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Copper-Catalyzed Double C(sp^3)−Si Coupling of Geminal Dibromides: Ionic-to-Radical Switch in the Reaction Mechanism

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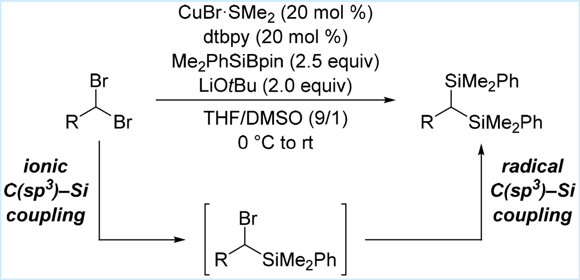
Supporting Information

ABSTRACT: A method for converting geminal dibromides into 1,1-disilylated alkanes is reported. The reaction is promoted by a copper(I) catalyst generated in situ from $CuBr{\cdot}SMe_2$ as a precatalyst and 4,4′-di-*tert*-butyl-2,2′-bipyridine (dtbpy) as a ligand. A Si−B reagent is used as the silicon pronucleophile. It is shown that the two C(sp^3)−Si bond-forming events differ in mechanism, with the first being ionic and the second being radical.



Molecules containing two main-group elements such as boron and/or silicon at the same sp^3-hybridized carbon atom are useful synthetic building blocks (Figure 1).[1] Several efficient methods for the direct and stepwise preparation of 1,1-diborylated alkanes from a diverse set of precursors are available.[2−7] The installation of a boryl and a silyl substituent is also known but less established.[8,9] Likewise, examples of the direct introduction of two silicon moieties is equally scarce,[10] except for a recently reported palladium-catalyzed insertion of benzylic carbenes into Si−Si bonds.[11]

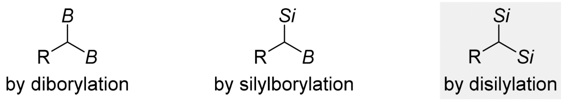
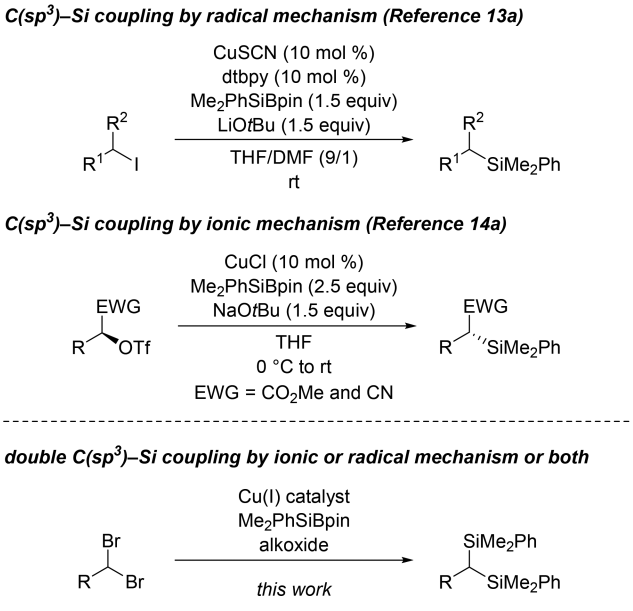


Figure 1. Boron and silicon attached to the same sp^3-hybridized carbon atom.

The formation of two carbon−element bonds in a single synthetic operation by (formal) substitution of geminal dihalides is often difficult due to their propensity to undergo β-elimination. While this was successfully accomplished in the case of twofold borylation,[2] the related C(sp^3)−Si bond formation is unprecedented. As part of our ongoing program directed toward C(sp^3)−Si coupling of unactivated alkyl electrophiles, we developed copper-catalyzed cross-coupling reactions using Si−B reagents[12] as silicon pronucleophiles (Scheme 1, top).[13,14] It is worth mentioning that unactivated alkyl iodides (and bromides) react by a radical mechansim,[13a] whereas substitution of alkyl triflates α to an electron-withdrawing group (EWG) proceeds by an ionic mechanism with inversion of the configuration.[14a] Based on these results, we felt that the double C(sp^3)−Si coupling of geminal dibromides could become feasible (Scheme 1, bottom). Herein, we report a copper-catalyzed synthesis of 1,1-disilylated alkanes that involves both an ionic and a radical C(sp^3)−Si coupling step.

Scheme 1. Catalytic C(sp^3)−Si Coupling of Alkyl Electrophiles by Radical or Ionic Mechanism



A systematic optimization of the reaction setup was performed (see the Supporting Information for details). From this, a combination of $CuBr{\cdot}SMe_2$ as a precatalyst, 4,4′-di-*tert*-butyl-2,2′-bipyridine (dtbpy) as a ligand, and lithium *tert*-butoxide as an alkoxide in THF/DMSO (9/1) emerged as optimal (Table 1). At 0 °C, an olive green solution formed after 5 min to which $Me_2PhSiBpin$[15] and dibromide **1a** were successively added. After the mixture stirred overnight at room temperature, this procedure furnished disilylated **2a** in

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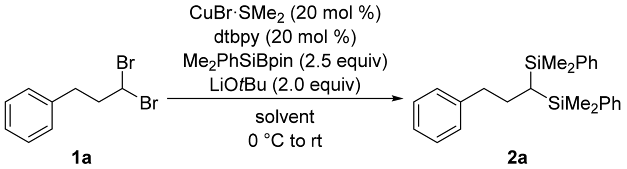
Table 1. Selected Examples of the Reaction Optimization[a]



entry	variation	solvent	yield[b] (%)
1	none	THF/DMSO (9/1)	95 (74[c])
2	w/o CuBr·SMe$_2$	THF/DMSO (9/1)	–
3	w/o dtbpy	THF/DMSO (9/1)	–
4	w/o LiO*t*Bu	THF/DMSO (9/1)	–
5	–	THF/DMF (9/1)	64
6	–	THF	57
7	CuBr	THF/DMF (9/1)	22
8	CuSCN	THF/DMF (9/1)	–
9	phen[d]	THF/DMF (9/1)	13
10	NaO*t*Bu	THF/DMSO (9/1)	19[e]

[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 after purification by flash chromatography on silica gel. [d] 1,10-Phenanthroline. [e] Decomposition of the starting material.

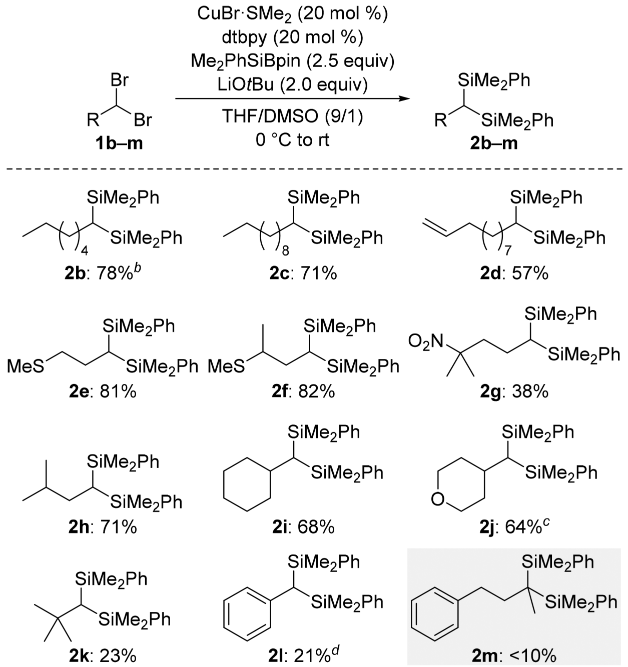
74% isolated yield (entry 1). Monitoring the reaction by GLC analysis showed that 75% of the starting material had been consumed after 2 h, but reactions were nevertheless routinely run overnight. Control experiments showed that each of the components is necessary (entries 2–4). Replacing DMSO by DMF in the THF solvent system led to a lower yield (entry 5), which further decreased with no additive (entry 6). The copper source had a dramatic effect on the reaction outcome as did the ligand and the alkoxide base (entries 7–10). As expected, no reaction was seen with the related dichloro-substituted derivative (not shown).[13a]

With the optimized reaction conditions in hand, we explored the substrate scope of the sequential double silylation (Scheme 2). Yields were consistently good for terminal dibromides with no branching in the proximity (**1b–g** → **2b–g**). The functional-group tolerance was reasonable, including a terminal alkene as in **1d** and a nitro group as in **1g**. Branching closer to the reaction site as in **1h** with an isobutyl group and in **1i** with a cyclohexyl group was not detrimental. However, the yield dropped substantially with *tert*-butyl as the R group (**1k** → **2k**). Also, benzylic substrate **1l** transformed into **2l** in low yield, accompanied by oligomerization of the starting material. Internal dibromide **1m** reacted sluggishly, mainly forming the monosilylated coupling product (gray box); this is consistent with our earlier observation that tertiary alkyl halides do not participate in these cross-coupling reactions.[13]

To exclude base-mediated *β*-elimination followed by copper-catalyzed addition of the silicon nucleophile across the C–C triple bond, we performed a series of control experiments. Vinyl bromide **3a** and/or terminal alkyne **4a** did not form by treatment of **1a** with lithium *tert*-butoxide in the absence (Scheme 3) or presence (not shown) of the Si–B reagent. We further confirmed that **4a** does not participate in the copper-catalyzed silylation under the standard reaction conditions without an additional proton source.[16]

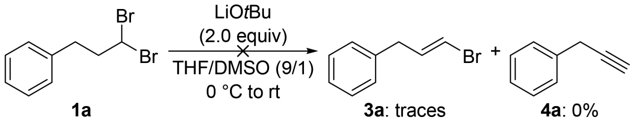
From our earlier work we knew that these copper-catalyzed C(sp^3)–Si couplings do follow distinctly different mechanisms depending on the alkyl electrophile (see Scheme 1, top).[13a,14] To probe this and to distinguish between the two C(sp^3)–Si bond-forming events, we designed the radical-clock experiment outlined in Scheme 4 (top). The formation of the conventional product **2n** from **1n** would be the result of two ionic steps, while radical steps would be involved in the generation of the ring-

Scheme 2. Scope of the Copper-Catalyzed C(sp^3)–Si Coupling of Geminal Dibromides[a]

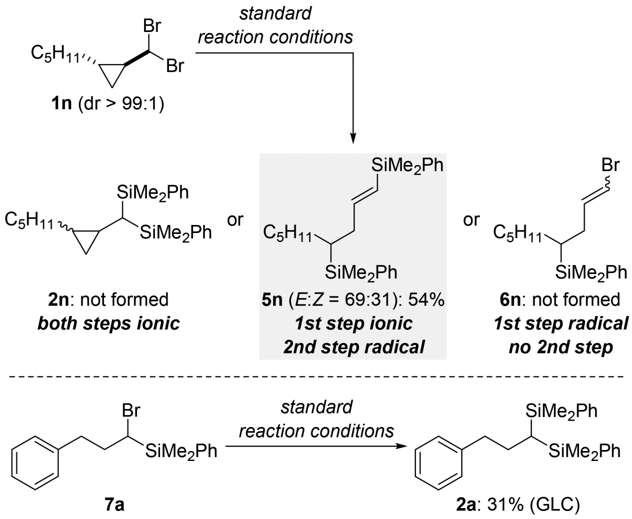


[a] Unless otherwise noted, isolated yields after purification by flash chromatography on silica gel. [b] 54% isolated yield on a 1.0 mmol scale. [c] Contaminated with 10% of the monosilylated compound. [d] Isolated yields after purification by preparative TLC.

Scheme 3. Control Experiment: Attempted Base-Mediated *β*-Elimination



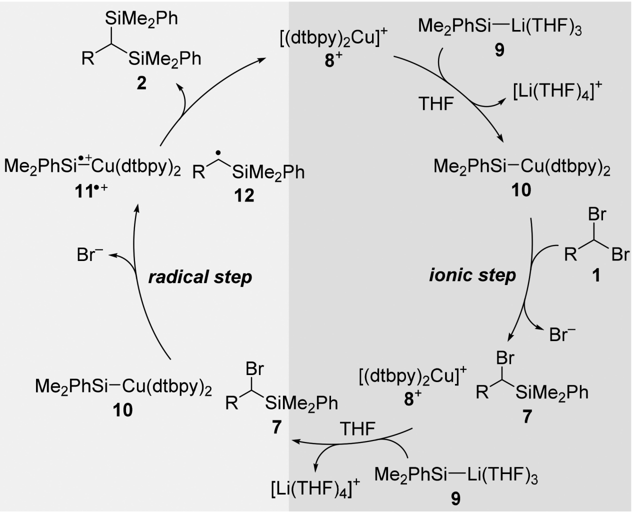
Scheme 4. Control Experiment: Radical-Clock Experiment



opened products **5n** and **6n**, respectively. Neither **2n** nor **6n** was obtained, but **5n** (gray box) was isolated in 54% yield. The formation of **5n** can be rationalized by a switch from an ionic in the first to a radical mechanism in the second C(sp^3)−Si coupling. In other words, α-bromo-substituted alkyl bromide **1n** reacts through the ionic pathway[14] and the intermediate α-silylated alkyl bromide couples through the radical pathway.[13a] To further verify this, we independently prepared the α-silylated bromide **7a** and subjected it to the standard protocol to afford the cross-coupling product **2a** in 31% GLC yield (Scheme 4, bottom).

On the basis of this insight as well as our previous quantum-chemical analysis of the radical process,[13a] we suggest the following catalytic cycle for the double C(sp^3)−Si cross-coupling reaction of geminal dibromides (**1** → **2**, Scheme 5).

Scheme 5. Proposed Catalytic Cycle



The copper-based silicon nucleophile **10** is generated from **8**$^+$ and **9** (**10** is in situ released from the Si−B reagent with the aid of lithium *tert*-butoxide[13a]). Nucleophile **10** then displaces one of the bromine atoms in activated **1** to furnish the α-silylated bromide **7**.[14a] Unactivated **7** subsequently engages in the radical coupling with another molecule of **10**,[13a] passing through silicon-stabilized radical[17] **12**. Radical cation **11**$^{\bullet+}$ and carbon-centered radical **12** finally recombine to yield the 1,1-disilylated alkane **2**.

To summarize, we described here a new synthesis of 1,1-disilylated alkanes starting from readily available geminal dibromides. The approach merges two copper-catalyzed C(sp^3)−Si cross-coupling reactions from our laboratory.[13a,14] The first displacement of bromide at the activated carbon atom follows an ionic mechanism, while the second at the intermediate unactivated carbon atom follows a radical pathway.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02281.

General procedures, experimental details, and characterization/spectral data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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