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Palladium-Catalyzed Cross-Coupling of Monochlorosilanes And Grignard Reagents

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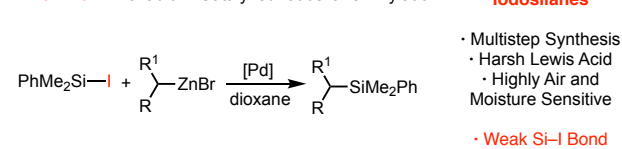
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Supporting Information Placeholder

ABSTRACT: Using a palladium catalyst supported by DrewPhos, the direct alkylation of monochlorosilanes with primary and secondary alkylmagnesium halides is now possible. Arylation with sterically demanding aromatic magnesium halides is also enabled. This transformation overcomes the high bond strength of the Si–Cl bond (113 kcal/mol) and is a rare example of a transition-metal catalyzed process involving its activation. Due to the availability of both chlorosilanes and organomagnesium halide reagents, this method allows for the preparation of a wide range of alkyl and aryl silanes.

Alkyl silanes are broadly useful materials with a vast range of applications,¹ including in materials,² pharmaceuticals,³ and agrochemicals,⁴ as well as organic synthesis.⁵ Although hydrosilylation is useful for the synthesis of primary silanes,^{2d, 6} the synthesis of secondary silanes has been a long-standing challenge. Classical methods, such as the addition of organometallic nucleophiles without the aid of catalyst, normally fail.⁷ In the rare cases where they do work, harsh conditions or exotic reagents are required, and yields are typically very poor.⁸ Recently, Fu and Oestreich have independently developed approaches to secondary silanes using transition metal-catalyzed umpolung cross-couplings of silyl nucleophiles with alkyl electrophiles, which provide one solution to this problem.^{7,9}

Prior Work: Palladium-Catalyzed Iodosilane Alkylation



This Work: Palladium-Catalyzed Chlorosilane Alkylation

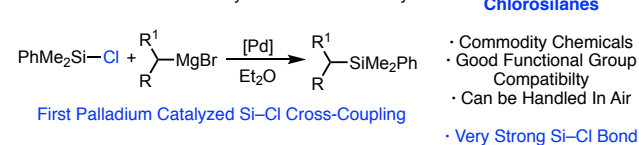


Figure 1. Palladium-Catalyzed Silyl Halide Alkylation

Earlier this year, as part of our study of transition metal-catalyzed cross-couplings of silicon electrophiles,¹⁰ we demonstrated that primary and secondary silanes could be prepared via the cross-coupling of silyl iodides and alkyl zinc halides using palladium catalysis (Figure 1, top).¹¹ This "silyl-Negishi" strategy represents the natural polarity of the Si–C bond and takes advantage of the natural electrophilicity of silicon centers. While this reaction is highly complimentary to umpolung methods mentioned above and provides a useful strategy for preparing secondary silanes, it was limited to the use of silyl iodide

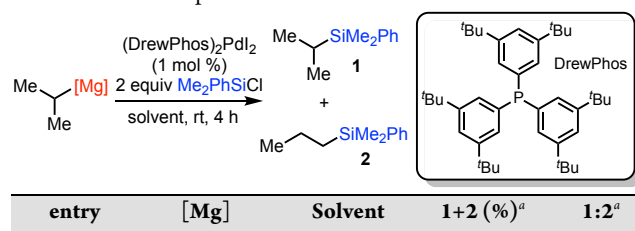
electrophiles. Critically, silyl chlorides failed to provide more than trace yield of product.¹¹

The development of cross-coupling conditions that allow for the use of silyl chlorides would be a significant advance, as silyl chlorides are not only much less air and moisture sensitive, they are much more abundant and functional group tolerant than silyl iodides. Whereas silyl iodides typically require multiple steps to access, chlorosilanes are the product of the Müller-Rochow "Direct" Process,¹² which is widely practiced on commodity scale. Thus, the ability to directly engage monochlorosilanes in cross-coupling is important for the ability to modify feedstock chemicals of critical importance to the silane industry.

Despite this appeal, the high bond strength of the Si–Cl bond (113 kcal/mol)^{13,14,15,16} has severely hampered the development of transition metal methods involving its activation. Reports of productive chlorosilane activation have been limited to the weaker Si–Cl bonds of polychloro- or hydrochlorosilanes.¹⁷ However, those reactions have not been exploited in synthetic applications. In addition, three reports of monochlorosilane activation using iridium(I) complexes have also been described, but the resultant silyliridium chlorides are unstable to β -hydride elimination.^{17c, 17d, 18}

Finally, Oshima has reported on several metal-catalyzed arylations of monochlorosilanes.¹⁹ However, these reactions are believed to proceed via nucleophile activation, and not via activation of the Si–Cl bond. Moreover, none of those conditions exhibited any advantage in the case of alkyl Grignard reagents.

Table 1. Reaction Optimization



entry	[Mg]	Solvent	1+2 (%) ^a	1:2 ^b
1	MgCl	THF	45	38:62
2	MgCl-LiCl	THF	92	31:69
3	MgBr	THF	96	34:66
4	MgCl	Et ₂ O	24	>99:1
5	MgBr	Et ₂ O	99	>99:1
6	MgI	Et ₂ O	99	>99:1
7 ^b	MgBr	Et ₂ O or THF	0	---

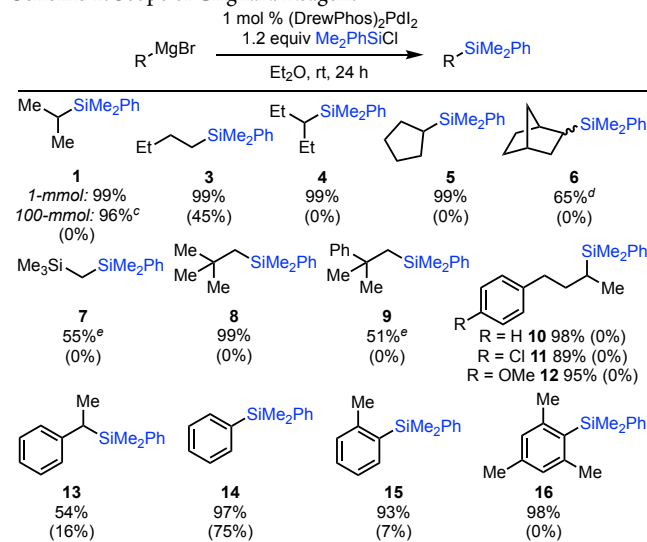
^a Determined by GC. ^b No Pd.

Herein we report conditions for the direct cross-coupling of silyl monochlorides with alkyl nucleophiles (Figure 1, bottom). We have found that these reagents participate in palladium-catalyzed cross-

coupling with primary and secondary Grignard reagents to provide primary and secondary alkyl silanes in very high yield. The scope of this formal silyl-Kumada reaction is high, and it represents a rare example of the direct utilization of monochlorosilanes in transition metal-catalyzed cross-coupling without the need for external activating agents. Moreover, as both silyl chlorides and Grignard reagents are inexpensive, broadly available, and routinely used in commodity scale synthesis, the potential for application of this reaction is high. Finally, we also report that the catalytic conditions are directly applicable to the cross-coupling of highly sterically demanding aryl magnesium halide reagents, making these conditions also relevant to the preparation of challenging aryl silanes.

As mentioned, our previous study showed that alkyl zinc halides failed to give more than trace alkylation of monochlorosilanes under palladium-catalyzed conditions.¹¹ Thus, we began this investigation by studying the use of other classes of alkyl nucleophiles. To this end, we investigated the reactivity of dimethylphenylsilyl chloride with isopropylmagnesium chloride using THF as solvent. Gratifyingly, we found modest reactivity using (DrewPhos)₂PdI₂ as catalyst, however selectivity was shifted from *sec*-alkylsilane **1** in favor of the linear alkylsilane product **2** (Table 1, Entry 1).²⁰ The use of ^tPrMgCl·LiCl (the so-called “Turbo Grignard”)²¹ and ^tPrMgBr both improved the yield of the reaction, but the selectivity remained poor (Entries 2-3). Critically, changing the solvent to the less polar Et₂O maintained the yield while providing complete selectivity in favor of the *sec*-alkyl product **1** (Entry 5). Alternative acyclic ethers such as Bu₂O, MTBE, and CPME were also effective in maintaining selectivity for the *sec*-alkyl product **1**.²² The halide of the Grignard reagent also affected reactivity, wherein I ≥ Br ≫ Cl (Entries 4-6). Similar phenomena have been observed in many Kumada cross-coupling reactions.²³ Control experiments in both THF and Et₂O showed no background reactivity (Entry 7). Additionally, the coupling was amenable to lower chlorosilane loading by extending reaction time.²²

Scheme 1. Scope of Grignard Reagent^{a,b}



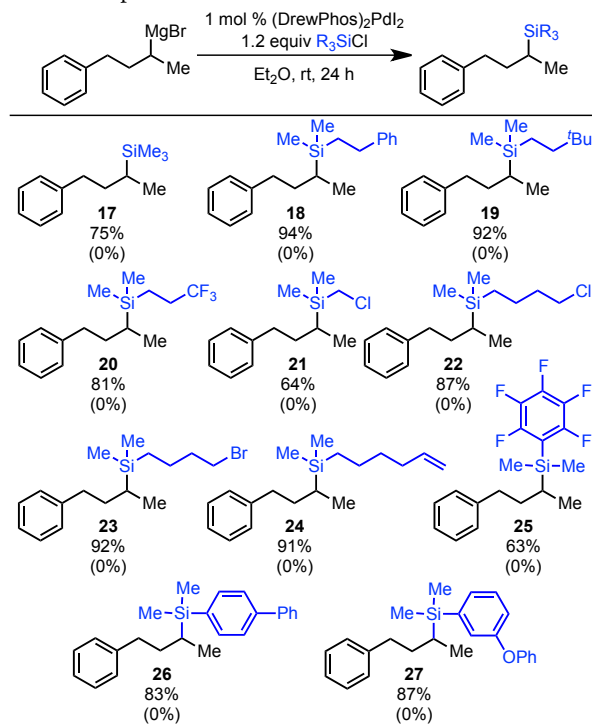
^a Isolated yields. ^b Parenthetical yields run without catalyst; determined by NMR. ^c 1.05 equiv Me₂PhSiCl ^d *exo:endo* 72:28. ^e From RMgCl.

Utilizing alkylmagnesium bromides, the scope of Grignard reagent was explored (Scheme 1). The model substrate **1** was isolated in quantitative yield on a 1-mmol scale. On a larger 100-mmol scale, the product could be isolated in nearly the same yield (96% yield, 17.2 g of product), demonstrating that the process is highly scalable.²⁴ Primary Grignard reagents show modest background reactivity; however, the catalyzed reaction resulted in quantitative yields (**3**). Acyclic and cyclic

secondary Grignard reagents were high yielding in the reaction (**4-6**, **10-13**). Stereoselectivity in the formation of product **6** is notable. ¹H NMR analysis confirmed that the bicyclic norbornyl Grignard reagent was formed in a 41:59 *exo:endo* ratio (as has been reported in the literature).²⁵ However, the product is formed in a 73:27 *exo:endo* ratio, suggesting a stereoconvergent mechanism may be at play.²⁶ α -Trimethylsilylmagnesium chloride was effective at generating disilylmethane **7**, a highly useful class of carbon pronucleophiles for Peterson olefination and related reactions.^{27,27c, 28} Sterically hindered neopentylsilanes **8** and **9** were also successfully synthesized even when utilizing the less active alkylmagnesium chloride reagents (**9**).²⁹

Aryl halides and aryl ethers (**11-12**) were tolerated in the reaction, and offer further cross-coupling handles for downstream manipulation.^{16c-e, 30} Benzylic substrate **13** was successfully formed while avoiding the formation of styrene byproducts, exemplifying the ability of the catalyst to disfavor β -hydride elimination. While sterically unencumbered aryl Grignard reagents add to chlorosilanes efficiently without catalysis (**14**), *ortho* substitution severely diminishes the uncatalyzed yield. Palladium catalysis allows full conversion of bulky aryl groups to form encumbered silanes (**15-16**). The addition of *ortho*-tolyl magnesium bromide to prepare **15** compares well with the prior catalytic conditions reported by Oshima,¹⁹ however, those studies did not report the addition of larger Grignard reagents, such as mesityl magnesium bromide. These examples demonstrate the ability of this catalytic system to accommodate highly sterically hindered coupling partners to form silanes that are otherwise inaccessible.

Scheme 2. Scope of Chlorosilane^{a,b}



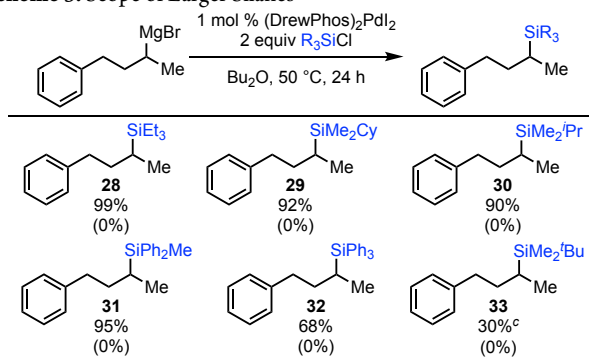
^a Isolated yields. ^b Parenthetical yields run without catalyst; determined by NMR.

After establishing the generality of the Grignard coupling partner, we sought to determine the scope of chlorosilane (Scheme 2).³¹ Various alkyl substitutions such as trimethyl- (**17**), dimethylphenethyl- (**18**), and dimethylneohexyl- (**19**) all reacted cleanly. Trifluoromethyl substitution (**20**) was also tolerated. Primary alkyl chloride (**21-22**) and bromide (**23**) substrates performed well, demonstrating remarkable selectivity of this catalyst for Si–Cl over C–halide activation and

allowing further reactivity such as substitution and cross-coupling reactions.^{16c, 32} In contrast to our previously published silyl-Negishi reaction,¹¹ synthetically useful terminal alkenes³³ (**24**) also progressed without incident. Aryl substitution such as pentafluoroaryl (**25**), biphenyl (**26**), and phenyl ether (**27**) substrates were well tolerated. Overall, this cross-coupling demonstrates a wide functional group tolerance that allows for a wide range of downstream manipulations.

Although larger chlorosilanes gave moderate yields at rt, increasing the temperature to 50 °C in Bu₂O allowed for highly efficient reactions (Scheme 3). Triethylsilyl chloride gave quantitative yields of **28**. Again, this directly contrasts the silyl-Negishi reaction, wherein sterically encumbered reagents as small as triethylsilyl iodide showed poor reactivity.¹¹ Cyclohexyl- and isopropylidimethylsilyl chloride also gave excellent yields of bis-secondary silanes **29** and **30**. Increasing aryl substitutions such as diphenyl- (**31**) and triphenylsilyl chloride (**32**) showed minimal effect on the reaction. Increasing the reaction temperature to 100 °C even allowed for modest reactivity of *tert*-butyldimethylsilyl chloride, resulting in a 30% yield of **33**. While modest in yield, the only other example of *tert*-butyldimethylsilyl halide (TBS-X) activation is through the use of more reactive TBS-OTf under nickel catalysis.^{10c}

Scheme 3. Scope of Larger Silanes^{a,b}



^a Isolated yields. ^b Parenthetical yields run without catalyst; determined by NMR. ^c Run at 100 °C.

From a synthetic standpoint, the ability to directly alkylate silyl chlorides with simple Grignard reagents represents a major advance in the synthesis of alkyl silanes. From a mechanistic standpoint, however, considering that both the Grignard reagent and the palladium precatalysts introduce heavier halides (bromide and iodide) to the reaction, we cannot rule out the possibility that the reactions in Schemes 2–4 are proceeding via initial halogen exchange at the silicon center.^{10a, 34} To better understand the role of the various halides in the reaction, we investigated reaction conditions that excluded heavier halogens. Using isopropyl magnesium chloride and the palladium chloride precatalyst (DrewPhos)₂PdCl₂, the alkylation of Me₂PhSiCl was investigated (Table 2). Although under these "all chloride" conditions, low reactivity was observed at room temperature (entry 1), simply warming the reaction to 50 °C provided efficient cross-coupling (entry 2). These results clearly demonstrate that the heavier halogens are not required for the cross-coupling to proceed. Alkyl magnesium chloride reagents are known to be highly aggregated in solution, and are often inferior Grignard reagents compared to their heavier halogen congeners.²¹ We believe that aggregation may be the reason for the sluggish reactivity observed in this study. Supporting this, addition of substoichiometric TMEDA, which is known to break up RMgCl aggregates, dramatically increased the observed reactivity under the "all chloride" conditions (entry 3).³⁵ Taken together, these results support the hypothesis that this catalytic system is capable of direct Si–Cl bond activation. Studies

to further elucidate the mechanism of this transformation are currently underway.

In conclusion, we report a general, palladium-catalyzed alkylation of chlorosilanes with primary and secondary alkylmagnesium halides. This transformation tolerates a multitude of reactive functional handles such as ethers, halogens, and alkenes, as well as sterically demanding nucleophilic and electrophilic coupling partners, which opens the products to a wide range of down-stream manipulations. Overall, utilizing widely available Grignard reagents and chlorosilanes, this methodology allows access to a vast range of primary and secondary alkyl silanes, as well as sterically demanding aromatic silanes, in a simple and straightforward manner.

Table 2. All Chloride Conditions

Reaction scheme showing the alkylation of Me₂PhSiCl with an alkylmagnesium chloride reagent (Me-CH₂-CH₂-MgCl) under catalytic conditions (1 mol % (DrewPhos)₂PdCl₂, 1.2 equiv Me₂PhSiCl, 24 h) to form product **1** (Me-CH₂-CH₂-SiMe₂Ph).

Entry	Solvent	Temp	Additive	Yield (%)
1	Et ₂ O	rt	---	6
2	Bu ₂ O	50 °C	---	70
3	Et ₂ O	rt	0.25 equiv TMEDA	52

^aDetermined by GC.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectral data. This material is available free of charge on the ACS Publications website.

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Notes

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The authors declare the following competing financial interests: UD has applied for a provisional patent related to this methodology.

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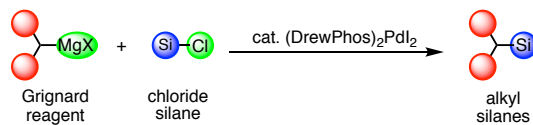
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Silyl-Kumada Reaction



- Direct Alkylation of Chlorosilanes Using 1° and 2° Grignard Reagents
- Commodity Chemical Starting Material to Access 1° and 2° Alkyl Silanes
- Up to 99% Isolated Yield