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Green Chemistry

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

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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.*

Vinylsilanes 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 silylation,[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, $PhMe_2SiBpin$, 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 silylboranes, as described in a comprehensive review by Oestreich.[15] Traditional approaches to specifically *E*- or *Z*-β-silylenoates 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-silylation of conjugated alkynes,[19] and Ferreira 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 $PhMe_2SiBpin$ participates in transmetallation, we sought to develop a complementary method to that of Trost,[18] which would selectively provide entry to *E*-β-silyl-substituted carbonyl derivatives under mild and, in particular, greener conditions.

The initial reaction of ynoate **1** was performed with $PhMe_2SiBpin$ as the stoichiometric source of silicon. Also present were catalytic amounts of the air stable copper(I) source $CuF{\cdot}(PPh_3)_3{\cdot}2\,MeOH$ and bisphosphine ligand BDP,[22] while an aqueous solution of the commercially available surfactant TPGS-750-M (Figure 1) served as the reaction 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 $Cu(OAc)_2{\cdot}H_2O$ (entries 2, 5).[23] Likewise, attempts to use either CuI or CuBr led to no conversion under otherwise identical conditions (entries 3, 4).

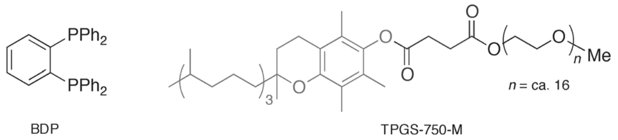

Figure 1. Structure of TPGS-750-M and the BDP ligand.

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 Ph_3P 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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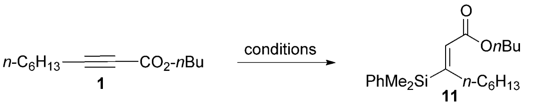
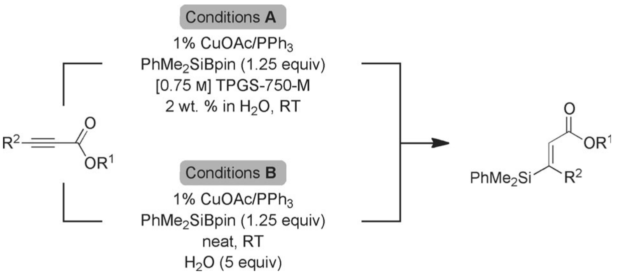
Table 1: Optimization of the reaction conditions.



Entry	Cu Souce (mol%)	Ligand (mol%)	Conc. [M]	*t* [h]	Conv. [%]
1	CuF (3)[c]	BDP (3)	0.50	9	82[a]
2	none	BDP (3)	0.50	9	< 2[b]
3	CuI (3)	BDP (3)	0.50	9	0[a]
4	CuBr (3)	BDP (3)	0.50	9	0[a]
5	Cu(OAc)$_2$·H$_2$O (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]

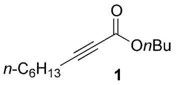
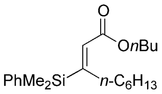
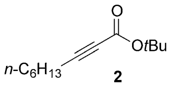
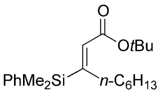
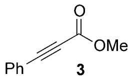
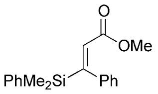
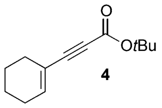
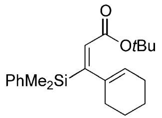
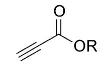
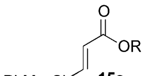
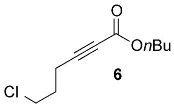
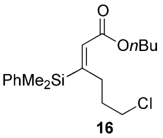
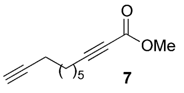
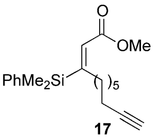
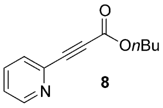
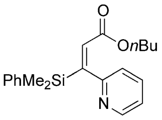
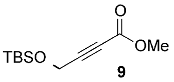
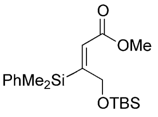
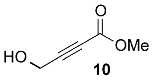
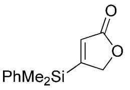
Unless otherwise noted, all reactions were run under an inert atmosphere in a 2 wt.% aqueous solution of TPGS-750-M with 1.25 equiv of PhMe$_2$Si-Bpin. [a] Conversion monitored by GC–MS. [b] Conversion monitored by NMR on the crude material. [c] Using CuF(PPh$_3$)$_3$·2 MeOH. [d] Using 5 equiv H$_2$O.

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.



Scheme 1. Optimized conditions for reactions of acetylenic esters.

Table 2: Substrate Scope: Acetylenic Esters.

Entry	Ynoate	Conditions Time (min)	Product	Yield (%)	*E/Z*
1	 **1**	**A, B** 5	 **11**	95 (**A**) >95 (**B**)	>20:1 >20:1
2	 **2**	**A, B** 5	 **12**	>95	>20:1
3	 **3**	**A** 30	 **13**	>95	>20:1
4	 **4**	**B** 30	 **14**	>95	>20:1
5	 **5a** R = Et **5b** R = *n*Oct	**A** 120 120	 **15a** **15b**	75 82	>20:1 >20:1
6	 **6**	**A** 240	 **16**	72 (82)[a]	>20:1
7	 **7**	**A** 30	 **17**	75	>20:1
8	 **8**	**A** 60	 **18**	82	12:1
9	 **9**	**A** 30	 **19**	88	>20:1
10	 **10**	**A** 30	 **20**	70	>20:1

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

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

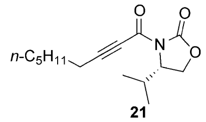
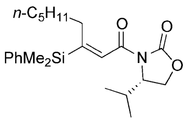
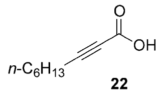
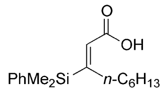
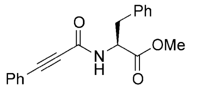
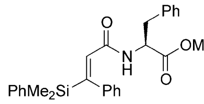
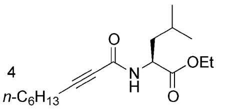
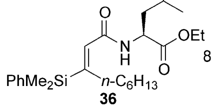
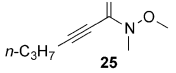
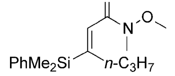
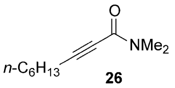
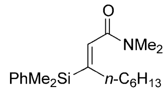
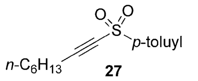
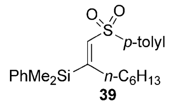
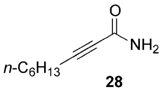
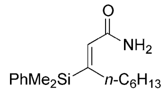
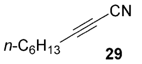
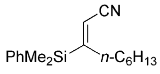
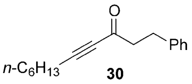
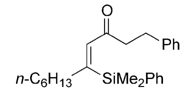
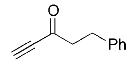
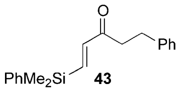
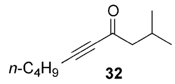
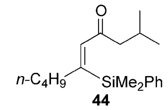
Other electron-withdrawing groups on the alkyne were then studied to evaluate the scope of the silylation (Table 3). The acetylenic oxazolidinone **21** could be utilized to produce **33**; the product was obtained predominantly as the *E* isomer in 70% yield, along with the *Z* isomer (12%), each easily separable by flash chromatography. The appearance of the second isomer in this case suggests stabilization of an O-chelated copper allenoate intermediate, prior to protio-quenching (see below). Silylation 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 silylation.[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 D_2O. The selective deuterium incorporation observed at the α-position implies that an α-vinylcopper(I) species is formed and leads to eventual protio-quenching[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]

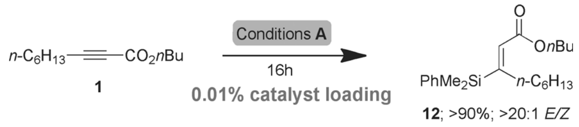
While the base-metal status of copper, and hence its cost, may not be a major factor governing its use, from an environmental perspective, it remains desirable to reduce the metal content in any catalytic process to the levels dictated by necessity. The short reaction times suggested that the level of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

Table 3: Scope of alkynes bearing electron-withdrawing groups.

Entry	Substrate	Conditions [a] Time (min)	Product	Yield (%)	*E/Z*
1	 **21**	**A** 30	 **33**	70 (*E*) 12 (*Z*)	
2	 **22**	**A** 30	 **34**	84 [b]	>20:1
3	 **23**	**A** 60	 **35**	84 [b]	>20:1
4	 **24**	**A** 30	 **36**	88 [b,c]	>20:1
5	 **25**	**B** 30	 **37**	90 [b]	>20:1
6	 **26**	**A** 30	 **38**	78	>20:1
7	 **27**	**A** 360	 **39**	>95	>20:1
8	 **28**	**A** 240	 **40**	85[b]	>20:1
9	 **29**	**A** 10	 **41**	>95	>20:1
10	 **30**	**C** 60	 **42**	91	1:17
11	 **31**	**D** 60	 **43**	61	>20:1
12	 **32**	**E** 120	 **44**	85	1:8

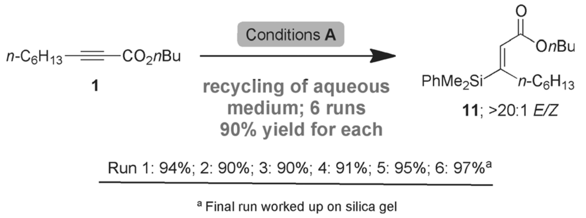
Conditions **A**: $PhMe_2SiBpin$ (1.25 equiv),, TPGS-750-M (2 wt.%), PPh_3/CuOAc (1 mol%), [0.75 M substrate]. Conditions **B**: $PhMe_2SiBpin$ (1.25 equiv), neat, H_2O (5 equiv), PPh_3/CuOAc (1 mol%). Conditions **C**: $PhMe_2SiBpin$ (1.50 equiv), on water, [0.3 M substrate], $(4\text{-F-}C_6H_4)_3P$/CuOAc (2 mol%). Conditions **D**: $PhMe_2SiBpin$ (1.00 equiv), ynoate (2.00 equiv), [0.75 M substrate], TPGS-750-M (2 wt.%), $(4\text{-F-}C_6H_4)_3P$/CuOAc (2 mol%). Conditions **E**: 1.25 equiv $PhMe_2SiBpin$, 1 mol% BDP/CuOAc, [0.75 M substrate], TPGS-750-M (2 wt.%), ice bath temperature. [a] Unless stated otherwise, all reactions were performed at ambient temperature. [b] Using 2 equiv $PhMe_2SiBpin$.

silylation of **1** could be achieved with only 0.01 % catalyst-to-substrate 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.

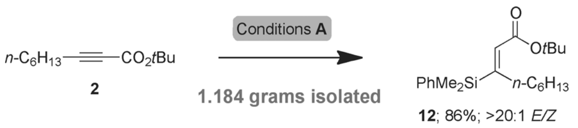
Recycling of the aqueous reaction medium containing the surfactant allows for even further reduction of aqueous and metal waste, in addition to minimizing the use of organic solvents. A simple in-flask extraction with a minimum amount of organic solvent leads to isolation of the product. The introduction 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.

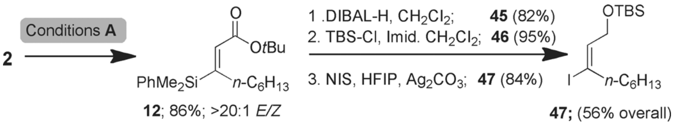
Although these reactions were routinely performed on a 0.1 to 0.4 mmol scale, these reactions are amenable to scale-up. Starting with 3.94 mmol of substrate **2**, 1.184 grams (86 %) of product **12** could be formed in less than 15 min (Scheme 4), with the remaining mass being recovered starting material.

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 values are only slightly elevated to 8.5 and 2.4 when the water used in the reaction medium is included.[30]



Scheme 4. Gram-scale silylation.

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). TBS-protection 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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[23] Cu^{II} sources could be used if first mixed with 2 equiv of a phosphine ligand (relative to Cu), thus suggesting that the phosphine reduces Cu^{II} to the catalytically active Cu^{I}. For details see the Supporting Information.

[24] See the Supporting Information for details regarding optimization of the reaction conditions for alkynyl ketones.

[25] Ice bath temperature; no freezing of the solution was observed.

[26] Attempts to trap this postulated α-cuprio intermediate with electrophiles other than deuterium (e.g., allylic carbonates) were unsuccessful.

[27] The energies for these types of intermediates have been computationally examined for the analogous copper catalyzed hydroboration of ynoates. See: B. H. Lipshutz, Z. V. Bošković, D. H. Aue, *Angew. Chem.* **2008**, *120*, 10337; *Angew. Chem. Int. Ed.* **2008**, *47*, 10183.

[28] β-Selectivity was confirmed by the presence of vinylic singlets in the ^{1}H spectra for all compounds possessing allylic hydrogens. *E*-Selectivity for the esters, while implicit in the formation of lactone **20**, was confirmed by *J*-coupling constants for products **15a** and **15b**, which possess a β-hydrogen. Additional ^{1}H–^{1}H NOESY spectra for compounds **13** and **14** confirmed *E* selectivity for these esters, and then by analogy, for all other esters. ^{1}H–^{1}H NOESY was also performed for products ***E*-33**, ***Z*-33**, **34**, **35**, **38**, **39**, **40**, **41**, **42**, **43**, and **44** to confirm the reported stereochemistry; see the Supporting Information for further details.

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