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Cu-Catalyzed Carbonylative Silylation of Alkyl Halides: Efficient Access to Acylsilanes

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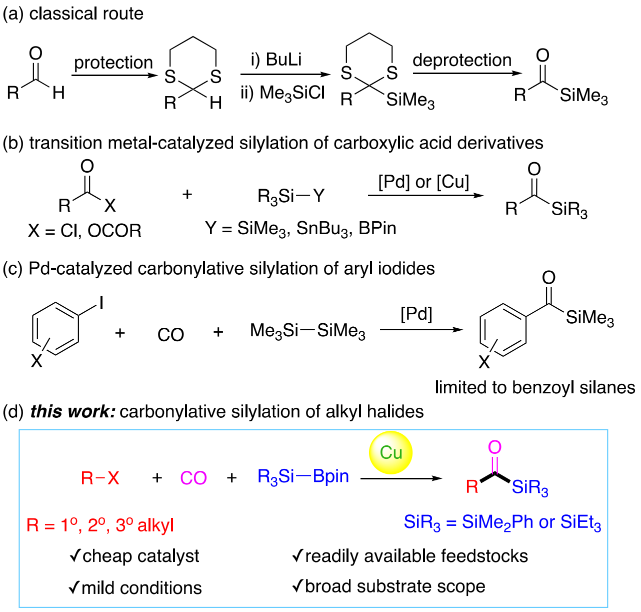
Supporting Information Placeholder

ABSTRACT: A Cu-catalyzed carbonylative silylation of unactivated alkyl halides has been developed, enabling efficient synthesis of alkyl-substituted acylsilanes in high yield. A variety of functional groups are tolerated under the mild reaction conditions, and primary, secondary and tertiary alkyl halides are all applicable. The practical utility of this method has been demonstrated in the synthesis of acylsilanes bearing different silyl groups as well as *in situ* reduction of a product to the corresponding α-hydroxylsilane in one pot. Mechanistic experiments indicate that a silylcopper intermediate activates alkyl halides by single electron transfer to form alkyl radical intermediates, and that carbon-halogen bond cleavage is not involved in the rate-determining step.

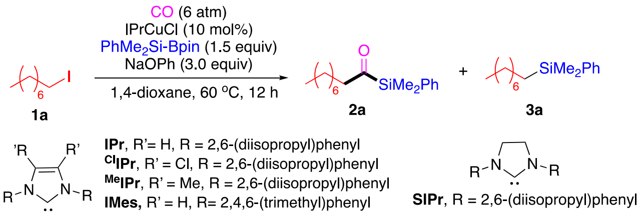
Organosilanes are highly important compounds and widely used in organic synthesis and materials science.[1] In particular, acylsilanes,[2] in which silicon units are attached to carbonyl groups, are versatile synthetic building blocks that have been used in various intriguing transformations with increasing frequency recently, including methods involving Brook-type rearrangements that are unique to the acyl silane moiety.[3] Given the importance of acylsilanes, much effort has been devoted to their synthesis.[4] However, most of the current methods either require multi-step preparation or exhibit limited substrate scope. For example, the classical route reported by Brook and Corey needs tedious protection/deprotection steps to access acylsilanes from aldehydes via dithiane intermediates (Scheme 1a).[4a, 4b] Although the direct addition of anionic silyl nucleophiles to carboxylic acid derivatives provides acylsilanes in a single step, it typically requires use of stoichiometric silylcopper reagents[5] or very reactive silyllithium reagents that limit functional group compatibility.[6] Notably, Pd-catalyzed silylation of acyl chlorides has been reported to enable synthesis of acylsilanes using disilane or silyltin reagents.[7] In addition, Riant recently developed the Cu-catalyzed silylation of anhydrides with silylborane reagents to approach mainly benzoylsilanes (Scheme 1b).[8] Although these protocols allow concise synthesis of acylsilanes under mild conditions, the use of moisture sensitive substrates such as acyl chlorides or anhydrides restricts their wide application.[9] In this regard, carbonylation reactions stand out as an attractive approach to synthesize acylsilanes, as they use CO to introduce the carbonyl group into simple precursors. Earlier, Seyferth and Weinstein reported the carbonylation of organolithium compounds at -110 °C to give acylsilanes.[10] Later, Beller reported a more practical palladium-catalyzed carbonylative silylation of aryl iodides to form benzoylsilanes (Scheme 1c).[11] However, to our best knowledge, the synthesis of alkyl-substituted acylsilanes via carbonylation of alkyl halides has not been investigated. This is probably due to the fact that compared to aryl electrophiles, the carbonylation of alkyl electrophiles is still a challenge[12] because of their notoriously slow rate of oxidative addition as well as competitive β-hydride elimination under carbonylative conditions.

Scheme 1. Synthesis of Acylsilanes



Recently, our group has developed Cu-catalyzed carbonylative C-C coupling reactions of alkynes with alkyl halides[13] and reductive carbonylation of unactivated alkyl halides[14] based on the (NHC)Cu-H or (NHC)Cu-Bpin catalysis (NHC = *N*-heterocyclic carbene).[15] In these reactions, acyl radicals were generated from alkyl halides and then coupled with various organocopper nucleophiles to afford corresponding carbonyl compounds. We hypothesized that a related strategy could serve as a platform for the synthesis of acylsilanes from alkyl halides by trapping the acyl radical using nucleophilic silylcopper species generated from the copper catalysts and a silylborane[16] (Scheme 1d). We expected the formed acylsilanes would be inert towards further nucleophilic addition of a second silylcopper species. However, the major challenge to overcome with this approach is the competitive direct silylation of alkyl halides reported by Fu and Oestreich.[17] Herein, we present our development of a direct, catalytic synthesis of alkyl-substituted acylsilanes from readily available alkyl halides through a Cu-catalyzed carbonylative silylation process.

Table 1. Optimization Studies[a]



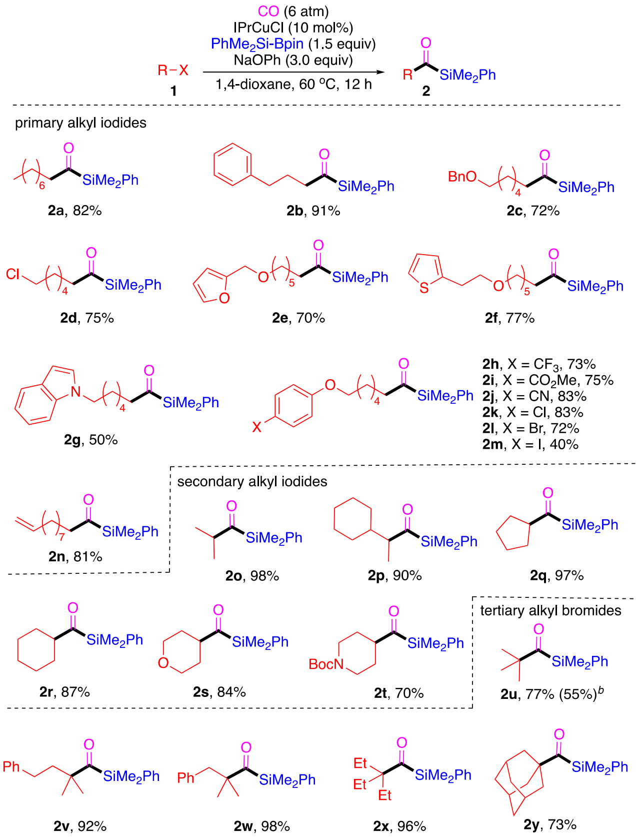
entry	variations from optimal conditions	2a (%)[b]	3a (%)[b]
1	None	93	<5
2	No IPrCuCl	0	0
3	^{Cl}PrCuCl instead of IPrCuCl	83	<5
4	^{Me}PrCuCl instead of IPrCuCl	30	<5
5	SIPrCuCl instead of IPrCuCl	52	<5
6	IMesCuCl instead of IPrCuCl	<5	80
7	Octyl-Br instead of Octyl-I	16	<5
8	Octyl-Cl instead of Octyl-I	0	0
9	NaOMe instead of NaOPh	0	<5
10	NaO^{t}Bu instead of NaOPh	0	35
11	LiOMe instead of NaOPh	28	0
12	1.2 equiv PhMe$_2$Si-Bpin instead of 1.5	89	<5
13	2.0 equiv NaOPh instead of 3.0	83	<5
14	THF instead of 1, 4-dioxane	75	<5
15	toluene instead of 1, 4-dioxane	25	<5
16	r.t instead of 60 °C	60	25
17	3 atm CO instead of 6 atm	90	<5
18	1 atm CO instead of 6 atm	72	<5

[a] Reaction performed on 0.05 mmol scale. [b] Yield determined by ^{1}H NMR integration against an internal standard.

We began our work by studying the reaction of 1-iodooctane with PhMe$_2$Si-Bpin under 6 atm CO pressure. After intensive investigation,[18] we found that the desired acylsilane **2a** could be selectively generated in 93% yield when commercially available IPrCuCl was used as catalyst in the presence of NaOPh as the base and 1,4-dioxane as solvent (Table 1, entry 1). A control experiment demonstrated that copper catalyst was necessary for the reaction to occur (Table 1, entry 2). The structure of NHC ligand had a significant effect on the reaction: while ^{Cl}IPr ligand gave slightly lower yield (Table 1, entry 3), SIPr and ^{Me}IPr ligands dramatically decreased the yield (Table 1, entry 4-5). Interestingly, less sterically hindered IMes ligand gave no product, and the alkyl silane **3a** was generated in high yield (Table 1, entry 6). The use of a less reactive electrophile, 1-bromooctane, provided the product in only 16% yield, and no reactivity was found with 1-chlorooctane (Table 1, entry 7-8). No desired acylsilane product was found when other bases such as NaOMe and NaO^{t}Bu were used, although low yield of product was obtained with LiOMe (Table 1, entry 9-11). Reducing the amount of PhMe$_2$Si-Bpin to 1.2 equivalents or amount of NaOPh to 2.0 equivalents still affords the product in 89% and 83% yield, respectively (Table 1, entry 12-13). Changing the solvent to THF gave the product in slightly lower yield, and much lower yield was obtained with toluene as solvent (Table 1, entry 14-15). Performing the reaction at room temperature led to generation of a significant amount of alkyl silane byproduct (Table 1, entry 16). It is noteworthy that, although we typically performed reactions under 6 atm CO pressure, conducting the reaction either under 3 atm or under atmospheric CO pressure also afforded the desired product in 90% and 72% yield, respectively (Table 1, entry 17-18).

With the optimal conditions in hand, we next investigated the substrate scope. The mild reaction conditions allow the use of a variety of alkyl iodides containing different remote functional groups, including benzyl ether (**2c**), chloroalkyl (**2d**) and terminal alkenes (**2n**). Heterocycles such as furan (**2e**) and thiophene (**2f**) were also compatible, although moderate yield was found with the substrate bearing an indolyl group (**2g**). The trifluoromethyl, ester, cyano, chloro and bromo groups on a remote phenyl ring (**2h-2l**) also survived during the reaction. However, deiodinaton side reaction was observed with the iodo-substituted substrate (**2m**). Under the same reaction conditions, the alkyl electrophile scope could be extended from primary alkyl iodides to secondary alkyl iodides. Both acylic and cyclic alkyl iodides gave the desired product in good yield. Increasing the steric hindrance of secondary alkyl iodide (**2o-2r**) had no effect on the yield. Ether (**2s**) and *N*-Boc (**2t**) functional groups within the cyclic electrophile were both tolerated. Moreover, we were delighted to find this method was also applicable to the more challenging tertiary alkyl electrophiles (**2u-2y**). Tertiary alkyl bromides were found to give products in higher yield than the corresponding iodides, which possibly suffer from elimination side reactions under the basic conditions.

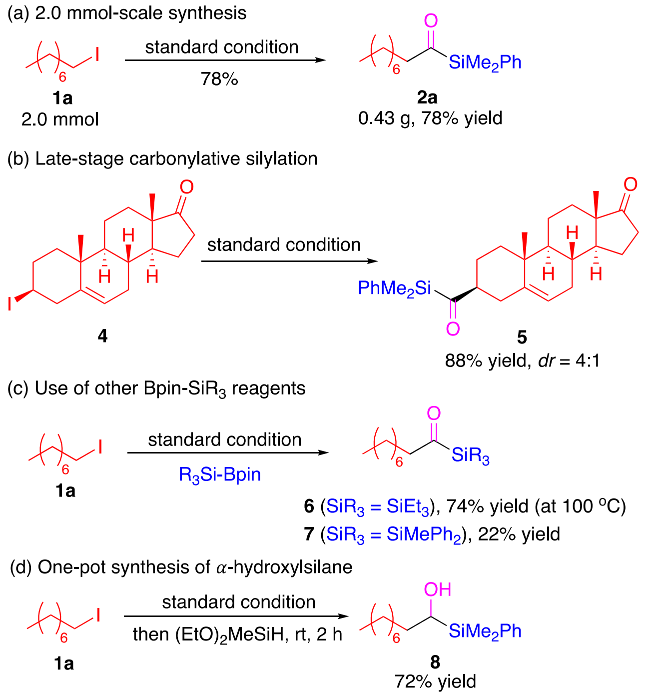
Table 2. Substrate Scope of Alkyl Halides[a]



[a] The reaction was conducted on 0.2 mmol scale. All yields are isolated yields. [b] *t*-Butyl iodide was used as substrate.

To demonstrate the practical utility of this methodology, we performed the reaction on 2.0-mmol scale, obtaining the expected acylsilane in good yield (Scheme 2a). In addition, the mild reaction conditions provide the opportunity for late-stage carbonylative silylation of natural products or drugs. For example, when an estrone derivative **4** was subjected to the reaction conditions, acylsilane **5** was diastereoselectively obtained in excellent yield (Scheme 2b). Furthermore, apart from $PhMe_2Si$-Bpin as a silyl source, the less reactive Et_3Si-Bpin was also proved to be a good coupling partner at elevated temperature,[19] although Ph_2MeSi-Bpin gave the product in low yield under standard reaction conditions (Scheme 2c). Moreover, after the reaction was complete, by adding a hydrosilane to the reaction mixture, we found the acylsilane could be further reduced by the same copper catalyst (Scheme 2d). Thus, this method also provides an efficient way to access to synthetically useful α-hydroxylsilanes[20] from alkyl halides in one pot.

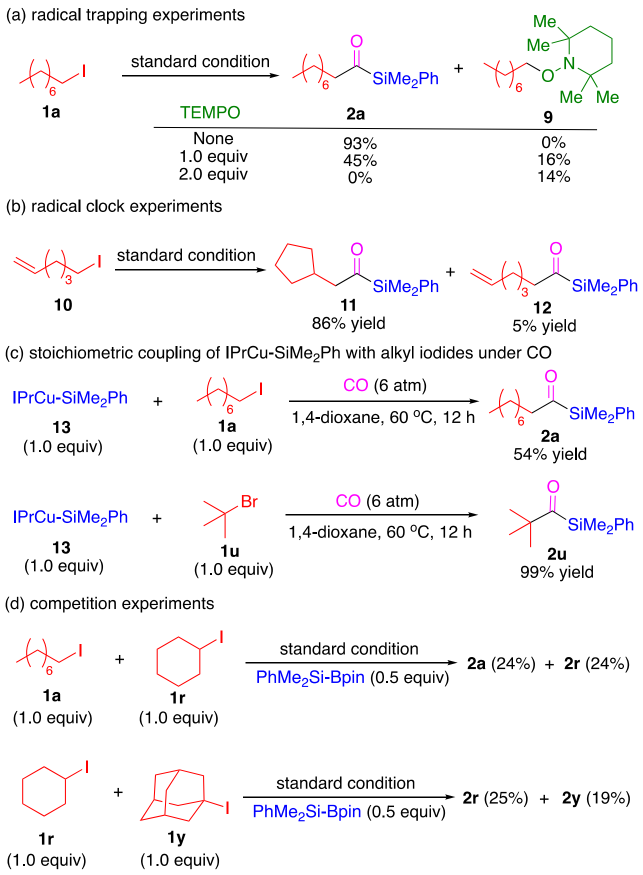
Scheme 2. Synthetic Utility



Next, several control experiments were performed to explore the mechanism. Previously, we have identified that copper-catalyzed carbonylative C-C coupling[13] and reductive carbonylation of alkyl halides[14] proceed via alkyl radical intermediates. For carbonylative silylation, our observations are also consistent with a radical mechanism. For example, when the TEMPO was added into the reaction, the product formation was inhibited and radical trapping product **7** was detected by ^1H NMR (Scheme 3a). In addition, radical clock experiment was performed with iodoalkane **10**, and the cyclization product **11** was isolated in 86% yield (Scheme 3b). We also prepared silylcopper species IPrCu-$SiMe_2Ph$ (**13**)[21] and performed stoichiometric reactions of **13** with primary alkyl iodide (**1a**) and tertiary alkyl iodide (**1u**) under CO atmosphere. The corresponding acylsilanes were formed in 54% and 99% yield, respectively (Scheme 3c), indicating that the silylcopper intermediate activates both primary and tertiary alkyl iodides by single electron transfer to enable a radical carbonylation process. This is contrast to our previous findings[13b] that no reaction was observed between an alkenylcopper intermediate and tertiary electrophiles in the absence of an initiator to start an atom transfer carbonylation (ATC) radical chain pathway.[22] Moreover, we examined the relative rates of product formation in a set of competition experiments between primary, secondary, tertiary alkyl iodides. Interestingly, similar yields of products were detected

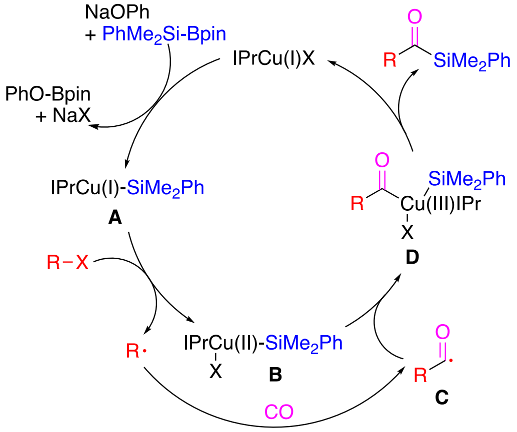
(Scheme 3d), which contrasts with previous reports that more substituted alkyl halides tend to be more reactive due to the generation of more thermodynamically stable tertiary alkyl radicals.[23] We reason that in our carbonylative silylation reaction, the carbon-halogen bond cleavage is not involved in the rate-determining step.

Scheme 3. Mechanistic studies



Based on these results and our previous work on carbonylation of alkyl halides,[12] we propose the following catalytic mechanism (Scheme 4). First, silylcopper(I) complex **A** was generated by the reaction of $PhMe_2Si$-Bpin with IPrCuOPh, which forms from IPrCuCl and NaOPh.[24,25] Next, consistent with the radical silylation of alkyl halides proposed by Oestreich,[17b] a single electron transfer (SET) between compound **A** and the alkyl halide generates an alkyl radical R・ along with the silylcopper(II) complex **B**. The radical species R・ then undergoes carbonylation to give an acyl radical species **C**,[19] which is expected to be more reactive than the alkyl radical species **C** and thus favorably collapses with copper (II) complex **B** to form the copper(III) intermediate **D**. Finally, reductive elimination affords the acylsilane and regenerates the copper(I) catalyst.

Scheme 4. Proposed Catalytic Cycle



In summary, we have developed an unprecedented procedure to synthesize alkyl-substituted acylsilanes from unactivated alkyl iodides via a Cu-catalyzed carbonylative silylation. This protocol is applicable to primary, secondary, and tertiary alkyl halides, and a variety of functional groups can be tolerated under the mild reaction conditions. The utility of this method was demonstrated by the late-stage carbonylative silylation of an estrone derivative as well as preparation of the acylsilanes bearing different silyl groups. In addition, the formed acylsilanes can be further reduced *in situ* by adding a hydrosilane reagent. In contrast to our previous findings in carbonylative C-C coupling reaction where primary and tertiary electrophiles went through different reaction pathways, mechanistic experiments indicate that the silylcopper intermediate activates both classes of alkyl iodides by single electron transfer to enable a radical carbnylation process, with carbon-halogen bond cleavage not being involved in the rate-determining step.

ASSOCIATED CONTENT

Supporting Information. The Supporting Information is available free of charge on the ACS Publications website. Experimental procedures & spectral data (PDF)

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[18] See Supporting Information for more details.

[19] When the reaction was performed at 60°C, the starting material **1a** had only 30% conversion and acylsilane **6** was observed in 29% yield by ^{1}H NMR analysis.

[20] For recent synthesis of α-hydroxylsilanes, see: (a) Cirriez, V.; Rasson, C.; Hermant, T.; Petrignet, J.; Álvarez, J. D.; Robeyns, K.; Riant, O. Copper-Catalyzed Addition of Nucleophilic Silicon to Aldehydes. *Angew. Chem. Int. Ed*. **2013**, *52*, 1785–1788; (b) Rong, J.; Oost, R.; Desmarchelier, A.; Minnaard, A. J.; Harutyunyan, S. R. Catalytic Asymmetric Alkylation of Acylsilanes. *Angew. Chem. Int. Ed*. **2015**, *54*, 3038–3042; (c) Nagy, A.; Collard, L.; Indukuri, K.; Leyssens, T.; Riant, O. Enantio-, Regio- and Chemoselective Copper-Catalyzed 1,2-Hydroborylation of Acylsilanes. *Chem. Eur. J*. **2019**, *25*, 8705-8708.

[21] Kleeberg, C.; Cheung, M. S.; Lin, Z.; Marder, T. B. Copper-Mediated Reduction of CO_2 with pinB-$SiMe_2Ph$ via CO_2 Insertion into a Copper–Silicon Bond. *J. Am. Chem. Soc*. **2011**, *133*, 19060-19063.

[22] Reviews on radical carbonylation: (a) Schiesser, C. H. Wille, U. Matsubara, H. Ryu, I. Radicals Masquerading as Electrophiles: Dual Orbital Effects in Nitrogen-Philic Acyl Radical Cyclization and Related Addition Reactions. *Acc. Chem. Res*. **2007**, *40*, 303-313. (b) Sumino, S.; Fusano, A.; Fukuyama, T.; Ryu, I. Carbonylation Reactions of Alkyl Iodides through the Interplay of Carbon Radicals and Pd Catalysts. *Acc. Chem. Res*. **2014**, *47*, 1563-1574. (c) Zhao, S; Mankad, N. Metal-catalyzed Radical Carbonylation Reactions, *Catal. Sci. Technol.* **2019**, *9*, 3603-3613.

[23] (a) Dudnik, A. S.; Fu, G. C. Nickel-Catalyzed Coupling Reactions of Alkyl Electrophiles, Including Unactivated Tertiary Halides, To Generate Carbon−Boron Bonds. *J. Am. Chem. Soc.* **2012**, *134*, 10693-10697. (b) Wang, G.-Z.; Shang, R.; Cheng, W.-M.; Fu, Y. Irradiation-Induced Heck Reaction of Unactivated Alkyl Halides at Room Temperature. *J. Am. Chem. Soc.* **2017**, *139*, 18307-18312.

[24] $PhMe_2Si$-Bpin was reported to react with IPrCuO^{t}Bu to afford IPrCu-$SiMe_2Ph$, which was fully characterized: Kleeberg, C.; Cheung, M. S.; Lin, Z.; Marder, T. B. Copper-Mediated Reduction of CO_2 with pinB-$SiMe_2Ph$ via CO_2 Insertion into a Copper Silicon Bond. *J. Am. Chem. Soc*. **2011**, *133*, 19060.

[25] It is worthy to note that in the recent silylation work (ref 17b), Oestreich has proposed an ionic release of silicon nucleophile pathway to form a similar silylcopper intermediate, in which the formation of $PhMe_2Si^-$ from $PhMe_2Si$-Bpin and base was found to be favorable by density functional theory (DFT) analysis. In our case, no reaction was observed when $PhMe_2Si$-Bpin and NaOPh were stirred in 1,4-dioxane at 60°C for 12 h.

TOC graphic: