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Copper-Catalyzed Cross-Coupling of Silicon Pronucleophiles with Unactivated Alkyl Electrophiles Coupled with Radical Cyclization

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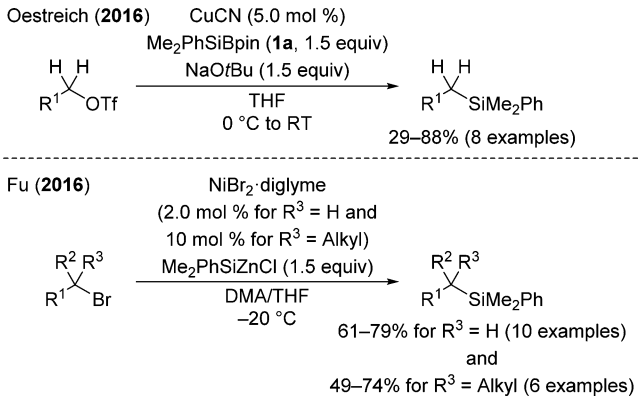
Supporting Information

ABSTRACT: A copper-catalyzed C(sp^3)−Si cross-coupling of aliphatic C(sp^3)−I electrophiles using a Si−B reagent as the silicon pronucleophile is reported. The reaction involves an alkyl radical intermediate that also engages in 5-exo-trig ring closures onto pendant alkenes prior to the terminating C(sp^3)−Si bond formation. Several Ueno−Stork-type precursors cyclized with excellent diastereocontrol in good yields. The base-mediated release of the silicon nucleophile and the copper-catalyzed radical process are analyzed by quantum-chemical calculations, leading to a full mechanistic picture.

Methods for the formation of carbon−silicon bonds by nucleophilic substitution or cross-coupling of unactivated alkyl electrophiles with silicon nucleophiles are extremely scarce. Early precedence had already suggested potential approaches to solving this challenge with transition-metal catalysis, but the yields were low.[1,2] Inspired by the copper-catalyzed substitution of activated alkyl electrophiles, i.e., allylic,[3] propargylic,[4] or benzylic[5−7] acceptors, using Si−B compounds **1** as silicon pronucleophiles,[8] we recently accomplished the nucleophilic displacement of primary aliphatic triflates with $Me_2PhSiBpin$ (**1a**) (Scheme 1, top).[9] At the same time, Fu and co-workers independently disclosed nickel-catalyzed cross-couplings of secondary and tertiary aliphatic bromides (and iodides) with $Me_2PhSiZnCl$ as the coupling partner (Scheme 1, bottom).[10,11]

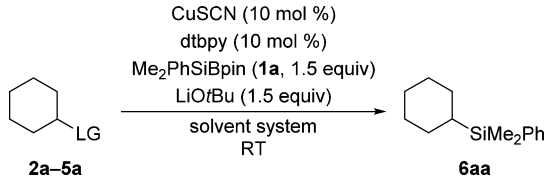
Scheme 1. Existing Methods for Aliphatic C(sp^3)−Si Bond Formation (R^1 and R^2 = Alkyl)



Extension of our procedure to secondary triflates and, likewise, bromides and iodides failed as a result of facile β-elimination.[9] However, thorough optimization led to the identification of a new catalyst/solvent system that enables the copper-catalyzed cross-coupling of several kinds of alkyl iodides. We report here the development of this general method and, due to its radical nature,[12] its coupling with radical cyclizations terminated by carbon−silicon bond formation. Moreover, both the full catalytic cycle and the activation of the silicon−boron bond have been computed.

An extensive screening of copper salts, additives, and solvents eventually led to the high-yielding combination of CuSCN with 4,4′-di-*tert*-butyl-2,2′-bipyridine (dtbpy) as the ligand in THF/DMF (9/1) for iodides (Table 1, entry 1; the complete set of optimization data is provided in the Supporting Information). This and all other reactions were maintained at room temperature overnight, but three-fourths of the starting material

Table 1. Selected Examples of the Optimization of the Reaction Conditions (LG = Leaving Group)[a]



entry	LG	variation	solvent system	yield (%)[b]
1	I (**2a**)	–	THF/DMF (9/1)	99 (94[c])
2	I (**2a**)	w/o CuSCN	THF/DMF (9/1)	trace
3	I (**2a**)	w/o LiO*t*Bu	THF/DMF (9/1)	8
4	I (**2a**)	w/o dtbpy	THF/DMF (9/1)	40
5	I (**2a**)	–	THF	64
6	I (**2a**)	–	DMF	20
7	I (**2a**)	–	THF/DMF (5/5)	63
8	I (**2a**)	–	THF/DMF (7/3)	70
9	Br (**3a**)	–	THF/DMF (9/1)	66 or 56[d]
10	Cl (**4a**)	–	THF/DMF (9/1)	4 or 4[d]
11	OTs (**5a**)	–	THF/DMF (9/1)	4 or 7[d]

[a]All of the 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]With NaI (1.0 equiv) as an additive.

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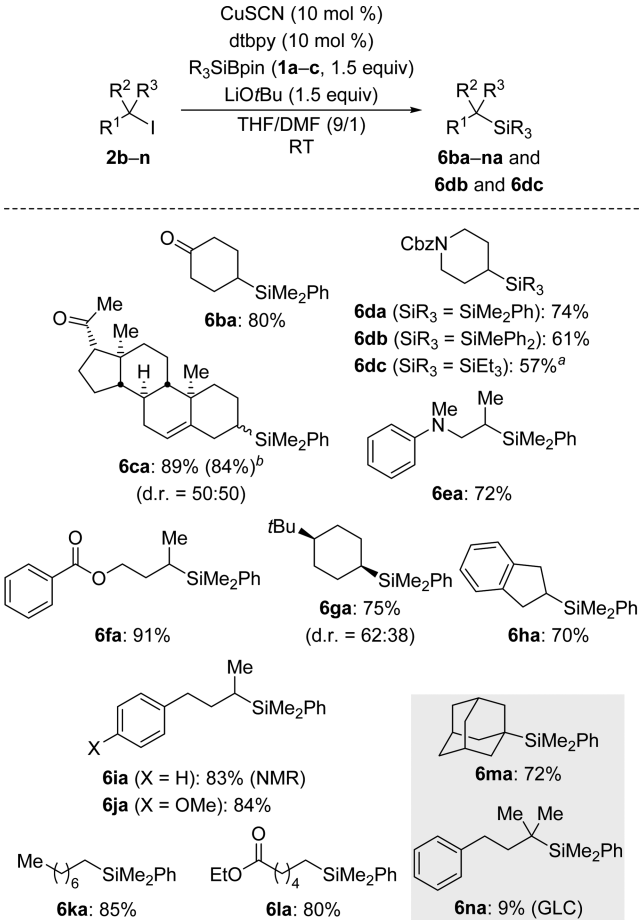
had already been comsumed after 2 h. Control experiments showed that both the copper salt and the alkoxide are essential (entries 2 and 3); also, the bipyridine ligand secures the high yield (entry 4). The influence of the solvent deserves particular mention: neither THF nor DMF alone nor THF/DMF in ratios other than 9/1 afforded the silane in excellent yield (entries 5–8). The corresponding bromide reacted in moderate yield, even with the addition of NaI (entry 9). Conversely, the chloride and tosylate were not converted into the desired silane (entries 10 and 11).

The scope of the new protocol is broad with good functional-group tolerance (Scheme 2). Secondary iodides containing C═O and C═C groups (as in **2b** and **2c**), Cbz-protected and tertiary amines (as in **2d** and **2e**), and a Bz-protected primary alcohol (as in **2f**) participated in the reaction. Apart from the usual Si–B reagent **1a**[8b] with an Me_2PhSi group, we applied $MePh_2SiBpin$ (**1b**)[8b] and less reactive $Et_3SiBpin$ (**1c**)[8c] to the coupling of **2b** with similar success.[13] However, the almost diastereomerically pure pregnenolone-derived iodide underwent the C(sp^3)–Si coupling with complete epimerization (d.r. > 98:2 for **2c** to d.r. = 50:50 for **6ca**). This was confirmed in the reaction of *cis*-1-*tert*-butyl-4-iodocyclohexane, where loss of stereochemical information was also seen (d.r. > 98:2 for **2g** to d.r. = 62:38 for **6ga**). These observations, together with the fact that 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO) inhibits the coupling,[14] are strong evidence for the involvement of radicals. Other (un)functionalized substrates **2h–j** worked equally well, and for the sake of completeness, primary iodides such as **2k** and **2l** afforded high yields. Interestingly, 1-iodoadamantane reacted cleanly whereas an unbiased tertiary iodide did so only sluggishly, mainly suffering β-elimination (**2m** → **6ma** vs **2n** → **6na**; gray box).

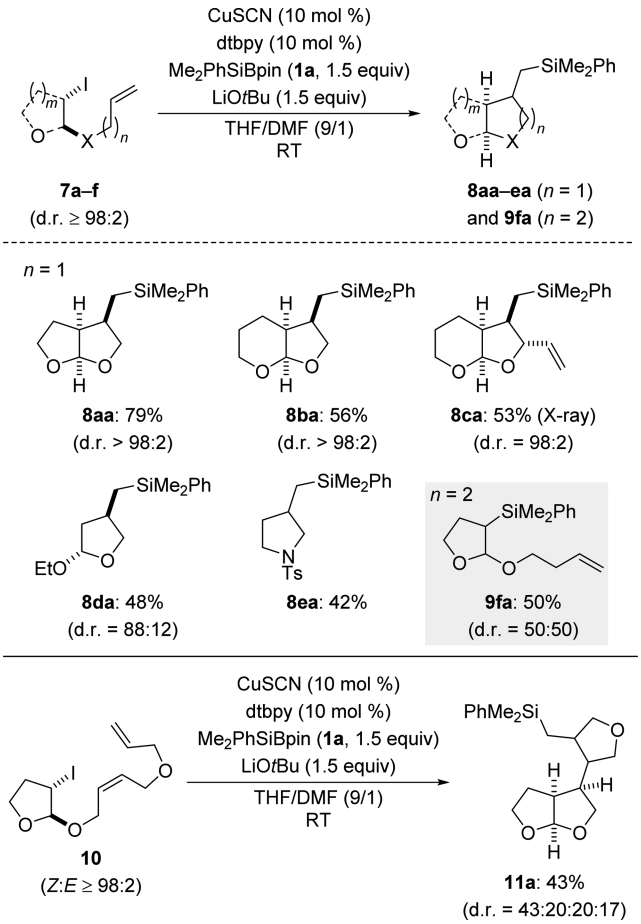
The radical nature of this copper catalysis prompted us to intercept the C(sp^3)–Si bond formation by a radical cyclization onto a tethered alkene.[15] The radical cascade would then be terminated by the formation of the C(sp^3)–Si bond remote from the starting C(sp^3)–I bond. The cyclization precursors chosen by us are typical model compounds[16] in tin-based and transition-metal-catalyzed ring closures (Scheme 3, top).[17−19] Indeed, the acetals **7a–c** cyclized in good yields to afford the bicyclic compounds **8aa–ca** with excellent diastereoselectivities. The "endo selectivity" is explained by a pseudochairlike conformation in the transition state of the 5-exo-trig ring closure, additionally favored by an anomeric effect.[20] The relative configuration of **8ca** was established by X-ray crystallographic analysis (see the Supporting Information for details). Open-chain acetal **7d** and amine **7e** reacted less efficiently, and tetrahydrofuran **8da** and pyrrolidine **8ea** were isolated in moderate yields. However, the 6-exo-trig cyclization starting from acetal **7f** failed, and silane **9fa** emerging from the conventional C(sp^3)–Si coupling was formed

Scheme 2. Copper-Catalyzed Cross-Coupling of Aliphatic C(sp^3)–I Bonds



[a]CuSCN (15 mol %), dtbpy (15 mol %), 40 °C (40% isolated yield under the standard conditions). [b]3.0 mmol scale.

Scheme 3. Copper-Catalyzed Cross-Coupling of Aliphatic C(sp^3)–I Bonds Coupled with 5-Exo-Trig Radical Cyclizations



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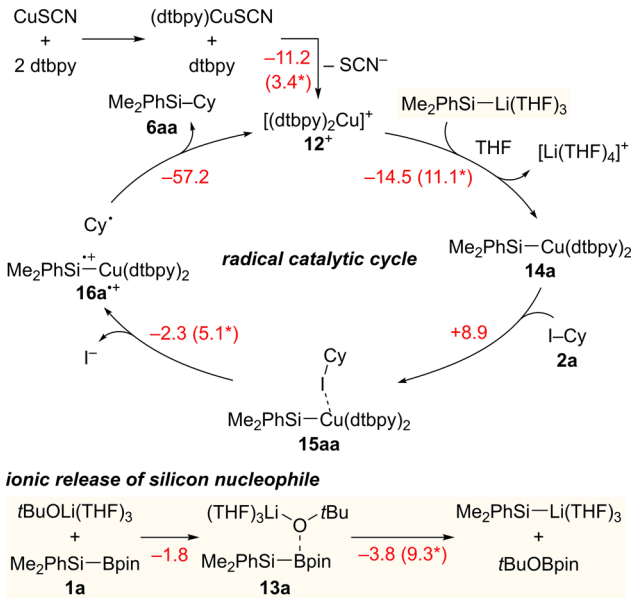
as a mixture of diastereomers (gray box). The cascade cyclization of Cárdenas' precursor[18c] (**10** → **11a**) also proceeded in reasonable yield (Scheme 3, bottom); as before,[18c] the relative configuration of the major isomer could not be assigned.

To gain deep mechanistic insights into this copper-catalyzed C(sp^3)−Si coupling reaction, the model reaction of iodocyclohexane (**2a**, I−Cy) as the substrate, *t*BuOLi, and $Me_2PhSiBpin$ (**1a**) with the precatalyst consisting of CuSCN and dtbpy as the ligand in THF solution was analyzed in detail by density functional theory (DFT) calculations at the TPSS-D3/def2-QZVP+COSMO-RS(THF)//TPSS-D3/def2-TZVP+COSMO(THF) level[21] (Scheme 4). In THF solution, the

Scheme 4. Computed Catalytic Cycle of the C(sp^3)−Si Coupling in THF Solution[a,b]



[a]Computed at the TPSS-D3/def2-QZVP+COSMO-RS(THF)//TPSS-D3/def2-TZVP+COSMO(THF) level. [b]For each step, the free energy change in kcal/mol is shown. Values in parentheses are estimated free energy barriers in kcal/mol.

precatalyst mixture eventually leads to the cationic complex $[(dtbpy)_2Cu]^+$ (**12**$^+$) as the most stable form along with the SCN^- counteranion, which is about 2.0 kcal/mol less coordinating to **12**$^+$ than the I^- anion. In the presence of THF, the alkoxide *t*BuOLi exists mainly as the solvated form *t*BuOLi$(THF)_3$ with three THF molecules coordinated to the Li^+ ion, which is 18.5 kcal/mol more stable than the separated ion pair $Li(THF)_4^+$ + *t*BuO$^-$. Such large lithium affinity eventually prevents the coordination of *t*BuO$^-$ to **12**$^+$, although binding of *t*BuO$^-$ to **12**$^+$ is 5.3 kcal/mol exergonic in THF solution. Importantly, the thus-formed copper(I) complex **12**$^+$ itself cannot reduce iodoalkane **2a** since the formation of the cyclohexyl radical (Cy$^\bullet$) and the copper(II) complex $(dtbpy)_2CuI^{\bullet+}$ would be 25.1 kcal/mol endergonic. We also note here that, as an alternative pathway, oxidative addition of the Si−B bond to **12**$^+$ to furnish a highly oxidized copper(III) complex is unlikely. According to our DFT calculations, copper(I) complex **12**$^+$ and **1a** could only lead to an adduct with an elongated Si−B bond, but this is 15.5 kcal/mol endergonic.

The alkoxide complex *t*BuOLi$(THF)_3$ may further coordinate to the Lewis acidic boron atom in **1a**[22] to form the Lewis pair **13a** in a step that is −1.8 kcal/mol exergonic (gray box in Scheme 4). Subsequent heterolytic Si−B bond cleavage (to form Me_2PhSi^-) and transfer of $Li(THF)_3^+$ to Me_2PhSi^- then leads to Me_2PhSi−$Li(THF)_3$, which is −3.8 kcal/mol exergonic over a low free energy barrier of 9.3 kcal/mol. This facile step is more likely than the direct reaction of **13a** with copper(I) complex **12**$^+$. The driving force for this step is the formation of a very strong B−O covalent bond in the neutral byproduct *t*BuOBpin. In contrast, weaker Lewis bases such as SCN^-, Cl^-, Br^-, and I^- are unable to realize such ionic Si−B bond activation in solution. The reactive $Me_2PhSiLi(THF)_3$ complex may dissociate into the metastable form Me_2PhSi^- together with the $Li(THF)_4^+$ counteranion (3.5 kcal/mol endergonic over a low barrier of 11.1 kcal/mol; not shown). Me_2PhSi^- is a rather reactive nucleophile toward the iodocyclohexane substrate, reacting via either nucleophilic substitution of the C−I bond or β-elimination at an adjacent C−H bond. Under the experimental conditions in the absence of the copper(I) catalyst, the β-elimination reaction turns out to be dominant (cf. Table 1, entry 2).

With the cationic copper(I) complex **12**$^+$ present in the solution, the metastable Me_2PhSi^- anion can be efficiently trapped by a dative Cu−Si bond to form the reductive complex Me_2PhSi−Cu$(dtbpy)_2$ (**14a**). Loss of a dtbpy ligand from **14a** is 6.0 kcal/mol endergonic and hence unlikely. Complex **14a** may bind substrate **2a** by a loose dative Cu···I bond to form the metastable complex **15aa**, which is 10.0 kcal/mol lower in energy but 8.9 kcal/mol unfavorable in free energy because of entropy effects. Electron transfer may then occur through the Cu···I bond to form the cyclohexyl radical (Cy$^\bullet$) together with the metastable copper(II) complex Me_2PhSi−Cu$(dtbpy)_2I^\bullet$, which may further dissociate into radical cation **16a**$^{\bullet+}$ and anion I^- in solution. The electron transfer step is −2.3 kcal/mol exergonic over an estimated barrier of 5.1 kcal/mol due to the formation of the metastable complex Me_2PhSi−Cu$(dtbpy)_2I^\bullet$. As a result of the large spin population of 0.33e on the silyl group within the intermediate **16a**$^{\bullet+}$, selective C(sp^3)−Si coupling may then occur through radical recombination between Cy$^\bullet$ and **16a**$^{\bullet+}$, leading to the desired product **6aa** and regenerated copper(I) catalyst **12**$^+$ in a highly exergonic step.[23] The rate-limiting step is thus very likely the reduction of the C−I bond by complex **14a** with a overall free energy barrier of about 14.0 kcal/mol. When chlorocyclohexane (**4a**, Cl−Cy) is used instead, a very similar reaction mechanism is involved, but it proceeds over a 2.9 kcal/mol higher overall barrier because of the relatively smaller electron affinity of **4a** upon dissociative electron attachment in solution (see Table S6 in the Supporting Information).

With this work, we have added another example to the still very short list[9,10] of methods for carbon−silicon bond formation by transition-metal-catalyzed cross-coupling of unactivated alkyl electrophiles.[24] The present copper catalysis proceeds through a radical mechanism, and the catalytic cycle and the release of the silicon nucleophile from the Si−B pronucleophile have been computed. The quantum-chemical data explain the experimental observations, including the role of the ligand and the thiocyanate counteranion in the generation of the catalytically active copper complex. The radical nature of the coupling allowed for its combination with Ueno−Stork-type radical cyclizations terminated by carbon−silicon bond formation, also demonstrating the high functional-group tolerance of the protocol.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b09596.

Experimental procedures, spectral data for all new compounds, and crystallographic and computed data (PDF)

Crystallographic data for **8ca** (CIF)

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Notes

The authors declare no competing financial interest.

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(23) Alternatively, oxidative addition of $Cy^{\bullet}$ to $\mathbf{16a}^{\bullet+}$ is 9.1 kcal/mol exergonic, but the resultant copper(III) complex is highly unstable with an estimated barrier of only 3 kcal/mol for $C(sp^3)$−Si bond formation. Because of the large spin of 0.33e on the silicon center and possible solvent coordination to the copper(II) center, direct radical−radical recombination to form the $C(sp^3)$−Si bond is the more natural mechanism, although both paths lead to an almost identical picture of rapid $C(sp^3)$−Si bond formation without a significant potential energy barrier. However, a free energy barrier of about 10 kcal/mol due to entropy effects is expected for bimolecular recombination, making preceding cyclization of flexible radical intermediates possible.

(24) Our method is complementary to Fu's, where Si−B reagent **1a** failed to react.[10] In turn, a low yield was obtained when $(Me_2PhSi)_2Zn$[25] was used with our system.

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