silicon residue **4a** was observed in good yields. The highly sterically demanding 2-chloro-*meta*-xylene (**2j**) was methylated successfully (Table 1, entry 10). Performing the reaction on a 10 mmol scale allowed isolation of **4a** by distillation in 64% yield; the resultant residue was purified by flash chromatography on silica gel to give methylated arene **3k** in 89% yield (Table 1, entry 11). Recovered **4a** was treated with methyllithium to give **1** in 88% yield,[8] which demonstrates the facile synthesis of this methylsilane reagent. Heteroaryl electrophiles also underwent the methylation in modest to good yields (Table 1, entries 12 and 13).

We then turned our attention to the general alkylation of aryl halides based on this reagent design. First, butylation was examined with butyl[2-(2-hydroxyprop-2-yl)phenyl]diisopropylsilane (**7a**), wherein the three methyl groups on the silicon atom of **1** are substituted by one butyl group and two,

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[*] Dr. Y. Nakao, M. Takeda, T. Matsumoto, Prof. Dr. T. Hiyama
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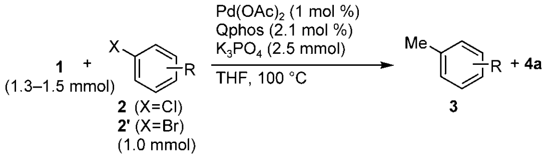
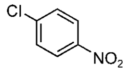
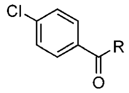
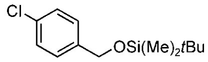
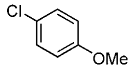
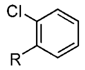
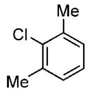
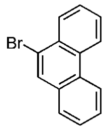
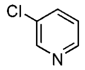
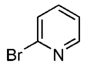
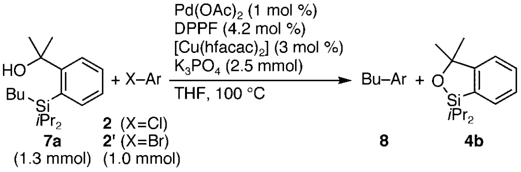
Table 1: Methylation of aryl halides with **1**.



Entry		**2** (R)	Time [h]	Yield of **3** [%][a]	Yield of **4** [%][b]
1		**2b**	3	77 (**3b**)	73
2[c]		**2b** (H)	3	70 (**3c**)	>95
3		**2d** (Me)	3	53 (**3d**)	75
4[c,d]		**2′d** (Me)	1	>95 (**3d**)	94
5		**2e** (O*t*Bu)	4	84 (**3e**)	94
6		**2f**	8	77 (**3f**)	>95
7		**2g**	8	63 (**3g**)	90
8		**2h** (Me)	4	70 (**3h**)	86
9		**2i** (MeO)	18	68 (**3i**)	81
10		**2j**	18	59 (**3j**)	69
11[e]		**2′k**	10	89[f] (**3k**)	64[f]
12[g]		**2l**	4	65 (**3l**)	>95
13		**2′m**	16	75 (**3m**)	82

[a] Estimated by ^{1}H NMR spectroscopy based on **2** (X=Cl) or **2′** (X=Br). [b] Estimated by GC or ^{1}H NMR analysis based on consumed **1**. [c] Run with DPPF (2.1 mol%) instead of Qphos. [d] Run with 4-bromoacetophenone (**2′d**) in the presence of [Cu(hfacac)$_2$] (3.0 mol%). [e] Run on a 10 mmol scale. [f] Yield of isolated product. [g] Run with 2.0 mmol of **1**.

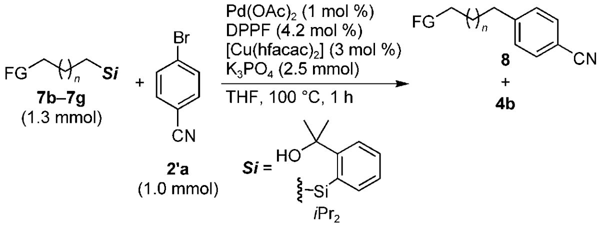
Table 2: Butylation of aryl halides with **7a**.

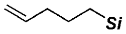
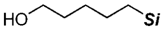
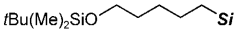
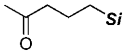
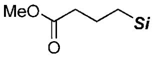


Entry	X–Ar	*t* [h]	Yield of **8** [%][a]	Yield of **4b** [%][b]
1[c]	**2a**	2	81 (**8aa**)	86
2	**2′b**	1	84 (**8ab**)	87
3	**2′c**	1	96 (**8ac**)	90
4	**2′d**	1	98 (**8ad**)	>95
5	**2′g**	1	79 (**8ag**)	>95
6[d]	**2′j**	5	82 (**8aj**)	>95
7	**2′l**	2	73 (**8al**)	>95
8	**2′m**	1	76 (**8am**)	>95

[a] Yield of isolated product based on **2** or **2′**. [b] Estimated by GC based on consumed **7a**. [c] Run with **7a** (1.5 mmol) and Qphos (2.1 mol%). [d] Run with **7a** (1.5 mmol) and DPPF (2.1 mol%). [f] Run at 50°C.

Table 3: Alkylation of **2′a** with functionalized alkylsilanes.



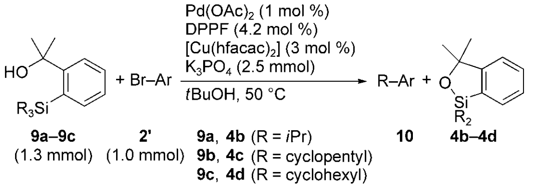
Entry	**7**		Yield of **3** [%][a]	Yield of **4** [%][b]
1		**7b**	93 (**8ba**)	>95
2		**7c**	76 (**8ca**)	95
3[c]		**7d**	73 (**8da**)	85
4		**7e**	86 (**8ea**)	>95
5		**7f**	92 (**8fa**)	>95

[a] Yield of isolated product based on **2′a**. [b] Estimated by GC based on consumed **7**. [c] Run with **7d** (1.5 mmol), **2a** (1.0 mmol), and Qphos (2.1 mol%) instead of **2′a** and DPPF.

presumably less reactive, isopropyl groups.[8] The presence of [Cu(hfacac)$_2$] (3 mol%) was found to be crucial to give the corresponding butylated arenes in good yields (Table 2);[8] its absence induced O-arylation and the Brook rearrangement of **7a** rather than the desired reaction pathway, which suggests that the alkyl copper species might play an important role in the copper-to-palladium transmetalation step. The scope of aryl halides that can be used in the reaction was found to be similar to the methylation reaction under these conditions. Furthermore, functionalized alkylsilane reagents also reacted successfully with **2′a** in good yields (Table 3).[8]

Finally, we extended the scope of this cross-coupling reaction to consider the intramolecular activation of secondary alkylsilanes. Compared with cross-coupling reactions of secondary-alkyl electrophiles,[11] the development of complementary protocols using secondary-alkyl nucleophiles has relied on the use of highly nucleophilic alkylmagnesium[9,12] alkylzinc,[13] or alkylmanganese[14] reagents. On the other hand, stable, isolatable, and storable nucleophiles that participate in such cross-coupling reactions is limited to secondary alkylboron reagents.[15–17] To the best of our knowledge, silicon-based cross-coupling reactions have never been performed with secondary alkylsilanes.[18] Therefore, triisopropyl[2-(2-hydroxyprop-2-yl)phenyl]silane (**9a**) was prepared[8] and reacted with 4-bromobenzonitrile (**2′a**; Table 4). To our delight, reaction under the standard reaction conditions in the presence of the copper catalyst gave an 18:1 mixture of 4-isopropylbenzonitrile (**10aa**) and 4-propylbenzonitrile (**10′aa**) in 74% yield as estimated by ^{1}H NMR spectroscopy. The latter would be derived from β-hydride elimination of an (aryl)isopropylpalladium(II) intermediate followed by re-insertion of the resultant propene that coordinates to the palladium center to give an (aryl)*n*-propylpalladium(II) species, which reductively eliminates the *n*-propylarene.[12] Use of *tert*-butyl alcohol as the solvent slightly increased the yield of **10aa**, and performing the reaction at lower temperature gave a better isopropyl/*n*-propyl ratio, although a longer reaction time was required for the reaction to proceed to completion (Table 4, entry 1). The optimized reaction conditions also worked effectively for the isopropylation of other aryl bromides (Table 4, entries 2–6) as well as cyclopentyl- and cyclohexylsilanes (**9b** and **9c**; Table 4, entries 7 and 8) to give a variety of arenes that contain a secondary alkyl substituent.[8]

Table 4: Alkylation of aryl bromides with *sec*-alkylsilanes.



Entry	9	2′	*t* [h]	Yield of **10** [%][a] (isopropyl/*n*-propyl ratio)[a]	Yield of **4** [%][b]
1	**9a**	**2′a**	75	84 (78[c]) (**10aa**, >20:1)	91 (**4b**)
2	**9a**	**2′d**	50	79 (71[c]) (**10ad**, >20:1)	>95 (**4b**)
3	**9a**	**2′g**	123	70 (**10ag**, 17:1)	85 (**4b**)
4[d]	**9a**	**2′h**	3	90 (**10ah**, >20:1)	>95 (**4b**)
5	**9a**	**2′l**	190	69 (**10al**, 16:1)	89 (**4b**)
6[d]	**9a**	**2′m**	3	82 (**10am**, 20:1)	>95 (**4b**)
7[d]	**9b**	**2′a**	3	84[c] (**10ba**)	99[e] (**4c**)
8[d]	**9c**	**2′a**	3	78[c] (**10ca**)	92[e] (**4d**)

[a] Estimated by ^{1}H NMR spectroscopy based on **2′**. [b] Estimated by GC based on consumed **9**. [c] Yield of isolated product based on **2′**. [d] Run at 100 °C. [e] Yield of isolated product based on consumed **9**.

In conclusion, we have demonstrated that 2-(2-hydroxyprop-2-yl)phenyl-substituted alkylsilanes selectively transfer an alkyl group to facilitate the alkylation of a range of aryl halides with the aid of palladium/copper catalysis and K_3PO_4 as a mild activator. The development of other alkylsilane reagents, such as 2-pyrrolidyl, 2-pyperidyl, and cyclopropylsilanes for not only cross-coupling reactions but also metal-catalyzed carbonyl-addition reactions[19] based on this reagent design is currently underway.

Experimental Section

General procedure for the cross-coupling of alkylsilanes with aryl or alkenyl bromides: Aryl or alkenyl bromide (1.0 mmol), *n*-dodecane (an internal standard, 88 mg, 0.50 mmol), and tetrahydrofuran (1.0–2.0 mL) were added sequentially by syringe to a mixture of K_3PO_4 (0.53 g, 2.5 mmol), [Cu(hfacac)$_2$] (15 mg, 30 μmol), DPPF (23 mg, 42 μmol), Pd(OAc)$_2$ (2.2 mg, 10 μmol), and an alkylsilane reagent (1.3 mmol) under an argon atmosphere in a screw-capped 3 mL vial that was sealed with a PTFE septum; the resulting mixture was stirred at 50–100 °C. After the specified time period, the mixture was filtered through a pad of silica gel and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel to afford the corresponding coupling product. Further purification was performed by preparative GPC to remove impurities in some cases.

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