Stereoselective Silylcupration of Conjugated Alkynes in Water at Room Temperature**

Roscoe T. H. Linstadt, Carl A. Peterson, Daniel J. Lippincott, Carina I. Jette, and Bruce H. Lipshutz*

Abstract: Micellar catalysis enables copper-catalyzed silylcupration of a variety of electron-deficient alkynes, thereby providing access to isomerically pure E- or Z- β -silyl-substituted carbonyl derivatives. These reactions take place in minutes, afford high yields and stereoselectivity, and are especially tolerant of functional groups present in the substrates. The aqueous reaction medium has been successfully recycled several times, and a substrate/catalyst ratio of 10,000:1 has been documented for this methodology.

 \mathbf{V} inylsilanes enjoy a rich history as valued intermediates in organic synthesis.^[1,2] Well established representative transformations of this functional group include Hiyama-Denmark couplings,^[3] iodode silvlation,^[4] and Brook rearrangement/anion relay chemistry.^[5] The use of vinylsilanes as tethers or halogen precursors has been pivotal in several total syntheses, in which they allow late stage functionalization.^[6-8] Traditionally, these substrates have been prepared by silylcupration; for example, by using Fleming's cuprate,^[9] but such processes often involve stoichiometric metals, and while these may be of low cost, they carry prohibitive waste disposal issues that usually preclude their use on a larger scale.^[10] Alternatively, Suginome's silylborane, PhMe2SiBpin, offers the possibility of performing nucleophilic organosilicon chemistry in water based on transmetallation from boron to the appropriate transition metal.^[11,12] Copper-catalyzed reactions involving this reagent actually require the presence of water or protic solvent for optimum efficiency.^[13,14] Many useful reactions have already been developed based on silvlboranes, as described in a comprehensive review by Oestreich.^[15] Traditional approaches to specifically *E*- or *Z*-βsilvlenoates rely on condensation of acylsilanes with ynolates^[16] or phosphonate esters.^[17] However, these approaches suffer from a lack of efficiency and require multiple steps. A more atom- and step-economical approach that has gained popularity in recent years is the catalytic silylation of an activated alkyne. Trost had shown previously that ruthenium catalysts perform hydrosilylations to give Z- β -vinylsilanes.^[18] Palladium catalysts were recently found to give highly selective α -silvlation of conjugated alkynes,^[19] and Ferreira

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disclosed a method for the regioselective hydrosilylation of internal alkynes using platinum catalysts.^[20] Most recently, and most closely analogous to the present work, Molander described a copper-catalyzed introduction of silicon into conjugated alkynes to give E- β -silyl-substituted carbonyl derivatives. This system, however, gave variable stereoselectivity and modest yields, and required the use of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU) at relatively high temperatures to activate a disilane to achieve conversion.^[21] Considering that copper-based reagents traditionally undergo cis-addition to alkynes, and considering the ease with which PhMe₂SiBpin participates in transmetallation, we sought to develop a complementary method to that of Trost,^[18] which would selectively provide entry to E- β -silylsubstituted carbonyl derivatives under mild and, in particular, greener conditions.

The initial reaction of ynoate **1** was performed with PhMe₂SiBpin as the stoichiometric source of silicon. Also present were catalytic amounts of the air stable copper(I) source $\text{CuF} \cdot (\text{PPh}_3)_3 \cdot 2$ MeOH and bisphosphine ligand BDP,^[22] while an aqueous solution of the commercially available surfactant TPGS-750-M (Figure 1) served as the reaction



Figure 1. Structure of TPGS-750-M and the BDP ligand.

medium. Under these room-temperature conditions, the *E*- β silylenoate (**11**) was generated as a single isomer (Table 1, entry 1). Control reactions revealed that a copper(I) source is required for the reaction, since no reaction took place in its absence, even when this Cu^I salt was replaced with Cu-(OAc)₂·H₂O (entries 2, 5).^[23] Likewise, attempts to use either CuI or CuBr led to no conversion under otherwise identical conditions (entries 3, 4).

Surprisingly, the use of Cu^I acetate was observed to give full conversion after one hour (entry 6), thus suggesting that the reaction was faster than originally anticipated and that lower catalyst loadings could be employed. Performing the reaction with ligand-free CuOAc led to limited conversion (entry 7), confirming the benefits of a ligand on copper. Reduced catalyst loading with the less expensive ligands TMEDA and Ph₃P gave roughly similar results (entries 8,9), with the latter giving complete reaction in five minutes. Interestingly, this model reaction could even be run "on

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Table 1: Optimization of the reaction conditions.

	<i>n</i> -C ₆ H ₁₃	conditions	PhMe ₂ S	i n-C ₆ H ₁	iu 13
Entry	Cu Souce (mol%)	Ligand (mol %)	Conc. [м]	<i>t</i> [h]	Conv [%]
1	CuF (3) ^[c]	BDP (3)	0.50	9	82 ^[a]
2	none	BDP (3)	0.50	9	< 2 ^[b]
3	Cul (3)	BDP (3)	0.50	9	0 ^[a]
4	CuBr (3)	BDP (3)	0.50	9	0 ^[a]
5	$Cu(OAc)_2 \cdot H_2O(3)$	BDP (3)	0.50	9	0 ^[a]
6	Cu ^I OAc (3)	BDP (3)	0.50	1	100 ^[b]
7	Cu ^I OAc (3)	none	0.50	1	44 ^[b]
8	Cu ^I OAc (3)	TMEDA (3)	0.75	6	98 ^[b]
9	Cu ^I OAc (3)	PPh ₃ (1)	0.75	5 min	100 ^[b]
10	Cu ^I OAc (3)	PPh_3 (1)	neat ^[d]	5 min	100 ^[b]

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Unless otherwise noted, all reactions were run under an inert atmosphere in a 2 wt.% aqueous solution of TPGS-750-M with 1.25 equiv of PhMe₂Si-Bpin. [a] Conversion monitored by GC–MS. [b] Conversion monitored by NMR on the crude material. [c] Using CuF(PPh₃)₃·2 MeOH. [d] Using 5 equiv H₂O.

water", where the reactants, silylboronate, and copper catalyst were mixed together neat with only five equivalents of water (entry 10). Nevertheless, such "on water" reactions are limited to mainly liquid substrates, while the use of a surfactant offers flexibility by accommodating both solid and liquid materials. Moreover, with greater volumes present, opportunities exist for in-flask recycling of the aqueous reaction medium.

With optimized conditions in hand (Scheme 1), the scope of the reaction was next investigated with a variety of acetylenic esters (Table 2). Several simple alkyl esters, such as



Scheme 1. Optimized conditions for reactions of acetylenic esters.

n-butyl (1), *tert*-butyl (2), and methyl (3) esters showed no variation in terms of yield or stereochemical outcome. In the case of extended conjugation such as that found in ynoate 4, only the 1,4-addition product 14 was observed. Terminal alkynes 5a and 5b afforded products 15a and 15b, respectively, with complete *E* selectivity. A product enoate bearing an alkyl chloride (16) could be obtained, albeit in modest yield; increasing the amount of catalyst to 5% and the silylboronate to two equivalents yielded the desired product in 82% yield. The presence of an additional terminal alkyne within ynoate 7 led to product 17 in 75% yield, with the





[a] With 5 mol % catalyst, 2 equiv $\mathsf{PhMe}_2\mathsf{SiBpin},$ overnight, at room temperature.

remaining mass balance being terminal alkyne addition products and recovered starting material. To assess the effects of an internal chelating residue on the stereochemical outcome, a substrate with a 2-pyridyl group (8) was used and it gave acceptable 12:1 *E* selectivity (entry 8). On the other hand, a protected (9) or free (10) alcohol could be employed with stereochemical impunity, although in the latter case, spontaneous cyclization to the corresponding γ -lactone (20)

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was observed, thus indicating that the reaction proceeded with E selectivity.

Other electron-withdrawing groups on the alkyne were then studied to evaluate the scope of the silvlation (Table 3). The acetylenic oxazolidinone 21 could be utilized to produce 33; the product was obtained predominantly as the E isomer in 70% yield, along with the Z isomer (12%), each easily separable by flash chromatography. The appearance of the second isomer in this case suggests stabilization of an Ochelated copper allenoate intermediate, prior to protioquenching (see below). Silvlation of acetylenic acid 22 was uneventful and gave at enoate 34 in 84% yield as a single isomer. β -Silylation of acetylenic Weinreb amide 25 to give product 37 represents a desirable transformation because it offers routes to potential aldehyde and ketone derivatives. A tertiary (26) or primary (28) amide could be used without incident to give adducts 38 and 40, respectively. Alkynyl peptides 23 and 24 led successfully to products 35 and 36, both formed exclusively as E isomers. These conjugate additions are thus tolerant of acidic N-H functionality, and proceed without erosion of the existing central chirality. The advantage of the surfactant becomes especially apparent in the case of alkynyl peptide 23 and amide 28, where the reactants are crystalline solids and cannot be used "on water." Both acetylenic sulfone 27 and nitrile 29 reacted smoothly in >95% yield, a notable result because the analogous vinylic derivatives were previously reported to be sluggish towards copper catalyzed silvlation.^[13]

Ketones were also investigated by using **30** as a model substrate. The use of optimized conditions **A** (Table 3) led to a disappointing 4:1 selectivity. However, to our surprise, 2D-NOESY revealed that the *Z*-isomer was the major product. With optimization, a combination of tri(*p*-fluorophenyl)phosphine-complexed copper(I) acetate, and performing the reaction on water (conditions **C**), this value could be elevated to give **42** as a 1:17 *E/Z* mixture.^[24] Surprisingly, the analogous isobutyl ketone led to lower selectivity (1:3 *E/Z*; **44**) under identical conditions. When the reaction was run in aqueous surfactant with BDP as the ligand (conditions **D**) in an ice bath, an acceptable 1:8 selectivity was obtained.^[25] In contrast to results from β -substituted ynones **30** and **32**, terminal ynone **31** afforded product **43** with complete *E* selectivity, albeit in modest (61%) yield.

To probe the mechanism of addition, the reaction was conducted in aqueous surfactant solution derived from TPGS-750-M dissolved in D₂O. The selective deuterium incorporation observed at the α -position implies that an α vinylcopper(I) species is formed and leads to eventual protioquenching^[26] (see the Supporting Information). The high *E* selectivity observed for esters likely arises from an unfavorable energetic barrier to enolization to the corresponding isomeric O–Cu allenoate.^[27,28]

While the base-metal status of copper, and hence its cost, may not be a major factor governing its use, from an environmental perspective, it remains desirable to reduce the metal content in any catalytic process to the levels dictated by necessity. The short reaction times suggested that the level of copper required for this catalytic process could be lowered considerably. This proved to be the case, since β -



Conditions A: PhMe₂SiBpin (1.25 equiv), TPGS-750-M (2 wt.%), PPh₃/ CuOAc (1 mol%), [0.75 \mbox{mu} substrate]. Conditions B: PhMe₂SiBpin (1.25 equiv), neat, H₂O (5 equiv), PPh₃/CuOAc (1 mol%). Conditions C: PhMe₂SiBpin (1.50 equiv), on water, [0.3 \mbox{mu} substrate], (4-F-C₆H₄)₃P/ CuOAc (2 mol%). Conditions D: PhMe₂SiBpin (1.00 equiv), ynoate (2.00 equiv), [0.75 \mbox{mu} substrate], TPGS-750-M (2 wt.%), (4-F-C₆H₄)₃P/ CuOAc (2 mol%). Conditions E: 1.25 equiv PhMe₂SiBpin, 1 mol% BDP/ CuOAc, [0.75 \mbox{mu} substrate], TPGS-750-M (2 wt.%), ice bath temperature. [a] Unless stated otherwise, all reactions were performed at ambient temperature. [b] Using 2 equiv PhMe₂SiBpin.

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silvlation of **1** could be achieved with only 0.01 % catalyst-tosubstrate loading (i.e., S/C = 10,000:1), in which case 16 h were required for complete conversion (Scheme 2).



Scheme 2. Reaction with 0.01 mol% catalyst loading.

Recycling of the aqueous reaction medium containing the surfactant allows for even further reduction of aqueous and metal waste, in addition to minimizing the use of organic solvents. A simple in-flask extraction with a minimum amount of organic solvent leads to isolation of the product. The introduction of fresh substrate and silylborane to the recycled aqueous medium, without additional surfactant or copper catalyst, allows the reaction to be performed sequentially for at least six cycles (Scheme 3). For each of these runs, the product was isolated in excellent yield without adverse effects regarding the reaction time or the purity of the product.



Scheme 3. In-flask recycling of the catalyst and reaction medium.

Although these reactions were routinely performed on a 0.1 to 0.4 mmol scale, these reactions are amenable to scaleup. Starting with 3.94 mmol of substrate 2, 1.184 grams (86%) of product 12 could be formed in less than 15 min (Scheme 4), with the remaining mass being recovered starting material.

E Factors have become a commonly used metric to evaluate the environmental impact of a given reaction.^[29] They are commonly defined as the ratio of the mass of waste to the mass of desired product formed, and vary depending upon the nature of the industry involved. Historically, only organic solvents, and not water, are used in the calculation because the inclusion of water can significantly increase these already elevated values. Nevertheless, for the representative silylation of 1 to enoate 11, run in aqueous surfactant (conditions A) or neat (conditions B), the E Factors are calculated to be 4.2 and 2.1 respectively. These



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Scheme 4. Gram-scale silylation.

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values are only slightly elevated to 8.5 and 2.4 when the water used in the reaction medium is included. $^{\rm [30]}$

The product β -silylenoates can serve as precursors to a variety of useful secondary products. For example, we have previously demonstrated that nonracemically ligated copper hydride can reduce *E* or *Z* β -silylenoates to afford chiral β silanes with excellent enantioselectivity.^[31] Alternatively, these substrates can be used to construct stereochemically pure vinyl iodides. DIBAL-H reduction of **12** afforded the corresponding β -silyl allylic alcohol (82 %; Scheme 5). TBSprotection and then iodination according to Vilarrasa's modification^[32] of Zakarian's conditions^[4] gave *E*-vinyl iodide (**47**) in 56 % yield over four steps from ynoate **2** with complete retention of stereochemistry.



Scheme 5. Production of vinyl iodide **47**. DIBAL-H = diisobutylaluminum hydride, TBS = *tert*-butyldimethylsilyl, NIS = N-iodosuccinimide, HFIP = 1,1,1,3,3,3-hexafluoro-2-propanol.

In summary, a new method has been developed that allows especially facile copper-catalyzed silylcupration of electron-deficient alkynes in water at room temperature. Isomerically enriched β -silyl-substituted carbonyl derivatives are readily formed quickly and in high yields. The process is compatible with an array of electron-withdrawing groups and consistently provides the anticipated geometrical isomer. Considering the value of vinylsilanes in organic synthesis, together with the overall reaction efficiency, selectivity, options for scale-up, recyclability, and the environmentally benign conditions involved, this chemistry should find considerable utility.

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Green Chemistry

R. T. H. Linstadt, C. A. Peterson, D. J. Lippincott, C. I. Jette, B. H. Lipshutz*

Stereoselective Silylcupration of Conjugated Alkynes in Water at Room Temperature



Fast, cheap, and green: Micellar catalysis enables the selective construction of a variety β -silyl-substituted carbonyl derivatives under mild aqueous conditions. The reaction is catalyzed by low levels of Cu¹, is compatible with numerous electron-withdrawing groups, affords high yields, and provides opportunities for scale-up and recycling of the reaction medium. The environmental impact, as measured by E Factors, is very low.

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