C–CF_3 Bond Formation

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Copper-Catalyzed Trifluoromethylation of Allylsilanes**

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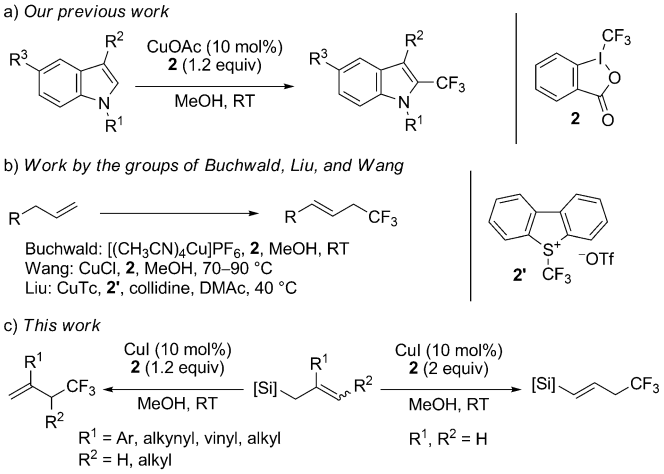
The trifluoromethyl group is of interest in the pharmaceutical and agrochemical fields because it is lipophilic, hydrophobic, and metabolically stable;[1] thus, great efforts have been made to develop reactions to introduce this group into organic molecules.[2] The formation of C_{sp^2}–CF_3 bonds is now a well-developed field of study.[3] On the other hand, C_{sp^3}–CF_3 bond formation is still generally achieved only through carbonyl groups,[4] by one of a variety of protocols.[2] New synthetic methods are still needed for the construction of C_{sp^3}–CF_3 bonds in a wider range of molecular contexts.

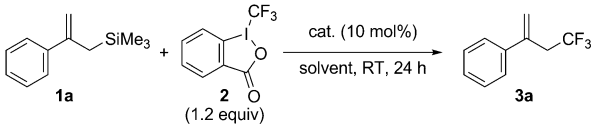
In 2010, we reported the trifluoromethylation of indole derivatives using Cu^I and Togni's reagent **2** (1-trifluoromethyl-1,2-benziodoxol-3-(1*H*)-one)[5] in MeOH (Scheme 1a).[6] As an extension of that work, we next focused on C=C bond trifluoromethylation. Groups led by Buchwald,[7] Liu,[8] and Wang[9] have recently reported the trifluoromethylation of unactivated olefins with a copper (I) salt and either Togni's reagent **2**[5] or Umemoto's reagent **2′**[10] (Scheme 1b). Although these reactions can provide structures bearing a trifluoromethyl group at the allylic position, the reported substrates are mostly limited to monosubstituted terminal olefins. We also independently investigated the trifluoromethylation of unactivated olefins, but when we applied our original Cu^I/**2**/MeOH system[6] to the trifluoromethylation of unactivated olefins, we also found the substrate scope to be limited. To overcome this problem, we focused on allylsilanes as substrates, anticipating that they would be more nucleophilic than unactivated olefins. Herein, we disclose the trifluoromethylation of allylsilanes to afford either *gem*-disubstituted terminal olefins or vinylsilanes bearing a trifluoromethyl group in the allylic position (Scheme 1c).



Scheme 1. Cu^I-catalyzed trifluoromethylation. CuTc = Copper(I)-thiophene-2-carboxylate, DMAc = *N*,*N*-dimethylacetamide, OTf = trifluoromethanesulfonate.

We initially examined the reaction of (2-phenylallyl)trimethylsilane **1a** with CuOAc and Togni's reagent **2** in MeOH.[6] The desired trifluoromethylation product was obtained in low yield along with the recovery of 65% of the starting material (Table 1, entry 1).[11] Other copper (I) salts were examined in order to increase the effectiveness of this reaction. The use of $[Cu(CH_3CN)_4]PF_6$ or CuCl gave slightly better results, but the yield was still low (entries 2 and 3). However, CuI was found to afford the desired product **3a** in

Table 1: Screening of reaction conditions.[a]



Entry	Catalyst	Solvent	Yield [%][b]
1	CuOAc	MeOH	27
2	$[Cu(CH_3CN)_4]PF_6$	MeOH	39
3	CuCl	MeOH	32
4	CuI	MeOH	72
5[c]	CuI	MeOH	63[d]
6	CuI	EtOH	36
7	CuI	CH_3CN	42
8	CuI	toluene	31
9	CuI	CH_2Cl_2	42
10	none	MeOH	0

[a] The reactions were carried out with catalyst (10 mol%) and Togni's reagent **2** (1.2 equiv) in MeOH (2 mL) at room temperature on a 0.2 mmol scale, unless otherwise mentioned. [b] Determined by ^1H NMR analysis using 4-bromoanisole as an internal standard. [c] Run on a 0.5 mmol scale. [d] Yield of isolated product.

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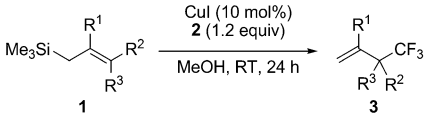
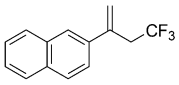
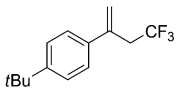
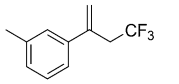
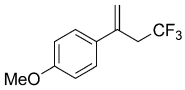
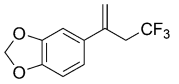
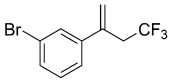
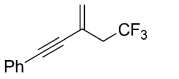
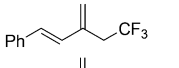
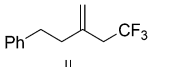
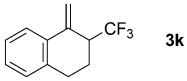
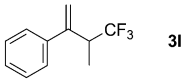
good yield (entries 4 and 5).[12] Among the solvents tested (entries 4 and 6–9), MeOH was the best. Cu^{I} plays a critical role in this method, as no reaction was observed in the absence of copper salts (entry 10).

Under the optimized reaction conditions, the trifluoromethylation of various 2-substituted allyltrimethylsilanes was next examined (Table 2). The reaction of **1b**, bearing a 2-naphthyl group, gave the desired product **3b** in 84% yield (entry 1). Alkyl groups in the 3- or 4-position on the phenyl ring had little effect on the reactivity (entries 2 and 3). An electron-donating group accelerated the desired trifluoromethylation and the starting materials were completely consumed. However, overreaction and side reactions were also observed.[13] To suppress such undesired results, the reactions were instead carried out at 0°C for **1e** and 10°C for **1f**, whereupon the mono-trifluoromethylated products **3e** and **3f** were obtained in 68% and 71% yield, respectively (entries 4 and 5). Bromine substitution on the phenyl ring was also tolerated under the reaction conditions (entry 6). The reaction of an ene–yne compound was slow, probably because of the coordination of either the substrate or the product to the copper ion. However, product **3h** was obtained in 70% yield when 50 mol% of CuI was used (entry 7). Allylsilanes with alkenyl and alkyl groups in the 2-position were also successfully converted into the corresponding trifluoromethylated products (entries 8 and 9). Notably, this reaction system was applicable to allylsilanes with substituents in both the 2- and 3-positions, which afforded products with a CF_3 group on the tertiary carbon center (entries 10 and 11). Although the chemical yield requires improvement, especially in the case of acyclic **3l**, this is in contrast to previous work,[7–9] in which a CF_3 group was incorporated only at the terminal position.

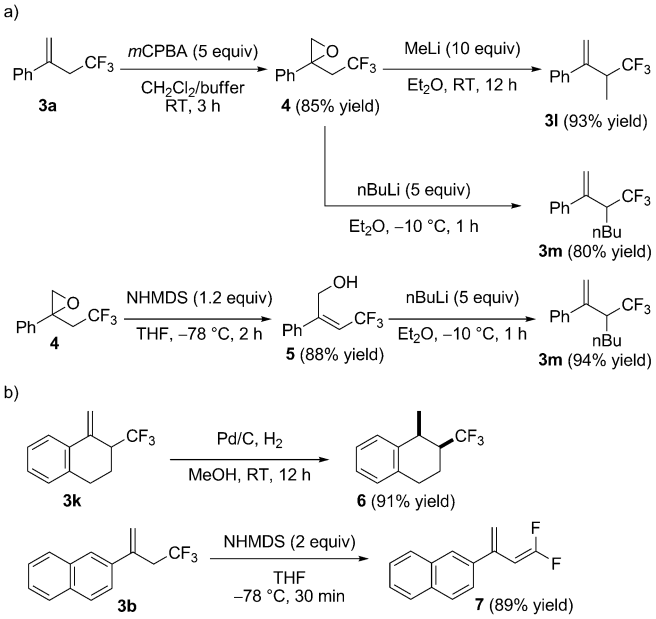
Table 2: Trifluoromethylation of 2-substituted allylsilanes.[a]



Entry	Product	Yield [%][b]
1[c]	 **3b**	84
2	 **3c**	54
3	 **3d**	63
4[d]	 **3e**	68
5[e]	 **3f**	71
6	 **3g**	55
7[f]	 **3h**	70
8	 **3i**	53
9	 **3j**	60
10	 **3k**	45
11[g]	 **3l**	36

[a] The reactions were carried out with CuI (10 mol%) and **2** (1.2 equiv) in MeOH (5 mL) at room temperature for 24 h on a 0.5 mmol scale, unless otherwise mentioned. [b] Yield of isolated product. [c] Run for 72 h. [d] Run at 0°C. [e] Run at 10°C. [f] CuI (50 mol%) was used. [g] [(*Z*)-3-Methyl-2-phenylallyl]trimethylsilane was used as the substrate.

The problem of low yield in the synthesis of branched acyclic **3l** was overcome by using an alternative method. The efficient conversion of **3a** to **3l** became possible by utilizing a novel coupling reaction. When epoxide **4**, easily obtained by treatment of **3a** with *meta*-chloroperoxybenzoic acid, was reacted with MeLi, the alkylation product **3l** was unexpectedly obtained in 93% yield (Scheme 2a). Similarly, the butylated product **3m** was obtained in 80% yield by using nBuLi. As compound **5** was formed in a stereoselective manner by treatment of **4** with a less nucleophilic base, sodium hexamethyldisilazide (NHMDS), and **5** was then converted into **3m** by reaction with excess nBuLi, we speculate that the alkylation of epoxide **4** proceeded through an allylic alcoholate intermediate. The reaction mechanism is currently being investigated in detail. It should be noted that this novel transformation provides ready access to more



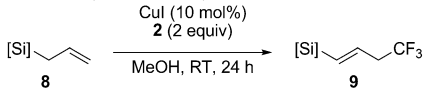
Scheme 2. Transformation of trifluoromethylated products. Buffer = phosphate buffer (pH = 7.0), *m*CPBA = *meta*-chloroperoxybenzoic acid, NHMDS = sodium hexamethyldisilazide.

highly substituted CF_3 compounds and is complementary to the direct trifluoromethylation of allylsilanes described in Table 2.

These unique allylic trifluoromethylated products can be further transformed into other potentially useful fluorine-containing building blocks (Scheme 2b). For example, the hydrogenation of **3k** with Pd/C proceeded in a highly stereoselective manner to give the *cis* product **6**, and the preparation of the difluorodiene compound **7** was achieved by the elimination of HF from **3b** using NHMDS.

Following our success in the reactions of highly substituted allylsilanes, we next examined the reactions of simple allylsilanes. To our surprise, vinylsilane **9a** was obtained in 80% yield from allyltrimethylsilane **8a** under the conditions described in Table 3 (entry 1). Encouraged by this result, we

Table 3: Trifluoromethylation of allylsilanes.[a]

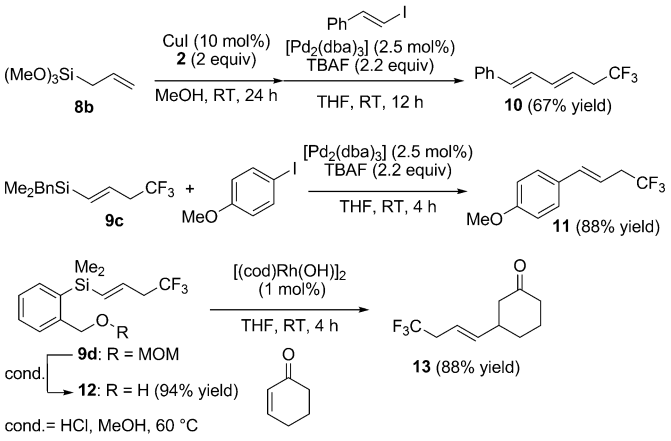


Entry	Product		Yield [%]
1	Me_3Si, CF_3	**9a**	80[b]
2	$(MeO)_3Si$, CF_3	**9b**	93[b]
3	Me_2BnSi, CF_3	**9c**	89[c]
4	Me_2Si, CF_3, OMOM	**9d**	58[c]

[a] The reactions were carried out with CuI (10 mol%) and **2** (1.2 equiv) in MeOH (5 mL) at room temperature on a 0.5 mmol scale. [b] Determined by ^{1}H NMR analysis using 4-bromoanisole as an internal standard. [c] Yield of isolated product. Bn = benzyl, MOM = methoxymethyl ether.

investigated other allylsilanes. The reactions of **8b** and **8c** proceeded smoothly and the corresponding vinylsilanes **9b** and **9c** were obtained in yields as high as 93% and 89%, respectively (Table 3, entries 2 and 3). Although the steric bulk of substituents on the silicon atom had a negative effect on the reaction, the desired product **9d** was still obtained in 58% yield (entry 4).

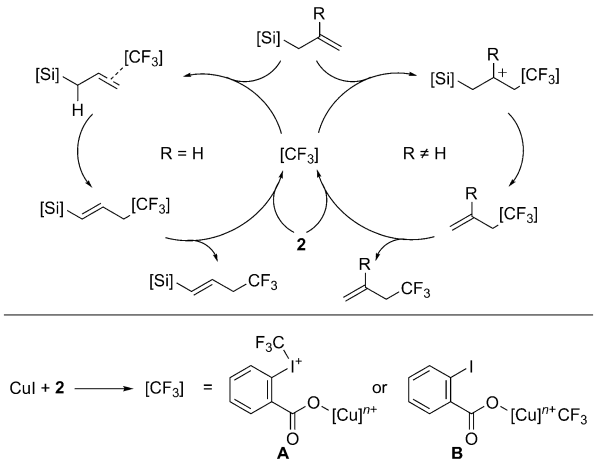
As vinylsilanes are known to undergo a range of transformations, we considered that our reaction could provide a means for the introduction of a 1,1,1-trifluoro-3-butene unit into organic frameworks to produce compounds that would be potentially useful as building blocks in the field of medicinal chemistry. An advantage of this method is that one can choose the substrate from a variety of silyl groups, as appropriate for the reaction conditions examined. As shown in Scheme 3, trimethoxyvinylsilane **8b** could be used in a cross-coupling reaction without purification, and the desired compound **10** was obtained under mild reaction conditions. Also, the Hiyama-coupling product **11** was obtained in 88% yield by using **9c** in the presence of tetrabutylammonium fluoride (TBAF) and $[Pd_2(dba)_3]$ (dba = dibenzylidene acetone) at room temperature.[14] Removal of the methoxymethyl (MOM) ether group from **9d** was achieved under acidic conditions in MeOH without significant loss of vinyl-



Scheme 3. Transformations of vinylsilane products. dba = dibenzylidene acetone, MOM = methoxymethyl ether, TBAF = tetrabutylammonium fluoride.

silane, and the resulting silane **12** could be subjected to a rhodium-catalyzed 1,4-addition reaction to give **13** in high yield (Scheme 3).[15]

Finally, the proposed mechanism of this trifluoromethylation reaction is depicted in Scheme 4. We speculate that the copper catalyst would react with **2** to generate reactive



Scheme 4. Proposed mechanism.

intermediates, such as **A** or **B**. It is likely that the reaction of a 2-substituted allylsilane proceeds via a cationic intermediate (right cycle). After generation of a carbocation at the β position of silicon, a silyl cation, which is probably trapped with either benzoate or methanol, is immediately released to generate the C=C bond. In the case of an allylsilane bearing no substituent in the 2-position, deprotonation at the allylic position and the simultaneous formation of a C–I or a C–Cu species may occur after coordination of the double bond to either an iodonium cation or a copper ion (left cycle). Finally, the product is released by a C–CF_3 bond-forming reductive elimination.

In summary, we have achieved the trifluoromethylation of allylsilanes using CuI and Togni's reagent **2** under mild conditions. To our knowledge, this is the first report of allylsilane trifluoromethylation. The reaction of 2-substituted allylsilanes gave desilylated products bearing a trifluoromethyl group in the allylic position, while the reaction of allylsilanes with no substituent in the 2-position provided the corresponding vinyl silane derivatives. Furthermore, we have found a novel α-alkylation reaction of epoxides bearing a trifluoromethyl group in the α position. These products were readily introduced into carbon frameworks by means of transition-metal-catalyzed cross-coupling reactions. Further investigation of this reaction system and mechanistic studies are under way in our laboratory.

Experimental Section

General procedure for the trifluoromethylation of allylsilanes: CuI (9.5 mg, 10 mol%) and Togni's reagent **2** (190 mg, 1.2 equiv) were weighed and added to a Schlenk flask, which had been flame-dried under vacuum. The flask was evacuated and backfilled with argon. Then, degassed methanol (5 mL) and allylsilane **1a** (95.2 mg, 0.5 mmol) were added. The reaction mixture was stirred for 24 h and diluted with n-hexane (5 mL). The solution was passed through a short pad of silica gel and the silica gel was washed with n-hexane. The organic solvent was evaporated and the residue was subjected to column chromatography on silica gel (n-hexane) to give the trifluoromethylated product **3a** (59.2 mg, 63%) as a colorless oil.

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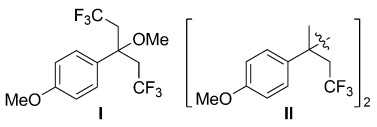
[11] No reaction of α-methylstyrene was observed with CuOAc and **2** in MeOH.

[12] A small amount of allyl iodide by-product was detected when CuI was used as catalyst.

[13] In the reaction of **1e** at room temperature, we detected by-products **I** and **II**.



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