

Copper(II)-Catalyzed Silyl Conjugate Addition to α,β -Unsaturated Conjugated Compounds: Brønsted Base-Assisted Activation of Si–B Bond in Water

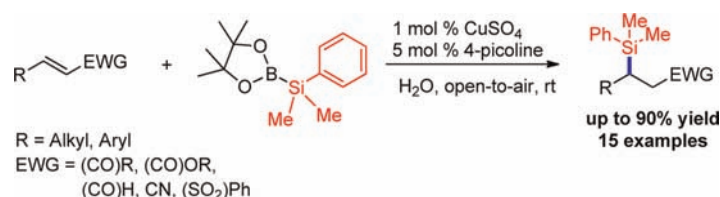
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ABSTRACT



A mild method for the installation of the dimethylphenylsilyl group on the β -carbon of electron-deficient olefins is reported. In the presence of a catalytic amount of copper(II) (1 mol %) and amine base (5 mol %) at rt, the transformation proceeds efficiently in water within 1.5–5 h to afford β -silylated products in yields of up to 90%.

The development of methods for the preparation of organosilicon compounds is important because of their utility as intermediates in the synthesis of complex molecules as well as their potential application in material science and medicine.¹ Initial reports for the preparation of β -silyl carbonyl compounds involved conjugate addition using stoichiometric amounts of silyl metal reagents such as silyllithiums, silylcuprates, or silylzincates.² However, methods that utilized catalytic amount of copper in the presence of silylzincates have been reported.³ Alternative methods that utilize catalytic amounts of transition metals have become state-of-the-art.⁴ Activation of the Si–X bond (wherein X = Si or B) in the presence of a transition metal can provide access to silicon–carbon

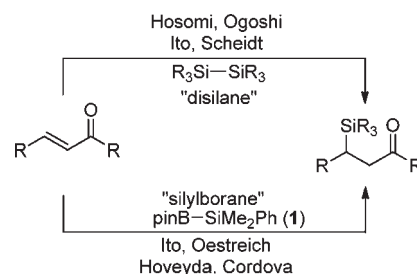


Figure 1. β -Silylation: nucleophilic silicon from Si–X bond.

bonds (Figure 1).⁵ Although disilanes are powerful sources of nucleophilic silicon, recent attention has focused on exploiting the unique reactivity of Suginome's dimethylphenylsilylpinacolatoboron (**1**)^{4a,6} as a means to transfer

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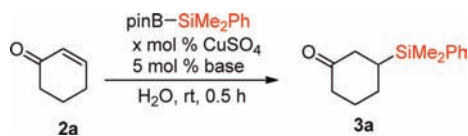
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Table 1. Screening of Base Additives^a

entry	base	Cu source	mol % Cu	Prod:SM ratio ^b
1	potassium acetate	CuSO ₄	1.0	3:1
2	potassium bicarbonate	CuSO ₄	1.0	5:1
3	pyridine	CuSO ₄	1.0	15:1
4	4-picoline	CuSO ₄	1.0	28:1
5	2,6-lutidine	CuSO ₄	1.0	22:1
6	6-methylquinoline	CuSO ₄	1.0	22:1
7	bipyridine	CuSO ₄	1.0	NR ^d
8	DBU ^c	CuSO ₄	1.0	13:1
9	triethyl amine	CuSO ₄	1.0	10:1
10	benzylamine	CuSO ₄	1.0	24:1
11	none	none	0	NR ^d
12	none	CuSO ₄	1.0	trace
13	4-picoline	none	0	trace
14	4-picoline	CuCl	1.0	13:1
15	4-picoline	Cu(OAc) ₂	1.0	21:1
16	4-picoline	Cu(BF ₄) ₂	1.0	26:1

^aGeneral procedure: Amine or base (5 mol %), cyclohexen-2-one (1 equiv), **2** (1.2 equiv), and 1 mL of 1.3 mg/mL of CuSO₄ solution were mixed at rt for 30 min. ^bDetermined by GC–MS of crude material. ^c1,8-Diazabicyclo[5.4.0]undec-7-ene. ^dNR = no reaction.

the dimethylphenylsilyl moiety to α,β -unsaturated carbonyl compounds. While Rh(I)-catalyzed methods have been reported,⁷ copper(I)-catalysis is emerging as a more convenient and efficient protocol.⁸ Indeed, a few enantioselective methods^{7a,c} are available as well as a metal-free⁹ variant catalyzed by N-heterocyclic carbenes (NHC).

An analogous reaction is the β -borylation of α,β -unsaturated carbonyl compounds catalyzed by copper.¹⁰ In this reaction,¹¹ transfer of the boron moiety from diboron

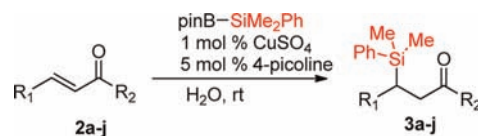
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Table 2. β -Silylation of α,β -Unsaturated Ketones and Esters^a

entry	substrate	product	time (h)	yield (%) ^b	
1			3a	5	90
2			3b	5	72
3			3c	5	74
4			3d	5	68
5			3e	3	84
6			3f	5	89
7			3g	1.5	88
8			3h	5	79
9			3i	5	62
10			3j	5	69 ^c

^aGeneral procedure: Amine (5 mol %), substrate (1 equiv), **2** (1.2 equiv), and 1 mL of 1.3 mg/mL of CuSO₄ solution were mixed at rt until the reaction was complete as determined by TLC. ^bIsolated yield. ^cNMR yield: 83%.

reagents such as bis(pinacolato)diboron or tetrahydroxydiborane¹² is initiated by activating Lewis bases.¹³ Consistent with our ongoing interest with Lewis base activation of boron, we recently disclosed an improved protocol that utilizes catalytic amounts of Cu^{II} and amine run at rt, open-to-air, and uses water as the solvent medium.¹⁴ A suggested mechanism proposes that the amine serves two roles: (1) as

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Table 3. β -Silylation of Other α,β -Unsaturated Conjugated Compounds^a

entry	substrate	product	time (h)	yield (%)	
1			5a	4	57
2			5b	5	73
3			5c	5	44
4			5d	3 ^b	NR ^c
5			5e	3 ^b	48

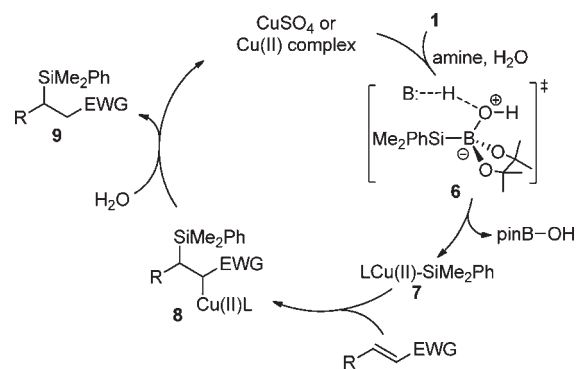
^aGeneral procedure: Amine (5 mol %), substrate (1 equiv), **2** (1.2 equiv), and 1 mL of 1.3 mg/mL of CuSO₄ solution were mixed at rt until the reaction was complete as determined by TLC. ^bReaction was heated at 50 °C. ^cNR = no reaction

a ligand for copper and (2) as a Bronsted base for the activation of a nucleophilic water molecule. We surmised that the same catalyst system would facilitate silyl conjugate addition to α,β -unsaturated carbonyl compounds. With such a procedurally simple protocol, silyl conjugate additions could be performed open-to-air using water as the solvent. Additionally, use of an inexpensive Cu^{II} source (i.e., CuSO₄) is advantageous because it is insensitive to moisture and resistant to oxidation upon exposure to air. Further, Lewis base additives that hydrolyze in the presence of adventitious water such as KO^tBu or DBU/NHC¹⁵ can be substituted with inexpensive amines commonly found in most laboratories. In this report, we disclose our efforts toward achieving such a protocol.

To determine the optimal conditions of the reaction, we treated cyclohexanone (**2a**) with **1** in the presence of a catalytic amount of copper catalyst and screened several amines as well as potassium acetate and potassium bicarbonate (Table 1). Although some conversion of **2a** to **3a** was observed with potassium acetate and potassium carbonate (entries 1–2), we found that amines that can form coordination complexes providing the desired product in much better conversions. For example, aromatic amines resulted in consistently high conversions with 4-picoline performing the best (entries 3–6). However, a bidentate

(15) NHCs have been suggested to undergo decomposition under aqueous conditions; see ref 9.

Scheme 1. Proposed Catalytic Cycle



ligand such as bipyridine was ineffective (entry 7), which is consistent with our previous observations.¹³ On the other hand, alkyl amines could also affect the conversion to **3a** (entries 8–10). Control reactions showed that both copper and amine are required in the reaction (entries 11–13). Further, it was confirmed that Cu(II) sources are superior catalysts than Cu(I) (compare entries 14 vs 15–16).¹⁶

With the optimum conditions determined (Table 1, entry 4), we explored the suitability of a variety of α,β -unsaturated conjugated compounds for silyl conjugate addition (Table 2). Cyclic ketones **2a,b** underwent β -silylation in good to excellent yields (entries 1–2). Acyclic ketones were also good substrates. For example, ketones bearing alkyl or aryl substituent on the β -carbon were converted to the desired products **3c–e** in 68–84% yield (entries 3–5). Further, a regioselective 1,4-addition occurred with a $\alpha,\beta,\gamma,\delta$ -unsaturated substrate **2f**, affording **3f** in excellent yield (entry 6). This result is surprising because Hoveyda observed 1,6-addition using a Cu^I–NHC protocol.^{8a} Hence, our method nicely complements the Cu^I–NHC protocol that affords the alternative 1,4-addition product. Indeed, we were delighted to demonstrate that electronically more demanding and sterically encumbered α,β -unsaturated esters are suitable as substrates. To date, only a handful of examples of esters as substrates have been reported.^{7b,8} Thus, the efficient transformation of **2g–2j** containing either a methyl or phenyl substituent on the α or β position to **3g–3j** demonstrates the utility of the developed reaction method (entries 7–10).

To further investigate the generality of the substrate scope of the reaction, substrates **4a–e** were subjected to the reaction conditions (Table 3). Although α,β -unsaturated aldehydes can suffer from competing 1,2- or 1,4-silyl conjugate addition, to our delight, **4a,b** were transformed to **5a,b** in good yields (entries 1–2). Acrylonitrile was also effectively silylated (**5c**) in 44% yield. A clear limitation of the reaction is with the less electrophilic α,β -unsaturated diethylvinylphosphonate **4d**, wherein no product was observed even under slightly elevated temperature. However,

(16) We suspect that the active catalyst in the presence of CuCl is Cu(II), which is formed by the disproportionation of Cu(I) to Cu(II) and Cu(0) in water. For a detailed discussion, see ref 14.

installation of the silyl group on the β -carbon of a more reactive phenylvinylsulfone **4e** proceeded in good yield (entry 5). To the best of our knowledge, this is the first report of a conjugative silylation that furnishes a β -silylsulfone.

A proposed catalytic cycle is illustrated in Scheme 1. We suspect that the role of the amine is to deprotonate a nucleophilic water molecule in a manner analogous to the activation of a diboron¹³ to form an sp^3 -hybridized boronate (**6**), which in turn activates the Si–B bond. In the presence of a Cu^{II} complex, transmetalation can occur to produce Cu^{II} –Si complex **7**. The resulting nucleophilic Si undergoes either a 1,4- or 3,4-addition reaction (only 3,4-addition is shown) with α,β -unsaturated carbonyl substrate to afford intermediate **8**; protonation by water leads to the desired product **9** and Cu^{II} -complex catalyst, completing the cycle.

In conclusion, we disclose, to the best of our knowledge, the first $Cu(II)$ -catalyzed protocol for the silyl conjugate

addition of α,β -unsaturated conjugated compounds. The method is highly tolerant of many electron withdrawing groups on the alkene substrate. The presence of catalytic amounts of amine base and copper allows for the protocol to be performed at rt, open-to-air, and with water as the solvent to provide β -silylated products in good to excellent yields. Further extension and application of the method is currently underway.

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Supporting Information Available. Experimental procedures and spectral data for all products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

The authors declare no competing financial interest.