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Palladium-Catalyzed C(sp^3)−C(sp^2) Cross-Coupling of (Trimethylsilyl)methyllithium with (Hetero)Aryl Halides

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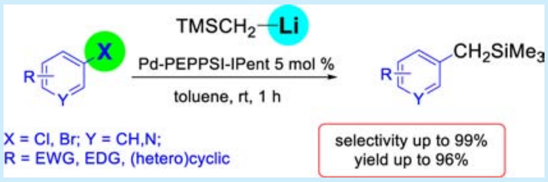
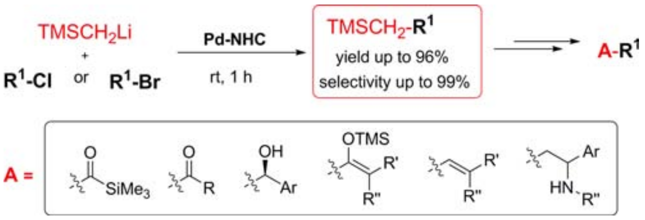
Ⓢ *Supporting Information*

ABSTRACT: The palladium-catalyzed direct cross-coupling of a range of organic chlorides and bromides with the bifunctional C(sp^3)-(trimethylsilyl)methyllithium reagent is reported. The use of Pd-PEPPSI-IPent as the catalyst allows for the preparation of structurally diverse and synthetically versatile benzyl- and allylsilanes in high yields under mild conditions (room temperature) with short reaction times.



The development of new catalytic methods for carbon−carbon bond formation continues to present major challenges in organic synthesis.[1] In particular, palladium-catalyzed cross-coupling of organometallic reagents with organic halides represents one of the most powerful methods for C−C bond formation.[2] Several well established methods for this transformation are available using different organometallic partners including organozinc,[3] organotin,[4] organoboron,[5] organosilicon,[6] and organomagnesium[7] reagents. Murahashi and co-workers pioneered the use of highly reactive aryl and alkyllithium reagents in catalytic cross-coupling reactions.[8] Our group recently described methods for the palladium-catalyzed direct cross-coupling of organolithium reagents with (hetero)-aryl- and alkenyl (pseudo)halides under mild conditions, avoiding side reactions such as lithium−halogen exchange or homocoupling.[9,10] Additionally, we also reported the reaction of sp^3 carbon nucleophiles with aryl bromides that allows a fast, selective, and high yielding coupling of primary and secondary alkyl groups with the notorious β-hydride elimination being suppressed in nearly all cases.[9a,e,11] Preliminary experiments showed the successful use of the functionalized C(sp^3) nucleophile $TMSCH_2Li$ in metal-catalyzed cross-coupling reactions.[9a,e] This bifunctional CH_2 moiety enables the preparation of stable $ArCH_2SiMe_3$ products that can further undergo a wide array of possible transformations including Peterson olefination,[12] photocatalyzed[13] and gold catalyzed[14] reactions, and oxidation to the corresponding acylsilanes[15] (Scheme 1). Furthermore, the CH_2 group can act as a nucleophile in fluoride-mediated processes giving rise to the formation of saturated products.[16a] Following our initial report,[9a] the use of this functionalized organolithium reagent recently attracted increasing attention in metal-catalyzed cross-couplings reactions, specifically using Ni catalysis.[16] Considering the relevance of the (trimethylsilyl)methyllithium nucleophile, we wondered if readily available but less reactive organic chlorides[17] could also be a precursors for the synthesis of highly versatile $TMSCH_2$-functionalized compounds. Costs, waste production, and availability benefit from the use of aryl chlorides as starting materials. However, due to their low reactivity, the use of high temperatures and long reaction times is usually required while the use of aryl chlorides in metal-catalyzed C(sp^3)−C(sp^2) cross-coupling reactions with organolithium reagents remains a challenge.[18]

Scheme 1. Pd-Catalyzed Cross-Coupling of Aryl Halides Employing $TMSCH_2Li$ and Possible Further Transformations at the $TMSCH_2$ Group



Here, we report the development of a Pd-catalyzed cross-coupling reaction employing aryl chlorides and $TMSCH_2Li$ that allows selective preparation of a variety of $ArCH_2TMS$ compounds in high yields under mild conditions (rt) and short reaction times (1 h) (Scheme 1).

The reaction between 4-methoxychlorobenzene **1a**, a reluctant aryl chloride in coupling reactions, and $TMSCH_2Li$ was chosen as a model system since conditions for the successful coupling of this substrate will enable access to a wide variety of other coupling partners. Under the optimized conditions for the cross-coupling of alkyllithium reagents with aryl bromides,[9a] using $Pd(PtBu_3)_2$[19] as a catalyst (Table 1, entry 1), less than 5% conversion to the coupling product **2a** was observed. The *in situ* prepared palladium complexes, using $Pd_2(dba)_3$ in combination with $P(tBu)_3$ or dialkylbiaryl phosphines,[20] previously reported to be effective for the Pd-catalyzed cross-coupling with other aryl and alkyllithium reagents, led to similar results (Table 1, entries 2−4). Employing NHC ligands, we were delighted to find that the air stable Pd-PEPPSI-IPent catalyst, introduced by the group of Organ,[21] afforded full conversion and nearly perfect selectivity

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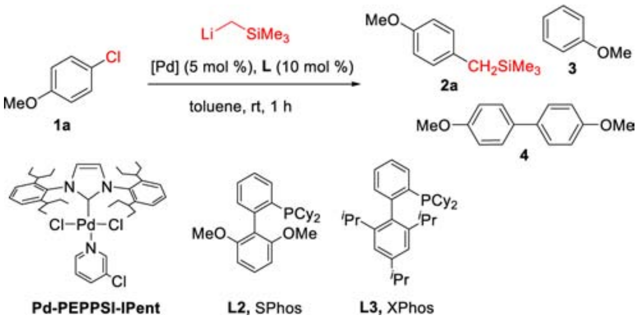
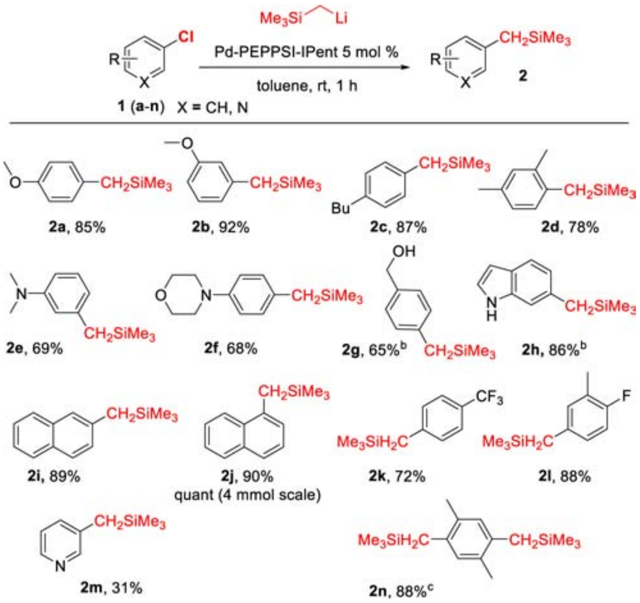
Table 1. Screening of Different Ligands



entry[a]	[Pd]	ligand	conv (%)	2a:3:4[b]
1	$Pd(PtBu_3)_2$		<5	
2	$Pd_2(dba)_3$	L1, $P(tBu)_3$[c]	<5	
3	$Pd_2(dba)_3$	L2, SPhos	<5	
4	$Pd_2(dba)_3$	L3, XPhos	<5	
5	Pd-PEPPSI-IPent		full	98:<1:< 1
6	Pd-PEPPSI-IPr		~85	98:<1:< 1

[a] Conditions: $TMSCH_2Li$ (0.72 mL, 1.0 M in pentane) was added to a solution of 4-bromoanisole (0.6 mmol) in toluene (2 mL). 1 h addition time. [b] **2a**:**3**:**4** ratios determined by GC analysis. [c] 7.5 mol % was used. dba = dibenzylideneacetone.

Scheme 2. Pd-Catalyzed Cross-Coupling of $TMSCH_2Li$ with (hetero)aryl chlorides.[a]



[a] Conditions: Aryl halide (0.6 mmol), $TMSCH_2Li$ (0.72 mmol, 1.0 M in pentane), toluene (2 mL). 1 h addition time. Selectivity >98%. Yield values refer to isolated yields after purification. [b] iPrMgCl (1.0 equiv, 2 M in Et_2O) was added over 5 min prior to the organolithium. [c] $TMSCH_2Li$ (1.44 mmol).

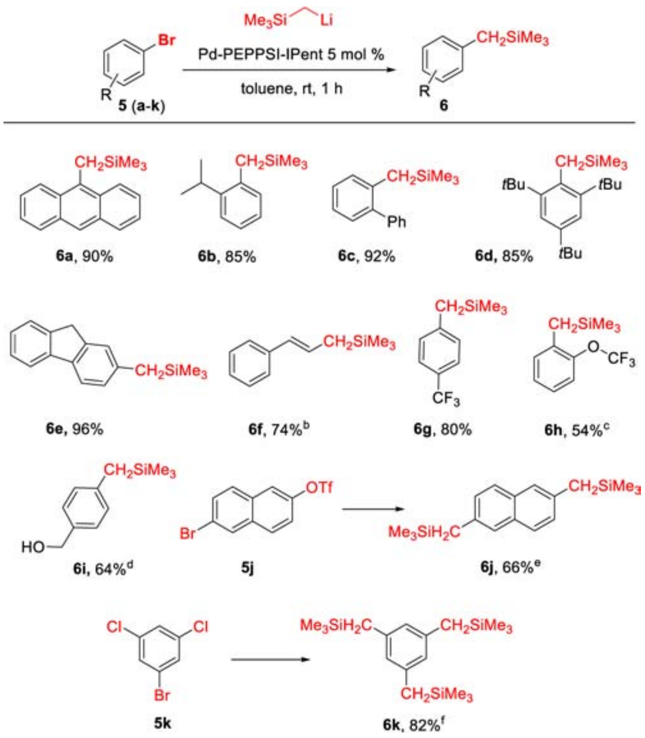
toward the coupled product **2a** at rt in 1 h, avoiding dehalogenation or homocoupling side products **3** and **4** (entry 5, Table 1). It should be mentioned that, for the corresponding Pd-catalyzed cross-couplings of **1a** with aryllithium reagents, higher temperatures (40 °C) and longer addition times (3 h) of the organolithium reagent were necessary to reach full conversion and high selectivity.[9c] The corresponding Pd-PEPPSI-IPr also performed well in the reaction, although full conversion was not reached (entry 6).

With Pd-PEPPSI-IPent as a highly efficient catalyst system, we set out to investigate the cross-coupling between $TMSCH_2Li$ and different aryl chlorides (Scheme 2). The reactions employing other electron-rich aryl chlorides such as **1b**, **1c**, or more sterically hindered **1d** also proceed with full conversion and high selectivity without the need to increase the temperature or reaction time. Remarkably, highly deactivated amine-substituted aryl chlorides **1e** and **1f**, which did not perform well in the cross-coupling with aryllithium reagents,[9c] were also converted under the optimized reaction conditions to the desired product in good yields and with excellent selectivities (Scheme 2). It should be emphasized that benzyl alcohol **1g**, as the Mg alkoxide, and 6-chloro-1*H*-indole **1h**, as the Mg amide, were also tolerated, affording products **2g** and **2h** with high selectivity. The catalytic system proved to be also efficient in the reaction with 1- and 2-chloronaphthalene **1i** and **1j**, providing the corresponding trimethyl(naphthalenylmethyl)silanes **2i** and **2j** with no trace of regioisomers, indicating that benzyne intermediates via 1,2-elimination are not formed. Importantly, **2j** was obtained quantitatively when the reaction was scaled up to 4.0 mmol. The electron-deficient 1-chloro-4-(trifluoromethyl)benzene **1k** and 4-chloro-1-fluoro-2-methylbenzene **1l** underwent clean coupling, giving high isolated yields of the fluorinated structures **2k** and **2l**. Pyridyl rings, which are susceptible to nucleophilic addition of alkyllithium reagents, also participated in the cross-coupling with high selectivity, albeit with lower yield after purification, as illustrated for substrate **1m**. Facile multiple coupling is illustrated in the reaction of **1n** with 2.1 equiv of $TMSCH_2Li$ providing bis-silylated product **2n** in good yield.

After having established Pd-PEPPSI-IPent as a highly efficient catalyst for the cross-coupling of $TMSCH_2Li$ with aryl chlorides, we studied the scope of this catalyst in the reaction with challenging organic bromides. Sterically hindered bromides, known for being more reluctant substrates for the coupling of alkyl units,[22] were tested for the first time in combination with $TMSCH_2Li$. As shown in Scheme 3, a variety of bulky organic bromides (**5a**−**d**) could be coupled with excellent selectivity at room temperature within 1 h, indicating that the transmetalation step takes place rapidly, facilitating a fast coupling process. Notably, di-*ortho*-substituted *tert*-butyl aryl bromide **5d** was tolerated, affording the TMS-functionalized product **6d** at rt in high yield. Remarkably, bromofluorene was successfully employed, despite the acidity of the benzylic protons (pK_a = 22). Alkenyl bromide **5f** also undergoes this cross-coupling, leading to allyltrimethylsilane **6f** with high selectivity with no presence of Fritsh−Butlenberg−Wiechell type rearrangement side products.[23] Fluorinated bromides **5g** and **5h** also underwent clean coupling without any traces of side products. Similar to the corresponding aryl chloride **1g**, (4-bromophenyl)methanol **5i**, bearing an unprotected hydroxyl group, could also be coupled with this organolithium reagent, provided the corresponding Mg alkoxide was first generated. In the presence of an excess of $TMSCH_2Li$, both the −OTf and −Cl groups present in aryl bromides **5j** and **5k** were also coupled leading to products which contain two or three $TMSCH_2$ functional groups.

As shown above, the Pd-PEPPSI-IPent complex has been shown to be an extremely efficient and versatile catalyst for the cross-coupling of (trimethylsilyl)methyllithium with (hetero)-aryl chlorides, bromides, and triflates. However, the use of aryl chlorides presents additional advantages compared to the

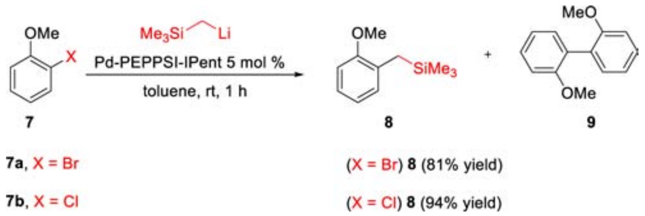
Scheme 3. Pd-Catalyzed Cross-Coupling of $TMSCH_2Li$ with Alkenyl and Aryl Bromides[a]



[a]Conditions: Aryl halide (0.6 mmol), $TMSCH_2Li$ (0.72 mmol, 1.0 M in pentane), toluene (2 mL). Selectivity >98%. Yield values refer to isolated yields after purification. [b]Yield determined by ^1H NMR using tetrachloroethane as internal standard. [c]Moderate yield obtained after purification by column chromatography. [d]*i*PrMgCl (1.0 equiv, 2 M in Et_2O) was added over 5 min prior to the organolithium. [e]$TMSCH_2Li$ (1.44 mmol). [f]$TMSCH_2Li$ (2.16 mmol).

aforementioned, as they are less prone to undergo halogen—lithium exchange with the organolithium compound, preventing the formation of homocoupling or dehalogenated side products.[24] We have recently shown that this different behavior is evidenced in the Pd-catalyzed cross-coupling of 2-alkoxy-substituted bromo- and chloroarenes where the coordination of the ortho-methoxy group with the organolithium compound facilitates the Li—Br exchange and further stabilizes the resulting aryllithium compound.[9f] Here, the $C(sp^3)$ character of $TMSCH_2Li$, when compared with $C(sp^2)$ in aryl lithium reagents, could further enhance this effect. As shown in Scheme 4, this difference in reactivity was confirmed in the cross-coupling with 1-bromo-2-methoxybenzene **7a**, where the $TMSCH_2$ functionalized product was obtained along with a homocoupling side product. However, the use of the corresponding aryl chloride **7b** led to the desired silylated product **8** with nearly perfect selectivity and high yield, in accordance with the reduced tendency to undergo halogen—lithium exchange, and this enhanced selectivity will be beneficial in synthetic applications.

Scheme 4. Comparison between the Pd-Catalyzed Cross-Coupling of $TMSCH_2Li$ with 1-Chloro- and 1-Bromo-2-methoxybenzene



In summary, we have shown the direct Pd-catalyzed cross-coupling of $TMSCH_2Li$ with organic (pseudo)halides, including reluctant but cheap and readily available organic chlorides, in high yields and excellent selectivity. The method is based on the use of the commercially available Pd-PEPPSI-IPent catalyst. The reactions take place under mild conditions with a broad substrate scope. The products formed are attractive, stable, α-C-activated,[25] and precursors for various further transformations.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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