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Title: Bench-Stable Stock Solutions of Silicon Grignard Reagents: Application to Iron- and Cobalt-Catalyzed Radical C(sp3)-Si Cross-Coupling Reactions

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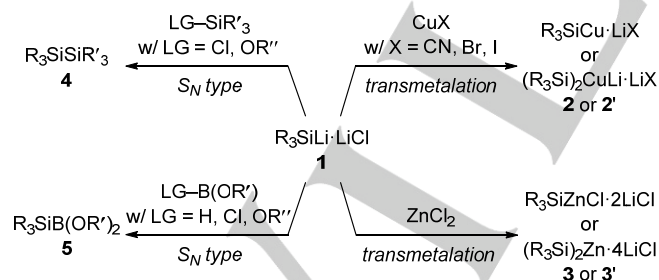
Bench-Stable Stock Solutions of Silicon Grignard Reagents: Application to Iron- and Cobalt-Catalyzed Radical C(sp^3)–Si Cross-Coupling Reactions

Weichao Xue, Ryosuke Shishido, and Martin Oestreich*

Abstract: A robust protocol for preparation of silicon-based magnesium reagents is reported. The MgBr$_2$ used in the lithium-to-magnesium transmetalation step is generated in situ from 1,2-dibromoethane and elemental magnesium in hot THF. No precipitation of MgBr$_2$ occurs in the heat, and transmetalation at elevated temperature leads to homogeneous stock solutions of the silicon Grignard reagents stable and storable in the fridge. This method avoids the preparation of silicon pronucleophiles such as Si–Si and Si–B reagents. The new Grignard reagents are applied to unprecedented iron- and cobalt-catalyzed cross-coupling reactions of unactivated alkyl bromides. The functional-group tolerance of these magnesium reagents is excellent.

A common way of forming carbon–silicon bonds is by the use of silicon nucleophiles and pronucleophiles, respectively. These are essentially all derived from R$_3$SiLi **1** where one of the R groups is inevitably an aryl group and, hence, Ar$_{3-n}$R$_n$Si with n = 0–2 is the more proper description. That constraint is the result of their preparation by reductive metalation of R$_3$SiCl with sodium-rich lithium metal.[1] Without an aryl group attached to the silicon atom, the reaction stops at the disilane stage.[2] The strong nucleophilicity and high basicity of **1** are however severely detrimental to functional-group tolerance and, as such, synthetic applications. The facile transmetalation from lithium to copper (**1 → 2/2'**) or zinc (**1 → 3/3'**) turns hard **1** into soft silicon nucleophiles (Scheme 1, right), and **2/2'**[3] and **3/3'**[4,5] have enjoyed tremendous popularity in synthetic chemistry. Another approach is to transform **1** into silicon- and boron-based pronucleophiles **4**[6] and **5**[7] by the reaction of **1** with appropriate electrophiles (Scheme 1, left). In this context, the widespread use of Si–B reagents **5** clearly stands out.[7c,7d]

Scheme 1. Selected approaches to the preparation of silicon (pro)nucleophiles.

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The preparation of silicon Grignard reagents R$_3$SiMgX ought to follow the same transmetalation approach but is almost unprecedented.[8] Part of the problem is the poor solubility of magnesium salts in ethereal solvents, merely affording the Grignard reagents in low concentration[8c,8d] (see Supporting Information for details). Also, the direct reductive metalation of R$_3$SiCl with less electropositive elemental magnesium does not arrive at R$_3$SiMgCl but at the corresponding disilane even with aryl substitution of the silicon atom.[1a] We disclose here a robust protocol for the preparation of silicon Grignard reagents which hinges on the temperature-controlled formation of a homogeneous solution of MgBr$_2$ in THF. The value of the new reagents is demonstrated in iron- as well as cobalt-catalyzed C(sp^3)–Si cross-coupling reactions that follow a radical mechanism.

The basic idea was to generate a precipitate-free ethereal solution of MgBr$_2$.[9] This was achieved by reacting 1,2-dibromoethane with magnesium turnings in THF with heating and *maintaining* the solution at reflux (Scheme 2, top). After 3 h, freshly made R$_3$SiLi **1** was added at that temperature to result in a colored but clear solution of R$_3$SiMgX **6** (the color is dependent on the R groups at the silicon atom; see the Supporting Information for details). This procedure was reliable and allowed for the preparation of 0.5M stock solutions of various aryl-substituted silicon Grignard reagents **6a–e** (Scheme 2, bottom); the concentration was estimated by titration against iodine. Likewise, heteroatom-substituted **6f** was obtained from Tamao's silicon nucleophile.[1b]

additional salts omitted for clarity (X = Cl and Br)
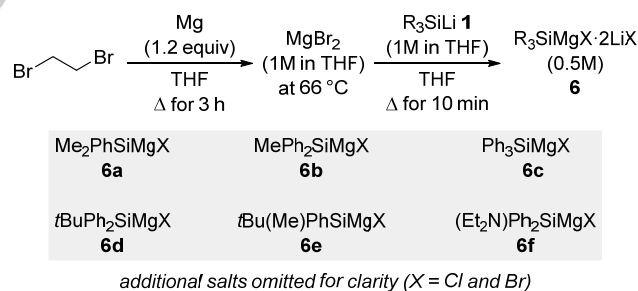
Scheme 2. Preparation of bench-stable stock solutions of silicon Grignard reagents.

There are several benchmark reactions, e.g., conjugate addition and allylic substitution, to which the aforementioned silicon (pro)nucleophiles **2**–**5** have been applied with success.[3,4b,7c,7d] However, we decided to probe **6** in a less established carbon–silicon bond-forming reaction, namely the transition-metal-catalyzed C(sp^3)–Si cross-coupling between unactivated alkyl electrophiles and silicon nucleophiles.[10–13] Fu and co-workers[10] and our laboratory[11,12] recently presented solutions for this challenging transformation, either using R$_3$SiZnCl **3** in a nickel-catalyzed coupling of alkyl bromides[10] or R$_3$SiBpin **5** in copper-catalyzed couplings of alkyl iodides.[11,14]
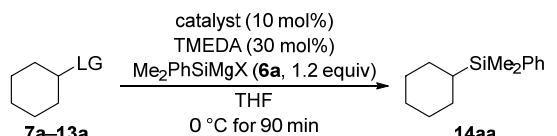
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Our investigations employing Me$_2$PhSiMgX **6a** showed that 10 mol% FeBr$_3$ or CoCl$_2$ as precatalyst together with 30 mol% TMEDA are competent catalysts for the chemoselective C(sp^3)–Si cross-coupling of the unactivated alkyl bromide **7a** (Table 1, entries 1 and 2). Systematic optimization revealed that yields decreased substantially with less than 20 mol% TMEDA (see the Supporting Information for details). We explain this with the formation of (TMEDA)$_2$Fe(III) or (TMEDA)$_2$Co(II) complexes at an early stage of the reaction. Also, it is important to note that slow addition of **6a** to the reaction mixture is crucial to suppress homocoupling, hydrodehalogenation, and β-elimination. MnBr$_2$ and the previously reported precatalysts NiBr$_2$·diglyme[10] and CuSCN[11] were not or far less effective (entries 3–5). Out of the other typical leaving groups, i.e., chloride, iodide, and tosylate (**8a**–**10a**), it was only alkyl iodide **9a** that participated in the cross-coupling (entries 6–8). We included *N*-hydroxyphthalimide ester[15a] **11a**,[16] 1-phenyltetrazole sulfone[15b] **12a**, and 2,4,6-triphenylpyridinumtetrafluoroborate[15c] **13a** into our survey but neither afforded any of the desired coupling product **14aa** (entries 9–11).

Table 1. Selected examples of optimization reactions.[a]

Entry	Alkyl electrophile	Catalyst	Yield [%][b]
1	**7a** (LG = Br)	FeBr$_3$	90 (93)[c]
2	**7a** (LG = Br)	CoCl$_2$	89 (90)[c]
3	**7a** (LG = Br)	MnBr$_2$	7
4	**7a** (LG = Br)	NiBr$_2$·diglyme	38
5	**7a** (LG = Br)	CuSCN	17
6	**8a** (LG = Cl)	FeBr$_3$	<5
7	**9a** (LG = I)	FeBr$_3$	50
8	**10a** (LG = OTs)	FeBr$_3$	<5
9	**11a**	FeBr$_3$	<5
10	**12a**	FeBr$_3$	<5
11	**13a**	FeBr$_3$	<5

[a] All reactions were performed on a 0.20 mmol scale. [b] Determined by GLC analysis with tetracosane as an internal standard. [c] Isolated yield on a 1.0 mmol scale. TMEDA = *N,N,N′,N′*-tetramethylethylenediamine, diglyme = 1-methoxy-2-(2-methoxyethoxy)ethane. LG = leaving group.

With iron- and cobalt-catalyzed protocols at hand, we continued with an in-depth investigation of the scope of the iron catalysis. Alkyl bromide **7b** was chosen as model substrate for testing the silicon Grignard reagents **6a–f** (**7b** → **14ba–bf**, Scheme 3). The couplings of Me$_2$PhSi (from **6a**), MePh$_2$Si (from **6b**), and Ph$_3$Si (from **6c**) were generally high-yielding while those of more hindered *t*BuPh$_2$Si (from **6d**) and *t*Bu(Me)PhSi (from **6e**) were less efficient even at elevated temperature. When (1*R*,2*R*)-*N,N,N′,N′*-tetramethylcyclohexane-1,2-diamine was used as a chiral ligand instead of TMEDA (not shown), no stereogenicity at the silicon atom was induced with racemic *t*Bu(Me)PhSiMgX (**6e**). Gratifyingly, Et$_2$N-substituted **6f** worked also reasonably well under the standard setup.
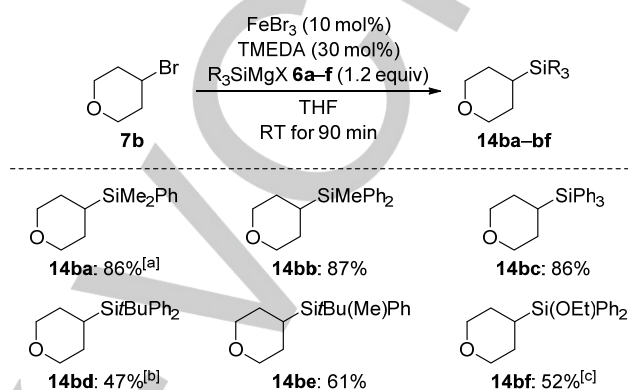
Scheme 3. Iron-catalyzed C(sp^3)–Si cross-coupling of an unactivated secondary alkyl bromide with various silicon Grignard reagents. [a] Run at 0 °C. [b] Run at 50 °C. [c] EtOH/NH$_4$Cl added after the reaction.

Proceeding with Me$_2$PhSiMgX (**6a**) as the silicon nucleophile, we subjected primary, secondary, and tertiary alkyl bromides to the general procedure (Scheme 4). Yields were high throughout except for secondary benzylic and tertiary electrophiles (*vide infra*). The functional-group tolerance is generally excellent and compares well with that of the existing nickel-[10] and copper-catalyzed[11] protocols. A broad range of carbonyl (including an aldehyde protected as acetal) and carboxyl groups and the cyano group was compatible; no addition of the silicon Grignard reagent to a methyl ketone (as in **14ua**) and acylated primary alcohols (as in **14ha** and **14wa**) were seen. As predicted from the optimization study (Table 1, entry 6), the displacement of the C(sp^3)–Br bond is favored of the C(sp^3)–Cl bond, chemoselectively forming **14ea** (trace amounts of the bissilylated compound were detected; see the Supporting Information for details). Alkenes did not interfere (as in **14da** and **14ua**) but the terminal alkene in 4-bromobut-1-ene (**7d**) shifted to the internal position, affording the thermodynamically more stable allylic silane **14da**. There was no diastereocontrol in this radical reaction: 1-bromo-4-methylcyclohexane (**7p**, d.r. = 50:50) afforded **14pa** with d.r. = 55:45 and isomerically pure **7u** (d.r. > 99:1) epimerized to d.r. = 54:46 for **14ua**. More biased *exo*-2-bromonorbornane (**7q**, d.r. > 99:1) reacted to **14qa** with preservation of the relative configuration (d.r. = 97:3).

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Scheme 4. Iron-catalyzed C(sp^3)–Si cross-coupling of primary, secondary, and tertiary alkyl bromides. [a] Prepared from 4-bromobut-1-ene with migration of the terminal double bond. Yield is for the mixture of isomers. [b] Determined by GLC analysis with tetracosane as internal standard. [c] 10 mol% CoCl$_2$ as catalyst.

Two-fold C(sp^3)–Si cross-coupling reactions were also possible [Eq. (1)]. The 1,3-dibromides **15a** and **15b** containing primary and secondary C(sp^3)–Br bonds converted into **16aa** and **16ab** at higher catalyst loading.

In analogy to the majority of iron-[18–20] and cobalt-catalyzed[21,22] cross-coupling reactions of alkyl halides, we believe that the present silylation of unactivated alkyl bromides also proceeds through radical intermediates. The usual evidence[11,16] was obtained from the radical-probe experiments

with (bromomethyl)cyclopropane (**7a'**), exclusively producing ring-opened **17a'a** with no trace of **14a'a** (Scheme 5, top). Also, 6-bromohex-1-ene underwent a 5-*exo*-trig ring closure (not shown; see the Supporting Information for details). Racemization experiments with (*S*)-**7b'** documented the complete loss of enantiopurity for **14b'a** (Scheme 5, bottom). Although a detailed mechanistic analysis is beyond the current report, we think that highly reactive low-valent Fe–Si and, likewise, Co–Si species are generated by reduction of the precatalysts with the silicon Grignard reagent. These, in turn, allow for the single-electron reduction of the C(sp^3)–Br bond according to the literature precedence.[18–22]

Scheme 5. Control experiments.

The present work provides a practical solution to the preparation, handling, and storage of silicon nucleophiles. The ethereal solution of the silicon Grignard reagents avoids the detour of transforming highly reactive lithiated silicon reagents into stable pronucleophiles. The new method relies on the in-situ generation of MgBr$_2$ in THF at elevated temperature where no precipitate, that is, hard-to-redissolve magnesium salts, is formed. These magnesium reagents have been applied to a current problem in synthetic chemistry, and iron- as well as cobalt-catalyzed C(sp^3)–Si cross-coupling reactions are now available. The functional-group tolerance of these silicon Grignard reagents is excellent.

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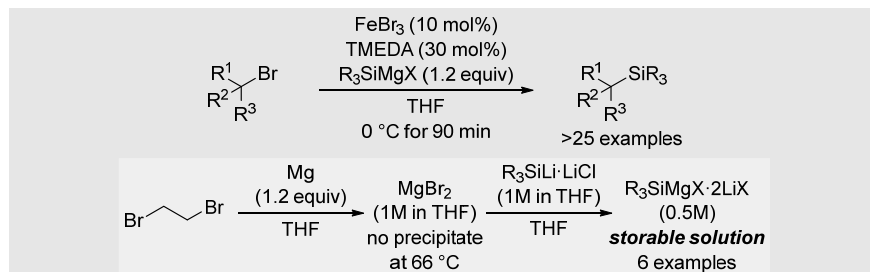
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Bottled silicon in stock. Lithium-to-magnesium transmetalation in the heat allows for the preparation of silicon-based magnesium reagents as bench-stable homogeneous ethereal solutions. Because of this, silicon nucleophiles do not have to be converted into less reactive pronucleophiles anymore. The new Grignard reagents display excellent functional-group tolerance in unprecedented iron- and cobalt-catalyzed cross-coupling reactions of unactivated alkyl bromides (see scheme).