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Copper(II)-Catalyzed Silylation of Activated Alkynes in Water: Diastereodivergent Access to (*E*)- or (*Z*)- β -Silyl- α,β -Unsaturated Carbonyl and Carboxyl Compounds**

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Abstract

Copper(II)-catalyzed silylation of substituted alkynylcarbonyl compounds was investigated. Via activation of $\text{Me}_2\text{PhSiBpin}$ in water at room temperature and open atmosphere, vinylsilanes conjugated to carbonyl groups are synthesized in high yield. A surprising diastereodivergent access to olefin geometry was discovered using a silyl conjugate addition strategy: aldehydes and ketones were *Z* selective while esters and amides were exclusively transformed to *E* products.

Keywords

silylation; copper catalysis; conjugate addition; vinylsilane; diastereoselection

Vinylsilanes are versatile building blocks in organic synthesis because of their utility in diverse types of chemical transformations such as C-C bond formation in Hiyama coupling, oxidation to a carbonyl with the Tamao-Fleming reaction, and alkene formation via protodesilylation.^[1] Owing to their stability, low toxicity, and affordability, methods for the preparation of organosilicon compounds have received increased attention.^[2] Transition metal-catalyzed regioselective hydrosilylation of alkynes provides the most straightforward and atom economical access to vinylsilanes.^[3] Synthesis of substituted vinylsilanes conjugated to carbonyl groups is challenging because of the difficulty in controlling regio- (α vs β) and stereoselectivity (*E* vs *Z*) of products (Figure 1).^[4] $\text{Pt}^{[5]}$ and $\text{Pd}^{[6]}$ -catalyzed hydrosilylation of alkynyl carbonyl compounds afford vinylsilanes with excellent regioselectivity, where the silicon group was transferred to the α position of the carbonyl, have been developed.^[7] In contrast, Ru-catalyzed hydrosilylation methods generate the complementary β -silyl- α,β -unsaturated carbonyl products with excellent *Z*-selectivity.^[8] Most recently, Molander and co-workers reported a copper (I)-catalyzed conjugate silylation method using disilane reagents to yield β -silyl- α,β -unsaturated esters in varying yields and modest *E/Z* selectivity.^[9] Hence, there is a paucity of methods capable of providing products with the necessary regioselectivity towards β silylation and selectivity with regards to olefin

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geometry. Furthermore, to the best of our knowledge, there are no examples of amides or aldehydes that have been employed as substrates in these reactions.

Given that a mild method with broad substrate scope, functional group tolerance and high stereoselectivity is currently lacking, and our interest in Cu-catalyzed boryl^[10] and silyl^[11] conjugate addition,^[12] we sought to develop a process to address these shortcomings. In particular, we employ commercially available Me₂PhSiBpin^[13] as the silicon source, which was recently used by Loh and co-workers in the synthesis of linear and branched vinylsilanes.^[14] Herein, we report a copper(II)-catalyzed conjugate addition of substituted alkynyl carbonyls to generate the corresponding β -silylated products. Surprisingly, the method furnishes a substrate-controlled diastereodivergent access to stereoisomeric products: aldehydes selectively afford *Z* olefins whereas esters and amides exclusively generate the opposite *E* alkene geometry. The protocol offers several practical advantages. Firstly, it utilizes a catalytic amount of redox stable and inexpensive transition metal—a copper(II) source—that is resistant to oxidation. Copper(I) sources require special handling that includes either Schlenck techniques or use of a glovebox. Secondly, the reaction is insensitive to moisture and provides a green chemistry process that utilizes water as the solvent. Finally, the method is mild, being performed open to the atmosphere at rt within 2–4 h.

We initiated our investigations by examining the appropriate base additive that can activate a B–Si bond (Table 1). We previously demonstrated that 4-picoline was sufficiently effective in acting as a Brønsted base to activate a nucleophilic water molecule towards Me₂PhSiBpin and chemoselectively transfer silicon to α,β -unsaturated carbonyl compounds in the presence of catalytic amounts of copper (II).^[11] An important aspect of our studies is the generation of a water stable, nucleophilic Cu–Si intermediate to initiate silyl transfer to the β carbon. A screen of bases confirmed that most organic and inorganic bases efficiently catalyzed the conversion of 2-octyn-1-al (**1b**) to (*E*)- and (*Z*)-**2b** within 2 hr (entries 1–7). However, 4-picoline and pyridine preferentially afforded **2b** in >97% conversion with 9:91 *E:Z* ratio. Surprisingly, the *Z* geometry of the double bond observed is contrary to that of a copper(I)-catalyzed addition to acetylenic esters recently reported by Molander.^[15] The double bond geometry was unambiguously assigned by nuclear Overhauser effect (nOe) experiments (see the Supporting Information for details). In addition, exclusive formation of β -silylated product was observed. Control experiments suggest both amine and copper were required for this reaction to proceed (entries 8–9). Finally, investigations on copper reagents indicate a number of copper (II) sources efficiently afford (*Z*)-**2b** in excellent conversion and selectivity (entries 10–12).

With optimized conditions established, we investigated the scope of the silyl conjugate addition reaction with aldehydes (Table 2). Use of 1.1 equiv Me₂PhSiBpin afforded product **2a** in 74% yield and 11:89 *E:Z* selectivity (entry 1). As the aldehyde starting material was not fully consumed in the reaction, the equivalency of Me₂PhSiBpin was increased to 1.5 in subsequent reactions. Thus, alkynyl aldehydes with alkyl substituents on the β -carbon ranging from a short pentyl to a much longer dodecyl chain were efficiently transformed to the corresponding vinyl silanes (**2b–2e**) in excellent yield (up to 98%) and in up to 5:95 *E:Z* selectivity (entries 2–5). A more sterically encumbered cyclohexyl group was also an

efficient substrate (entry 6) but a phenyl substituent suffered from a competing 1,2-addition to afford **2g** in 51% yield (entry 7).^[16] To explore functional group tolerance of the reaction conditions, propargyl amine **1h** was converted to the desired product in almost complete *Z* selectivity (entry 8). Additionally, $\alpha,\beta,\gamma,\delta$ -unsaturated ynal **1i** specifically reacted on the β -carbon to afford **2i** in 84% yield despite possible competing δ - and 1,2-addition (entry 9). Finally, cyclopropylacrylaldehyde efficiently underwent the reaction in excellent yield and selectivity affording the β -silylated product **2j** (entry 10).

With an efficient method for accessing (*Z*)-silylenals developed, we directed our efforts towards investigating the reaction outcome with esters (Table 3). Treatment of butynoate ethylester **3a** with 1.1 equiv of Me₂PhSiBpin, catalytic amounts of copper sulfate and 4-picoline in water at rt open to the atmosphere provided the desired vinylsilane **4a** in 95% yield (entry 1). To our delight, a single isomer was exclusively formed but nOe studies (see supporting information for details) unambiguously assigned the alkene geometry as *E*, which is in sharp contrast to the stereochemistry described for aldehydes (vide supra). To determine whether the switch in olefin geometry in the product was general, substrates with varying substituents on the ester and alkyne functionalities were investigated. Substrates with increasingly larger alkyl substituents on the β -carbon generated the corresponding products in excellent yields with exclusive (*E*)-selectivity (entries 2–5). Indeed, a hydrophobic dodecyl chain on the β -carbon efficiently afforded vinyl silane (*E*)-**4e** in 96% yield. While hydrogen on the β -carbon in ethyl propiolate generated product **4f** in a slightly lower yield (entry 6), aryl substituents were also effective substrates. For example, a phenyl group resulted in 98% yield and 100% (*E*)-selectivity (entry 7). Both electron donating and withdrawing groups on the aryl ring were tolerated and afforded the desired products in excellent yields and selectivity (entries 8–9). The nature of the ester functionality has negligible impact on the reaction yield (compare entries 3–4 vs entries 10–11); methyl, ethyl, isobutyl, and phenyl esters underwent the silylation reaction efficiently. Furthermore, no evidence of ester hydrolysis was observed even with phenyl ester (entry 10). To investigate the functional group tolerance of the protocol, substrates bearing heteroatoms were subjected to the reaction conditions. For example, propargyl ether with phenyl or silicon protecting groups (TBS) were tolerated and efficiently converted to the corresponding products **4l** and **4m** in 87% and 89% yields, respectively (entries 12–13). Interestingly, coordinating groups were also good substrates and did not affect the regio- and stereochemistry of the reaction. Tertiary amine and pyridine moieties exclusively gave *E* products in moderate to good yields (entries 14–15).

We were intrigued by the change in stereochemical outcome of the reaction based on the identity of the carbonyl. A key difference between these substrates is the nature of the electron withdrawing ability of the carbonyl groups. A proposed mechanism and origin of stereoselectivity observed is shown in Scheme 1. A nucleophilic silylcopper species (**5**) is generated via water-mediated activation of the Si—B bond and subsequent transmetallation.^[10d, 11] In the case of α,β -acetylenic esters, silylcupration across the triple bond (**6**) occurs in a syn fashion to afford intermediate **7** (path a); protonation affords (*E*)- β -silyl- α,β -unsaturated ester **8** as well as turns over the copper(II) catalyst. In this particular case, a formal 1,4-conjugate addition is disfavored because of electron donation to the

carbonyl group from the ester moiety. On the other hand, when more electron deficient aldehydes are used, addition of **6** may proceed through two possible pathways: (1) a syn addition in a similar path to that observed with esters (path a), generating the *E* isomer as a minor product, and (2) a competing 1,4-conjugate addition (path b) that leads to an allenolate intermediate-copper(II) complex **9**. Because the substituents on the α and δ position of allenolate **9** are orthogonal, protonation occurs on the site opposite the sterically encumbered dimethylphenylsilyl group to provide (*Z*)-isomer **10** as the major product. A similar mechanism has been proposed with trimethylgermyl copper addition to alkynyl esters, *i.e.*, protonation occurs from the side opposite a bulky trimethylgermanium group.^[17]

To test this hypothesis, carbonyl groups with better electron donating substituents such α,β -alkynyl amides were subjected to the reaction conditions. To our delight, amides bearing either a butyl (**11a**) or phenyl (**11b**) moiety on the alkyne provided products **12a-12b** in excellent yields with exclusive (*E*)-configuration (Figure 2). As predicted, substrates with intermediate carbonyl electrophilicity (*i.e.*, between aldehydes and esters), such as α,β -unsaturated ketones **11c-d**, afforded a mixture of isomers but with a slight preference for the *Z* alkene (**12c-d**).

In summary, we have reported the first example of a Cu(II)-catalyzed hydrosilylation of α,β -alkynyl carbonyl compounds. The mild method is a convenient and operationally simple protocol that affords β -silyl- α,β -unsaturated carbonyl compounds with excellent substrate control of diastereoselectivity. Notably, aldehydes and ketones are selectively converted to (*Z*)-isomeric products while esters and amides generate the complementary (*E*)-isomers. The developed reaction offers an environmentally friendly condition that utilizes water as the solvent and catalytic amounts of metal. The present method provides access to otherwise difficult intermediates, and hence, is of synthetic value. Further investigation towards extension of the method with more complex systems is underway.

Experimental Section

General Procedure: In a 1 dram vial, α,β -acetylenic carbonyl (1.0 equiv), 4-picoline (0.05 equiv), Me₂PhSiBpin (1.1 or 1.5 equiv), and 1 mL of 1.3 mg/mL CuSO₄ stock solution (0.01 equiv) were vigorously stirred together. The reaction was quenched with 1 mL of hexanes as followed by TLC. The aqueous layer was extracted 3× with hexanes. The combined hexanes layer was back extracted 5× with water and then dried over sodium sulfate. Silica gel chromatography was used to purify the product.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Strategies toward carbonyl conjugated vinylsilanes.

Figure 2.

Silyl Conjugate Addition to Amides and Ketones.

[a] Isolated Yield. [b] Determined by ¹H NMR of crude reaction mixture. [c] Reaction was performed with 1.1 equiv Me₂PhSiBpin for 2 h.

Scheme 1.
Proposed mechanism and origin of diastereoselectivity.

Table 1

Screening of Base Additives and Copper Source^a

entry	base	copper source	conv ^b (%)	E : Z ratio ^c
1	4-picoline	CuSO ₄	97	9:91
2	pyridine	CuSO ₄	98	9:91
3	DBU ^d	CuSO ₄	>99	22:78
4	TEA	CuSO ₄	97	30:70
5	NaO ^t Bu	CuSO ₄	>99	22:78
6	NaOH	CuSO ₄	>99	26:74
7	KOAc	CuSO ₄	69	25:75
8	none	CuSO ₄	trace	–
9	4-picoline	none	NR ^e	–
10	4-picoline	Cu(OAc) ₂	>99	11:89
11	4-picoline	Cu(BF ₄) ₂	>99	10:90
12	4-picoline	CuCl ₂	>99	10:90

[a] General procedure: Base (5 mol%), 2-octyn-1-ol (1 equiv), Me₂PhSiBpin (1.5 equiv), and 1 mL of 0.325 mg/mL CuSO₄ solution were mixed at rt for 2 h.

[b] Conversion values determined by ¹H NMR of crude reaction mixture.

[c] Determined by ¹H NMR of crude reaction mixture.

[d] 1,8-Diazabicyclo[5.4.0]undec-7-ene.

[e] no reaction.

Table 2

Silyl Conjugate Addition to Substituted Acetylenic Aldehydes^a

entry	substrate	product	yield ^b	<i>E</i> : <i>Z</i> ratio ^c
1			74 ^d	11:89
2			97	5:95
3			93	10:90
4			95	11:89
5			98	9:91
6			86	12:88
7			51 ^e	19:81
8			60	2:98

entry	substrate	product	yield ^b	<i>E</i> : <i>Z</i> ratio ^c
9			84	14:86
10			90	8:92

[a] General procedure: 4-picoline (5 mol %), substrate (1.0 equiv), Me₂PhSiBpin (1.5 equiv), and 1 mL of 1.30 mg/mL CuSO₄ solution are mixed at rt for 2 h. Each reaction is an average of at least two experiments.

[b] Isolated Yield.

[c] Ratio determined by ¹H NMR and assignment by nOe experiments; see the Supporting Information for details.

[d] 1,1 equiv of Me₂PhSiBpin was used.

[e] Competing 1,2-addition product was observed. Ratio of 1,4- vs 1,2-addition product was 2:1.

Table 3

Silyl Conjugate Addition to Substituted Acetylenic Esters^a

entry	substrate	product	yield ^b
1			4a 95
2			4b 83
3			4c 92
4			4d 93
5			4e 96
6			4f 57
7			4g 98
8			4h 89
9			4i 99
10			4j 94
11			4k 95
12			4l 87
13			4m 89

entry	substrate	product	yield ^b
14			50
15			74 ^{c,d}

[a] General procedure: 4-picoline (5 mol %), substrate (1.0 equiv), Me₂PhSiBpin (1.1 equiv), and 1 mL of 1.30 mg/mL CuSO₄ solution are mixed at rt for 2 h. Each reaction is an average of at least two experiments.

[b] Isolated Yield.

[c] Reaction run for 5 hours.

[d] NMR yield; product and starting material were chromatographically inseparable.