

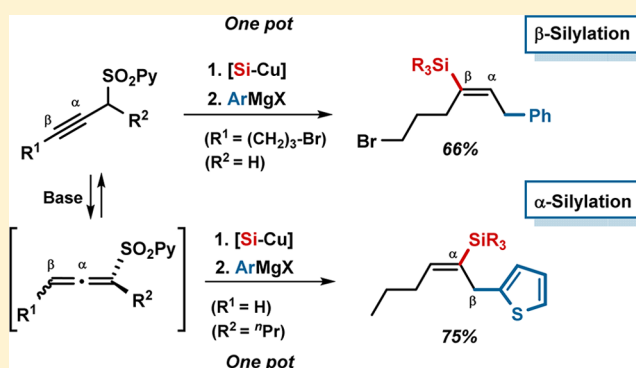
Cu-Catalyzed Silylation of Alkynes: A Traceless 2-Pyridylsulfonyl Controller Allows Access to Either Regioisomer on Demand

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S Supporting Information

ABSTRACT: The Cu-catalyzed silylation of terminal and internal alkynes bearing a 2-pyridyl sulfonyl group (SO₂Py) at the propargylic position affords a breadth of vinyl silanes in good yields and with excellent regio- and stereocontrol under mild conditions. The directing SO₂Py group is essential in terms of reaction efficiency and chemoselectivity. Importantly, this group also provides the ability to reverse the regiochemical outcome of the reaction, opening the access to either regioisomer without modification of the starting substrate by virtue of an in situ base-promoted alkyne to allene equilibration which takes place prior to the silylcupration process. Furthermore, removal of the directing SO₂Py allows for further elaboration of the silylation products. In particular, a one-pot tandem alkyne silylation/allylic substitution sequence, in which both steps are catalyzed by the same Cu species, opens up a new approach for the access to either formal hydrosilylation regioisomer of unsymmetrical aliphatic-substituted internal alkynes from propargyl sulfones.



INTRODUCTION

Vinyl silanes have found widespread applications in modern synthetic organic chemistry as versatile building blocks, and methods for their production continue to be an area of unquestionable interest.¹ The catalytic hydrosilylation of alkynes is arguably the most powerful and direct reaction for the synthesis of these reagents since it offers potential for complete control of the regio- and stereoselectivity.² While most of the examples reported in the literature have focused on the hydrosilylation of terminal alkynes, internal alkynes have received considerably less attention due to their lower reactivity and the inherent difficulty to achieve useful regiocontrol. Indeed, the problem of regioselectivity truly comes to the fore when unbiased unsymmetrical (internal) alkynes with close similarity in terms of electronic and steric properties of the acetylenic substituents are employed. It is thus of great importance to broaden the applicability of alkyne metalation reactions to this type of substrate, as it would open up new ground for design approaches.

The development of methods that result in a formal umpolung of the standard electrophilic reactivity of boron reagents to nucleophilic species³ (boryl–Cu complexes obtained by transmetalation of B₂Pin₂ with LCuOR species), independently reported in 2000 by the Miyaura and Hosomi groups,⁴ has fueled the invention of new technologies directed at solving the issue of regioselectivity in the hydrometalation of alkynes. Work pioneered by the Hoveyda laboratories using this nucleophilic boryl–Cu species has inspired solutions for the

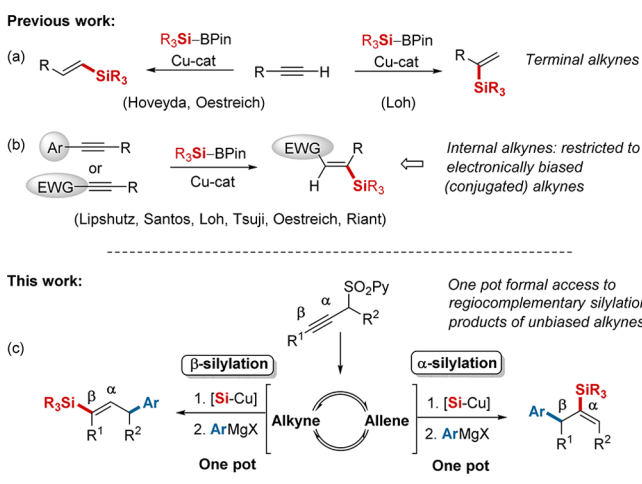
regioselective hydroboration of alkynes, both terminal⁵ and internal,⁶ in which the introduction of directing atoms at the propargylic position is crucial to effect regiocontrol.

The development of a family of boron–silicon reagents by Suginome and co-workers (most notably PhMe₂Si–BPin)⁷ has facilitated the extension of some of the prototypical B₂Pin₂ reactivity to the hydrosilylation of alkynes via silyl–Cu complexes (it is only the R₃Si group in the transmetalation with LCuOR that is transferred to an acceptor molecule).^{8–14} However, the regioselectivity trends observed for the borylation of alkyl-alkynes do not appear to be extensible to silylation. For instance, in a recent elegant example of sequential silylation/borylation of terminal alkynes catalyzed by Cu–NHC complexes,⁹ Hoveyda observed exclusive generation of the β-hydrosilylation isomer (linear), regardless of the electronic attributes of the alkyne substituent (Scheme 1a), which is in sharp contrast with the analogous borylation process.^{5,6} In 2011, Loh described the complementary highly α-regioselective synthesis of vinylsilanes (branched) through PhMe₂Si–BPin addition to alkyl-substituted terminal alkynes catalyzed by a Cu–bulky phosphine complex (Scheme 1a).¹⁰ More recently, Oestreich has reported a linear-selective Cu-catalyzed PhMe₂Si–BPin-silylation of terminal alkynes without added ligand, in which the solvent was found to greatly influence the regioselectivity.¹¹

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Scheme 1. Control of Regioselectivity in the Cu-Catalyzed Hydrosilylation of Alkynes



However, even after these important advances, the regiocontrolled silylation of internal alkynes still represents a major challenge. Only recently have appeared the first successful reports on the Cu-catalyzed silylation of internal alkynes, albeit high regiocontrol has only been achieved in substrates with a marked electronic bias such as conjugated electron-deficient internal alkynes (e.g., propiolates),¹² 1-aryl-1-alkynes, or 1,3-enynes,^{11,13} (Scheme 1b). To the best of our knowledge, a general method to achieve the direct catalytic hydrosilylation of unbiased unsymmetrical aliphatic-substituted internal alkynes with high regiocontrol is yet to be reported. Moreover, the ability to reverse the regiochemical outcome of the reaction without modification of the starting substrate or the catalyst, thereby providing access to both regiocomplementary alkyne silylation products, would notably expand further the structural scope of vinyl silane synthesis. Literature precedents for tuning of regioselectivity in metalation of alkynes are rare and typically rely on structural modification of the starting substrate or ligand control;¹⁵ however, an emerging alternative for controlling regioselectivity based on the use of alkynes as allene surrogates is receiving increasing attention from the synthetic community.¹⁶

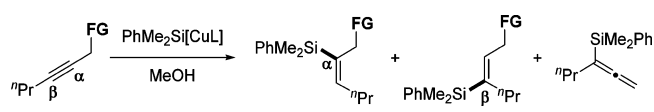
We recently described the development of a two-step protocol to access formal hydroboration products of unbiased internal alkynes.^{6a,17} This strategy relies on the use of a propargylic SO_2Py group¹⁸ as a traceless element of site-selectivity control to produce one specific regioisomer. We envisioned that our findings could be brought further to bear on the formulation of unique methods that would facilitate switching of the regiochemistry of a given reaction on demand, starting from the same substrate, by simply changing the reaction conditions (e.g., by virtue of an in situ base-promoted alkyne to allene isomerization). Herein, we demonstrate the successful implementation of this concept applied to the α - and β -regioselective silylation of alkynes using the SO_2Py as powerful element of regiochemistry and reactivity control, as well as a flexible handle for further elaboration of the resulting products, which enables ready regiodivergent access to structurally diverse vinyl silanes (Scheme 1c).

RESULTS AND DISCUSSION

Optimization Studies: Search for a Convenient Directing Group. At the outset of our studies, we prepared

several internal alkynes bearing polar functions at the propargylic position that could act as directing groups, and explored their reactivity under standard conditions extrapolated from borylation precedents^{5,6} and using Suginome's reagent $PhMe_2SiBPin$ as the silicon source (substrates 1–9, Table 1).

Table 1. β -Silylation of Propargylic Substituted 2-Hexynes



entry	FG (alkyne)	conv (%) ^b	α/β /allene ^b	yield (%) ^c
1	OH (1)	95	43:57:<2	33
2	OTIPS (2)	>98	38:62:<2	62 ^d
3	NHTs (3)	80	19:81:<2	60
4	OPO(OEt) ₂ (4)	35	<2:<2:>98	
5	OCO ₂ Me (5)	87	<2:<2:>98	64
6	S(2-Py) (6)	9	<2:>98:<2	
7	SO ₂ Ph (7)	74	15:85:<2	60
8	SO ₂ (2-Py) (8)	>98	4:96:<2	78
9	SO ₂ (4-Py) (9)	85	22:78:<2	68

^aReaction conditions: alkyne (1.0 equiv), $PhMe_2SiBPin$ (1.1 equiv), $CuCl$ (10 mol %), PCy_3 (11 mol %), $NaOtBu$ (12 mol %), $MeOH$ (2 equiv), toluene, rt, 2 h. ^bDetermined by ¹H NMR in the crude mixture. ^cIsolated yield in major product after chromatography. ^dObtained as an inseparable mixture of regioisomers.

In contrast to the high regioselectivity observed in hydroborations,^{5,6} the hydrosilylation of substrates bearing typical O- and N-based functional groups at the propargylic position, such as OH (entry 1), the bulkier OTIPS (entry 2), or tosylamino (entry 3), afforded silylation products in high conversion but poor regioselectivities. In agreement with observations reported by Sawamura and Szabó for Cu-catalyzed borylations of propargylic carbonates,¹⁹ and by Oestreich in the Cu-catalyzed silylation of propargylic chlorides and phosphates,²⁰ the use of functional groups with high leaving group abilities such as phosphate or carbonate (entries 4 and 5, respectively) resulted in formation of the corresponding silyl-allene. Finally, we observed that the installation of sulfur-based moieties at the propargylic position had a marked effect on regioselectivity, although only sulfones afforded hydrosilylated compounds in high yields (entries 7–9). Among them, the use of 2-PySO₂ (entry 8) resulted in almost exclusive β -silylation and 78% of pure isolated product **10**. Although the precise role of the 2-PySO₂ group in this transformation is unclear at this stage, this result suggests that the 2-pyridyl unit has an additional effect on regiocontrol that enhances the primary effect of the sulfonyl group (entry 7). This secondary effect could be due to the potentially coordinating ability of the 2-pyridyl unit since the use of the electronically related 4-PySO₂ group led to a lower regioselectivity level (entry 9).

Influence of the Ligand. During the development of the hydrosilylation reaction, we noticed that the use of a proper phosphine ligand was crucial in terms of both reactivity and selectivity. This observation was in accordance with literature precedents. For example, in the context of Cu-catalyzed silylation of terminal alkynes, the utilization of an electron-rich and bulky monophosphine ligand such as $PtBu_3$ and Johnphos²¹ was found to be crucial by the group of Loh to achieve high levels of reactivity and branched (α) selectivity,^{10a} whereas exclusive linear (β) selectivity was achieved by Hoveyda's group using copper complexes of NHC ligands

(SIMes).^{5a,b} To evaluate the effect of the ligand in the silylation of the model internal propargyl sulfone **8**, a ligand screen was performed which corroborated that PCy₃ was optimal in fulfilling the subtle balance of steric and electronic requirements for achieving high reactivity and regiocontrol in this reaction (Table 2). The IMes NHC ligand was poorly effective,

Table 2. β -Silylation of Propargylic Substituted 2-Hexynes

entry ^a	ligand (L)	α/β ratio ^b	conv (%) ^b
1	IMes ^c	25:75	40
2	SIMes ^d		<5
3	PPh ₃	14:86	71
4	P(2-furyl) ₃	9:91	28
5	P(ⁿ Bu) ₃	10:90	47
6	PCy ₃	4:96	>98
7	P(^t Bu) ₃	16:84	26

^aReaction conditions: alkyne (1.0 equiv), PhMe₂SiBPIn (1.1 equiv), CuCl (10 mol %), PCy₃ (11 mol %), NaOtBu (12 mol %), MeOH (2 equiv), toluene, rt, 3 h. ^bDetermined by ¹H NMR in the crude mixture. ^cIMes: 1,3-bis(2,6-diisopropylphenyl)imidazolium chloride. ^dSIMes: 1,3-bis(2,6-diisopropylphenyl)-1,3-dihydro-2H-imidazol-2-ylidene. SO₂Py = 2-PySO₂.

providing the hydrosilylation product **10** in 40% conversion and modest levels of β -regioselectivity ($\beta/\alpha = 75:25$, entry 1). Unexpectedly, the saturated analogue SIMes ligand was totally ineffective (no reaction observed, entry 2). The use of Ph₃P improved both yield (71%) and regioselectivity ($\beta/\alpha = 86:14$) of the vinyl silane **10**, albeit to unpractical levels (entry 3). Phosphines with more electron-donating ability such as P(2-furyl)₃ or PⁿBu₃ slightly improved further the β -selectivity to 90%, but at the cost of a decline in reactivity (<50% conversion, entries 4 and 5). Finally, whereas PCy₃ provided full conversion and excellent β -regioselectivity ($\beta/\alpha = 96:4$, entry 6), the bulkier P^tBu₃ was found to be much less effective in terms of both reactivity (26% conversion) and regioselectivity ($\beta/\alpha = 16:84$; entry 7), thus suggesting that the steric hindrance of the ligand is also an important factor for catalytic activity and selectivity.

Cu-Catalyzed β -Silylation of Propargylic 2-Pyridyl Sulfones. With the optimal catalysis conditions in hand, we next sought to examine the scope of the alkyne substitution of this new β -silylation protocol. As shown in Table 3, the reaction of a range of structurally diverse internal propargylic (2-Py)-sulfones resulted in formation of the corresponding trisubstituted β -silylated allylic sulfones in good yields (products **18–24**, 61–80%) and good to excellent selectivities (β/α ratio 77:23 to 97:3). The mild reaction conditions allow for good compatibility with a variety of functional groups: substrates bearing primary alkyl bromides, aryl bromides, or potentially coordinating nitriles (products **20**, **21**, and **22**, respectively) were shown to be amenable to the transformation, which demonstrates the ability of this silylation protocol to generate vinyl silane products containing synthetically useful functional handles that might be readily exploited in subsequent transformations. The reaction was found to be equally effective for the more sterically congested internal alkynes with branched propargylic substitution ($R^2 = \text{Me}$ or $n\text{Pr}$, **22–24**).

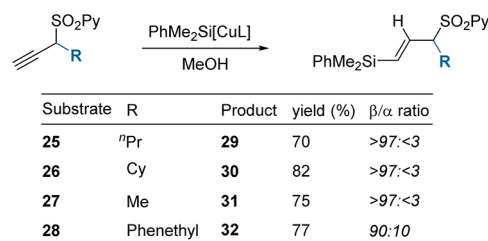
Table 3. β -Silylation of Internal Propargylic 2-Pyridyl Sulfones^a

Substrate	Product	Yield (%)	β/α ratio
8 , 11–17	10 , 18–24		
10	10	78% (96:4)	
18	18	75% (80:20)	
19	19	73% (94:6)	
20	20	67% (95:5)	
21	21	65% (87:13)	
22	22	61% (77:23)	
23	23	77% (97:3)	
24	24	80% (97:3)	

^aSame reaction conditions as in Table 1; reaction time 2–3 h. In parentheses, regioselectivity (β/α ratio) determined by ¹H NMR in the crude mixtures. Isolated yield for the mixture of regioisomers. SO₂Py = 2-PySO₂.

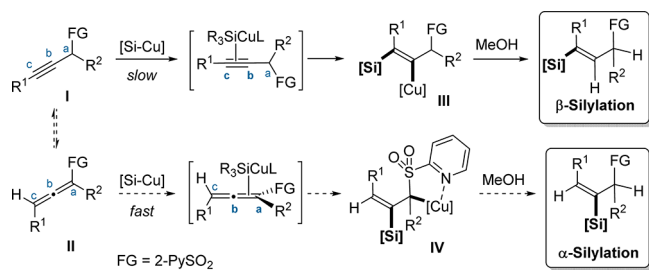
We also examined the feasibility of extending this reactivity profile to propargyl 2Py-sulfones derived from terminal alkynes. This was indeed the case, and several terminal propargylic sulfones reacted cleanly under the optimized conditions to afford the corresponding β -silylated allylic sulfones (**29–32**) in good yields and satisfactory regioselectivities (ranging from 90:10 to >97:<3, Scheme 2).

Scheme 2. Extension of the β -Silylation to Terminal Alkynes



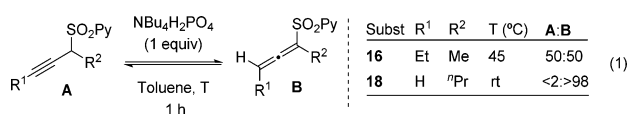
Studies toward Regioselectivity Switch: From β - to α -Selective Silylation. Once an efficient silylation protocol that provides high control of both β -regioselectivity and stereoselectivity across a broad range of substrates had been established, our attention was shifted to developing a method with the ability to reverse the regiochemical outcome of the reaction, since it would provide access to the opposite α -regioisomer without modification of the starting substrate. The accumulated knowledge on the chemistry of sulfones led us to envision an opportunity to invert the regioselectivity of the silylation process: taking advantage of a well-known isomerization process that transforms propargylic sulfones (**I**) into allenyl sulfones (**II**, Scheme 3).²² Allenes have been shown to undergo hydrosilylation and hydroboration processes, with the regiochemistry of these processes being significantly affected by substitution.^{12c,23} In particular, previous work in Cu-catalyzed hydroboration^{23c} and hydrosilylation^{12c} of electron-deficient allenes has shown that the electron density bias imposed by the electron withdrawing group directs the exclusive installation of the boryl or silyl moiety on the central allene carbon, leading to

Scheme 3. Propargyl and Allenyl (2-Py)-sulfones: Potential Divergent Reactivity



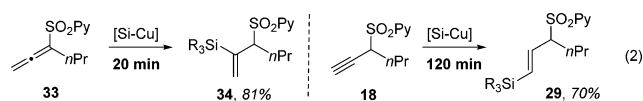
a stabilized allyl Cu-enolate intermediate which then undergoes protonolysis by ROH. On the basis of these precedents, we reasoned that the putative intermediate allenyl sulfone **II** would undergo addition of the Si–Cu complex across the C^a–C^b double bond (instead of the C^b–C^c centers of the starting propargyl sulfone **I**), resulting in the allylic copper intermediate **IV**, which could find additional stabilization by coordination of the metal to the pyridyl nitrogen of the SO₂Py group¹⁸ (Scheme 3). If a base-promoted equilibration between **I** and **II** occurs prior to the hydrosilylation reaction, and assuming that the allene species (**II**) is more reactive than the parent alkyne, this regime for reversible alkyne–allene interconversion would provide a Curtin–Hammett scenario, thus enabling a complementary approach for α -selective silylation. Under such conditions, product selectivity should be largely dependent upon the relative silylation rate constant of both equilibrating species (**I** and **II**) rather than their relative stability. If successful, this method would provide access to both regioisomers of the same starting material by simply switching the reactive species.

To secure the success of our work plan, two conditions needed to be fulfilled: first, the base required to effect the rearrangement should not inhibit the silylation reaction. Along these lines, several bases have been shown to be compatible with Me₂PhSi–BPin in related transformations.¹¹ Second, the allene should be more reactive than the corresponding alkyne in order to shift a hypothetical equilibrium. To examine these hypotheses, we treated substrates **16** and **18** with several bases in toluene, and observed that a number of them promoted this rearrangement; the propargyl/allenyl ratio was shown to depend on the substitution pattern of the starting material: in particular, we observed that for terminal alkyne **18** the equilibrium was completely shifted toward the allene, whereas a 1:1 mixture of species in equilibrium was detected in the case of internal alkyne **16** (eq 1).²⁴ Among the bases tested,



NBu₄H₂PO₄ was chosen in light of its very low coordinating ability, which should not inhibit the formation of the required copper catalyst. Additionally, its poor nucleophilicity constitutes an additional advantage in terms of functional group tolerance.

Strong support for the second premise was found in silylation experiments carried out using preformed allenyl sulfone **33**. When this compound was submitted to the optimized silylation reaction conditions (eq 2), the corresponding α -silylated allyl sulfone **34** was exclusively formed after only 20 min, as



opposed to 120 min required for the β -silylation of the corresponding propargylic sulfone **18**. This result indicates that the allenyl sulfones are more reactive than the propargylic sulfones under our Cu-catalyzed silylation conditions.^{25,26}

Cu-Catalyzed α -Silylation of Propargylic 2-Pyridyl Sulfones. With this information in hand, we reasoned that prestirring our substrates in the presence of an equivalent of base would result in a relatively fast equilibration of the initial propargylic sulfone to the allenyl sulfone.²⁷ Assuming that the allene species are more reactive than the alkyne, this scenario could enable a new approach for a selective α -silylation process.

Gratifyingly, under these reaction conditions, we found that both terminal and internal alkynes underwent a smooth α -silylation process (Table 4), in which the only products

Table 4. α -Silylation of Propargylic 2-Pyridyl Sulfones^a

Substrate	Yield (%)	Rotamer Ratio
terminal alkynes		
34 , R ² = ⁿ Pr	83%	
35 , R ² = Me	70%	
36 , R ² = ^t Bu	76%	
37 , R ² = Phenethyl	79%	
38 , R ² = Cy	72%	
internal alkynes		
39	65%	(93:7) ^b
40	57%	(87:13) ^b
41	63%	(92:8) ^b
42	69%	(80:20) ^b
43	66%	(91:9) ^b
44	60%	(84:16) ^b
45	52%	(98:2) ^b
46	49%	(91:9) ^b
47	57%	(94:6) ^b

^aReaction conditions: alkyne (1.0 equiv), NBu₄H₂PO₄ (1.0 equiv), toluene, rt for internal alkynes or 50 °C for terminal alkynes, 1 h; then, PhMe₂SiBPin (1.0–1.5 equiv), CuCl (10 mol %), PCy₃ (11 mol %), NaOtBu (12 mol %), MeOH (2 equiv), rt or 50 °C. ^bIn parentheses, ratio of rotamers determined by ¹H NMR in the crude mixtures. SO₂Py = 2-PySO₂.

detected in the reaction mixtures were the desired regio- and diastereomerically pure α -silylated isomers. When internal alkynes were used as substrates, the silylation products were obtained as mixtures of rotamers about the C–S/C–Si σ bond (ranging from 80:20 to 98:2). The high chemoselectivity was also demonstrated in the α -silylation reaction of alkynes bearing functional groups such as silyl ethers, alkyl chlorides, or nitriles (**45**, **46**, and **47**, respectively).

The presence of rotamers in equilibrium was unambiguously determined by NMR studies on compound **42** (Figure 1). In particular, ¹H NMR studies at variable temperatures resulted in

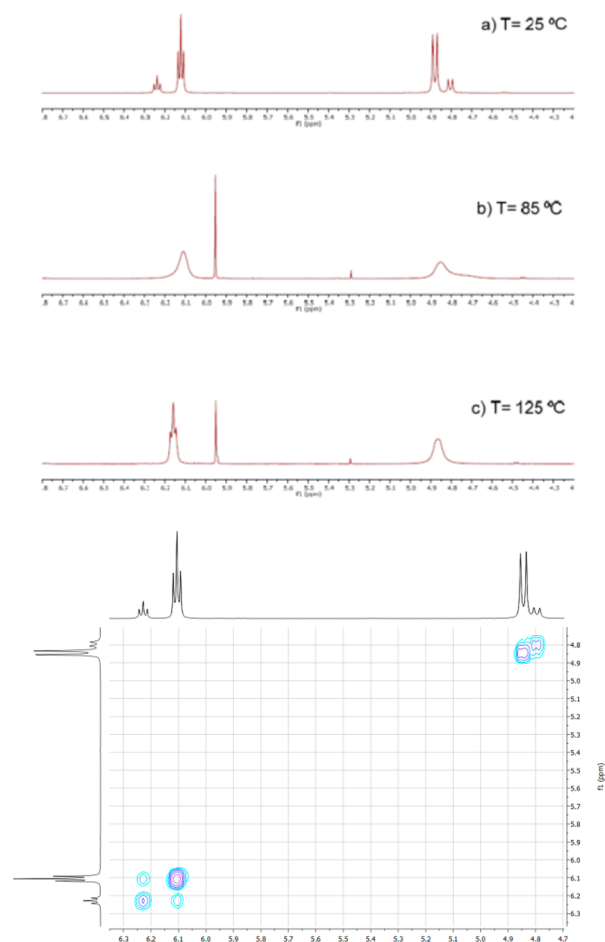


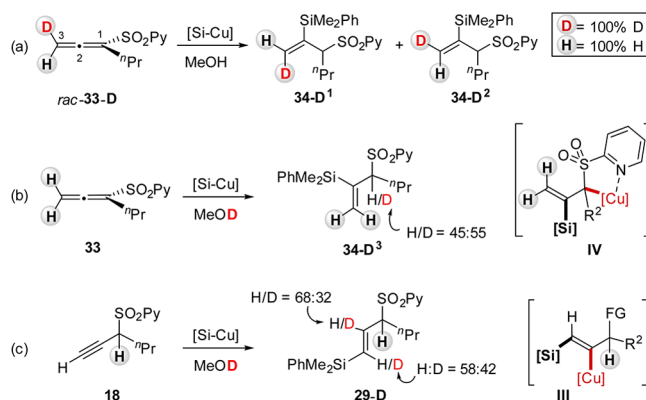
Figure 1. Olefinic and allylic peaks attributed to rotamers in compound **42**. (i) Coalescence at higher temperature. (ii) Exchange cross peaks observed in a 2D NOESY experiment.

coalescence of those peaks attributed to equivalent protons at temperatures above 85 °C. Additionally, cooling back to 25 °C resulted in recovery of exactly the same ratio of rotamers, while no signs of decomposition were observable in the spectrum. Furthermore, the existence of an equilibrium between the two rotamers in **42** was supported by the observation of strong exchange cross peaks (EXSY) between equivalent protons of each rotameric pair in a 2D NOESY experiment (signals derived from NOE or from chemical exchange will appear in different phases).²⁸

Mechanistic Insights: Isotope Tracer Experiments.

Support for the participation of the catalytic intermediate species **IV** and **III** in the α -silylation via allene and β -silylation via alkyne, respectively (see Scheme 2), was obtained from deuterium labeling experiments shown in Scheme 4. First, a 1:1 mixture of deuterated diastereoisomers across the terminal double bond (**34-D**¹ + **34-D**²) was obtained after 20 min when the deuterated allene *rac*-**33-D** was submitted to the standard reaction conditions (Scheme 4a), adding additional weight to our previous observations depicted in eq 2. The formation of both diastereomers in equal amounts is consistent with a silylcupration process at C₁ and C₂ of the proposed allene intermediate. Assuming the accepted mechanism of coordination/*syn*-addition of the Si–Cu complex to the unsaturated substrate, the formation of the diastereomer **34-D**² would be largely unexpected if an equilibration of *rac*-**33-D** to the

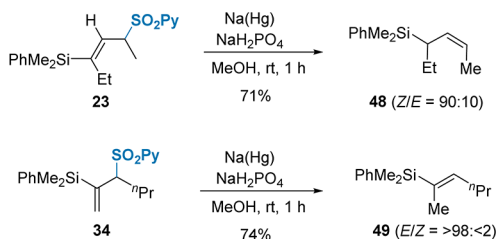
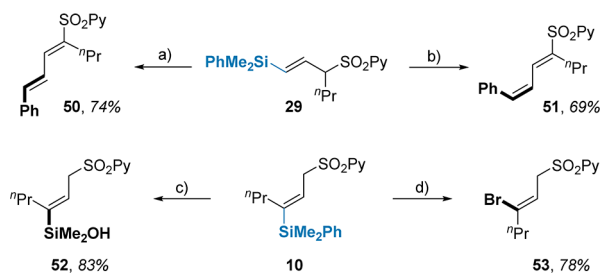
Scheme 4. D-Labeling Studies on the Reaction Mechanism



corresponding alkyne followed by silylcupration on the latter intermediate had taken place. In addition, hydrosilylation of substrate **33** in the presence of MeOD resulted in significant levels of deuterium incorporation at the allylic position, whereas no deuterium scrambling was detected at the vinylic positions (product **34-D**³): this observation is consistent with the participation of the proposed pyridinium-stabilized Cu intermediate **IV** (Scheme 4b).²² Conversely, the hydrosilylation of alkyne **18** in the presence of MeOD allowed the deuterium interception of the presumed intermediate **III**, furnishing the β -silylated product **29-D** with significant incorporation of deuterium at the α -vinylic position. Notably, hydrogen was completely retained at the methine adjacent to the sulfonyl group, which strongly supports the participation of the proposed intermediate **III**. The partial H/D exchange observed at the terminal vinylic position is ascribable to partial deprotonation of the acidic acetylenic position under the basic reaction conditions prior to silylcupration of the alkyne, which also might justify the incomplete deuteration at C₂. In agreement with this proposal, when propargyl sulfone **18** was subjected to the standard reaction conditions (*t*BuOCu-PCy₃) in the absence of the Si–B reagent and in the presence of MeOD, 17% deuterium incorporation at the acetylenic position was observed. Importantly, except for the latter case, no deuterium scrambling was observed in those positions not directly involved in the metalation step for each proposed mechanism (vinylic positions in the reaction from allene **33** and allylic position in the reaction from alkyne **18**, Scheme 4), which strongly supports the notion that both regiochemistry patterns originate from different reaction intermediates.

Further Elaboration of Vinyl Silanes: Selective Transformations on Vinyl Silanes/Allylic Sulfones. In hopes of illustrating further the utility of the method described above, we looked into representative transformations of vinyl silanes and allylic sulfones which would selectively remove either one of these functional groups. First, the sulfonyl group in the silylation products could be smoothly removed without interference by the silicon moiety by standard treatment with Na(Hg) with concomitant migration of the olefin to give rise to synthetically useful stereochemically enriched (or pure) allyl and vinyl silanes (Scheme 5, products **48** and **49**, respectively).

In our exploratory studies of the selective reactivity of the silicon group, we observed that treatment of vinyl silane **29** with a strong base (KHMDS), followed by addition of benzaldehyde, resulted in formation of sulfonyl diene **50** in 74% yield by formal Peterson olefination (Scheme 6). Interestingly, the stereochemistry of the process was easily

Scheme 5. Selective Removal of the SO₂Py GroupScheme 6. Transformations That Involve Removal of the Si(Me)₂Ph Group^a

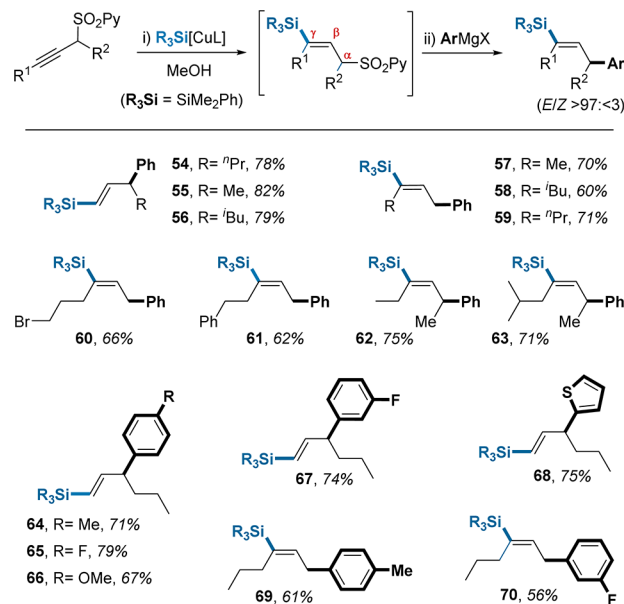
^aConditions: (a) KHMDS, DME, $-78\text{ }^{\circ}\text{C}$, 30 min; then, PhCHO. (b) LHMDS, 12-crown-4, DME, $-78\text{ }^{\circ}\text{C}$, 30 min; then, PhCHO. (c) TfOH, CH₂Cl₂, $0\text{ }^{\circ}\text{C}$, 1 h. (d) Br₂, CH₂Cl₂, rt. SO₂Py = 2-PySO₂.

inverted by switching to LiHMDS in the presence of the crown ether 12-crown-4 (product **51**, 69%). Other studies performed along these lines involved the transformation of the vinyl silanes obtained above in other practical functionalities. For example, vinyl silane **10** was smoothly converted in silanol **52** by treatment with TfOH in cold DCM.²⁹ The utility of silanols as partners in Hiyama couplings has been extensively studied by Denmark.³⁰ Also, treatment of **10** with bromine in DCM resulted in formation of vinyl bromide **53** in good yield and with complete stereocontrol (inversion of the *E/Z* stereochemistry).³¹

One-Pot Formal Access to Hydrosilylation Products of Unbiased Alkynes. In accordance with our desired goal of accessing formal hydrosilylation products of unsymmetrical aliphatic-substituted internal alkynes, we next focused on a potential Cu-catalyzed allylic substitution reaction with Grignard reagents, similar to the one reported by us for vinyl boronates.¹⁷ In this case, however, we pondered the feasibility of a condensed tandem one-pot silylation/allylic alkylation sequence starting directly from the alkyne instead of using the preformed vinyl-metal species, as it would significantly improve the synthetic value of this process while simplifying the reaction setup. The main challenge to be solved is that both steps need to be compatible under the same Cu-catalyst system. If such requirement is met, simple addition of a Grignard reagent to the reaction vessel on completion of the silylation step would in principle enable tandem silylation–arylation.

Ensuring high conversion in the overall process required, however, careful adjustments of the excess of MeOH used in the silylation step and the amount of Grignard reagent needed for the allylic substitution. We were glad to find that, when 2.0 equiv of MeOH and 2.0 equiv of RMgX were used, the tandem β -silylation/allylic substitution was productive for the model reaction of alkyne **18** using PhMgBr as Grignard reagent to give cleanly the S_N2'-type product **54**, resulting from α -addition to the unsymmetrical allyl sulfone intermediate, with complete

levels of regiocontrol (>98% α -selectivity, Table 5). The observed regioselectivity can be attributed to the high steric

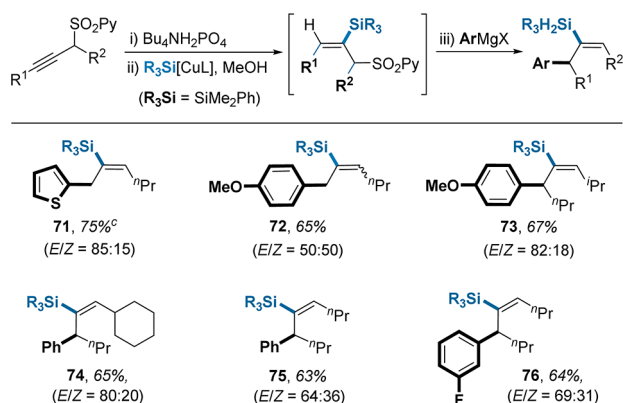
Table 5. One-Pot Regio- and Stereoselective Synthesis of Di- and Trisubstituted Vinyl Silanes^{a,b}

^aReaction conditions: Alkyne (1.0 equiv), PhMe₂SiBPIn (1.1 equiv), CuCl (10 mol %), PCy₃ (11 mol %), NaOtBu (12 mol %), MeOH (2 equiv), toluene, rt, 2 h; then, ArMgX (2 equiv), rt, 2–16 h. ^bIsolated yields after flash chromatography. SO₂Py = 2-PySO₂.

demand at the γ -allylic position imposed by the R₃Si group (attack favored at the less sterically congested allylic terminus).

By following the one-pot protocol, the scope of this reaction was next explored (Table 5). Other terminal alkynes with linear or branched substituents at the propargylic position (R²) proved to be equally effective (**55** and **56**, 82% and 79%, respectively). To our delight, this tandem reaction is not limited to terminal alkynes. Internal alkynes, with or without branched propargylic substitution, were also found to be fully compatible, affording the corresponding products in good yields while preserving the complete α -regiocontrol in the allylic substitution step (**57**–**63**, 60–75%). A sensitive alkyl bromide substitution was tolerated under the present conditions (**60**, 66%). A variety of aryl Grignard reagents of different steric and electronic properties (**64**–**70**, 56–79%), including heteroaromatics (**68**, 75%), are applicable. The current tandem one-pot reaction produced structurally elaborated vinyl silanes in good yields. In all examples described in Table 5 (17 cases studied), a single regioisomer (>98% β -site selectivity in the silylation reaction and >98% α -site selectivity in the allylic substitution) and diastereoisomer (>98% *E*-stereoselectivity) of the product is formed (products **54**–**70**, 56–82% yield).

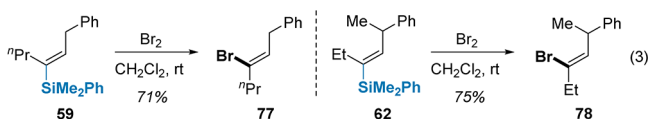
This one-pot silylation/allylic substitution sequence is also compatible with the base-promoted α -silylation via allene, even though the presence of stoichiometric amounts of NBu₄H₂PO₄ makes this process more challenging. Interestingly, in this case the regiochemical outcome of the allylic substitution step was reversed, providing exclusively the S_N2'-type product, as a result of the attack of the Grignard reagent to the γ -terminus of the allyl sulfone intermediate (>98% γ -selectivity Table 6). The lack of a sterically hindered silyl group at the γ -allylic position

Table 6. Extension to the One-Pot Regio- and Stereoselective α -Silylation/Allylic Substitution^{a,b}

^aReaction conditions: Alkyne (1.0 equiv), $\text{NBu}_4\text{H}_2\text{PO}_4$ (1.0 equiv), toluene, rt for internal alkynes or 50 °C for terminal alkynes, 1 h; then, $\text{PhMe}_2\text{SiBPin}$ (1.0–1.5 equiv), CuCl (10 mol %), PCy_3 (11 mol %), NaOtBu (12 mol %), MeOH (2 equiv), rt or 50 °C; then, ArMgX (2 equiv), rt, 2–16 h. ^bYields after flash chromatography. ^cAllylic substitution step performed at –78 °C. $\text{SO}_2\text{Py} = 2\text{-PySO}_2$.

could be the reason behind this $\text{S}_{\text{N}}2'$ -type selectivity, which on the other hand is typically observed in Cu-catalyzed allylic substitutions.³² A variety of trisubstituted vinyl silanes with different substitution pattern were obtained regioisomerically pure with acceptable yields in this protocol (products 71–76, 63–75% yields). The compatibility with heteroarenes at the substrate was remarkable (product 71, 75%). Unfortunately, however, the hydrosilylation products were obtained with consistently lower stereoselectivity, the E/Z ratio ranging from 1:1 to 5.7:1. Except for one case (product 71), no significant improvement of stereocontrol could be obtained by lowering the temperature (down to –78 °C). The different levels of stereoselectivity observed for both processes can be attributed to the divergence in the reaction mechanism (formal $\text{S}_{\text{N}}2$ versus $\text{S}_{\text{N}}2'$).

Finally, the facile silicon–bromine exchange process described for compound 52³⁰ was successfully applied to the synthesis of nonfunctionalized, trisubstituted, vinyl bromides 77 and 78 in good yields and with complete stereocontrol (eq 3).



At this point it is important to note that, in spite of the significance of alkenyl halides as versatile coupling partners in transition metal catalyzed cross-coupling reactions and as precursors to a wide range of organometallic reagents, the synthesis of alkenyl halides, especially those involving trisubstituted alkenes in a stereodefined manner, is challenging.

CONCLUSIONS

In summary, we report on a general and practical method for the regio- and stereocontrolled synthesis of di- and trisubstituted vinyl silanes by Cu-catalyzed hydrosilylation of both internal and terminal alkynes. The use of a SO_2Py group at the propargylic position is essential in three ways: first, it controls the reactivity of the system, preventing alternative reaction pathways such as nucleophilic displacement of the

directing group; second, it enables an alkyne/allene rearrangement that results in efficient control of the regioselectivity of the hydrosilylation process; third, its formal elimination promotes a series of useful transformations, even in a one-pot fashion. In particular, we have shown, for the first time, a tandem silylation/allylic arylation of propargyl sulfones, using the same Cu-catalyst to access in a single operation novel vinyl silanes that cannot be accessed directly from dialkyl alkynes. The overall transformation can be accomplished in the presence of a wide range of functional groups. The wide scope highlights the validity of the method to construct, in a one-pot operation, a variety of trisubstituted vinyl silanes having various substitution patterns from simple propargyl sulfones. This work thus contributes to the emerging use of alkynes as allene surrogates in transition metal catalyzed reactions as a strategy for selectivity control.

EXPERIMENTAL SECTION

General Methods. Dichloromethane, toluene, acetonitrile, and tetrahydrofuran were taken from a PureSolv MD purification system. Sodium amalgam [$\text{Na}(\text{Hg})$] 6% was prepared following a reported procedure.³³ Metal precatalysts, Grignard reagents, *m*CPBA ($\leq 77\%$ purity), tricyclohexylphosphine (20% in toluene, min 88% purity) and NaOtBu (2 M in THF) were purchased from commercial sources and used without further purification. All reactions were carried out under inert atmosphere, unless otherwise noted.

Typical Procedure for the β -Silylation of Propargylic Sulfones. CuCl (2.0 mg, 0.020 mmol, 10 mol %) was placed in a Schlenk tube. The tube was purged and backfilled with argon. Then were added dry toluene (0.7 mL), PCy_3 (20% in toluene) (50 μL , 0.022 mmol, 11 mol %), and NaOtBu (2 M in THF) (12 μL , 0.024 mmol, 12 mol %), and the solution was stirred at 22 °C for 5 min. Silylborane reagent (60 μL , 0.22 mmol, 1.1 equiv) was added to the solution, causing it to turn dark brown immediately. The mixture was stirred at 22 °C for 5 min under an argon atmosphere. The corresponding propargylic sulfone (0.2 mmol, 1.0 equiv), dissolved in toluene (0.5 mL), and MeOH (17 μL , 0.4 mmol, 2 equiv) were sequentially added through syringes. The resulting mixture was stirred at 22 °C until no starting material was detected (TLC monitoring, 2–16 h). Then, the reaction was quenched by passing the mixture through a short plug of Celite and silica gel, and then eluted with DCM (3 \times 4 mL). The filtrate was concentrated *in vacuo* and purified by silica gel chromatography.

Typical Procedure for the α -Silylation of Propargylic Sulfones. The corresponding propargylic sulfone (0.2 mmol, 1.0 equiv) and $(\text{NBu}_4)\text{H}_2\text{PO}_4$ (67.8 mg, 0.2 mmol, 1.0 equiv) were placed in a Schlenk tube. The Schlenk tube was purged and backfilled with argon, and dry toluene (1.0 mL) was added. The mixture was stirred at 50 °C for 1 h. In a separate Schlenk tube, CuCl (2.0 mg, 0.020 mmol, 10 mol %) was placed. The Schlenk tube was purged and backfilled with argon. Then, dry toluene (0.7 mL), PCy_3 (20% in toluene) (50 μL , 0.022 mmol, 11 mol %), and NaOtBu (2 M in THF) (12 μL , 0.024 mmol, 12 mol %) were sequentially added, and the solution was stirred at 22 °C for 5 min. Silylborane reagent (90 μL , 0.3 mmol, 1.5 equiv) was added to the solution, causing it to turn dark brown immediately. The mixture was stirred at 22 °C for 5 min under an atmosphere of argon. This solution and MeOH (17 μL , 0.4 mmol, 2 equiv) were sequentially added through syringes to the first Schlenk tube. The resulting mixture was stirred at 50 °C (for internal alkynes) or 22 °C (for terminal alkynes) until no starting material was detected (TLC monitoring, 30 min to 16 h). Then, the reaction was quenched by passing the mixture through a short plug of Celite and silica gel, and then eluted with DCM (3 \times 4 mL). The filtrate was concentrated *in vacuo* and purified by silica gel chromatography.

■ ASSOCIATED CONTENT

■ Supporting Information

Experimental details as well as spectroscopic and analytical data for new compounds. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b02667.

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Notes

The authors declare no competing financial interest.

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(25) See Supporting Information for experimental details.

(26) After completion of our study, Loh and Xu reported that preformed allenes with electron-withdrawing groups directly attached to the allene moiety undergo silylation at the internal position (ref 12c).

(27) A prestirring time of 1 h in the presence of 1 equiv of base (NBu₄H₂PO₄) before addition of the silylating reagent was found to be necessary for achieving complete α -regiocontrol. Nevertheless, even in the absence of pretreatment with base, a good, albeit not complete, α -silylation regioselectivity was observed in agreement with the higher reactivity of the allenyl sulfone over the propargyl sulfone. For example, the α -silylation reaction of the internal propargyl sulfone **16** in the presence of base but with no prestirring time (i.e., adding the silylborane reagent at time zero) produced product **39** with a regioselectivity ratio of $\alpha/\beta = 90:10$.

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