Glycidyl Silanes Enable Regioselective Hydrosilylation of Internal Propargyl Alcohols and Direct Transformation into Activated Silanes for Further Chemical Transformation

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ABSTRACT: Herein, we develop glycidyl silanes to facilitate highly regioselective hydrosilylation of internal propargyl alcohols, the products of which can in turn be converted to synthetically useful fluorosilanes for further chemical transformations under mild conditions. Structure–selectivity studies and density functional theory calculations are consistent with high regioselectivity arising from a critical intermolecular hydrogen bond between the glycidyl and propargylic hydroxy groups. A broad substrate scope illustrates the generality of this reaction to form *β-E* silylalkenes. Treatment of the *β-E* silylalkenes with a fluoride salt induces simultaneous removal of the glycidyl group and activation of the silane under mild conditions. The fluorosilane products can be converted into vinyl arene and ketone derivatives via Hiyama coupling and Tamao–Fleming oxidation reactions, respectively. The discovery that glycidyl silane improves hydrosilylation regioselectivity and is compatible with expedient silylalkene derivatization may prove applicable to a variety of similar alkyne hydrofunctionalization reactions.

Alkyne functionalization is integral in both organic chemistry and chemical biology because of the ready availability of alkynes and utility of the products.[1] The sequence of alkyne hydrosilylation and silyl group conversion via the Hiyama coupling and Tamao–Fleming oxidation reactions[2] provides functionalized alkenes and carbonyl compounds, respectively, which are useful building blocks for the synthesis of valuable pharmaceutical, agrochemical, and material products. Transition-metal-catalyzed hydrosilylation of alkynes is a direct and atom economical synthetic method to obtain vinylsilanes,[3] but is challenging to achieve due to the need to control stereo- (*E* or *Z*) and regio- (*α* or *β*) selectivity (Figure 1A).[4] Generally, stereoselectivity is controlled by the identity of the metal catalyst,[5] while control of regioselectivity depends on the type of substituent on the alkyne.[3a,4c] Although excellent regiocontrol has been reported for the intermolecular hydrosilylation of terminal alkynes,[6] unsymmetrical internal alkynes are more challenging due to small differences between the electronic and/or steric properties about the two alkyne carbon atoms.[4d, 6e] Regiocontrol in hydrosilylation of internal propargyl alcohols, which provides valuable allyl alcohol derivatives,[7–9] is especially problematic. Although *α-Z*,[7] *α-E*,[8] and *β-Z*[9] regioselective hydrosilylation of internal propargyl alcohols has been achieved through excellent catalyst- and directing group-controlled strategies, high regiocontrol in the synthesis of *β-E* products has not been reported, to the best of our knowledge (Figure 1B).[10]

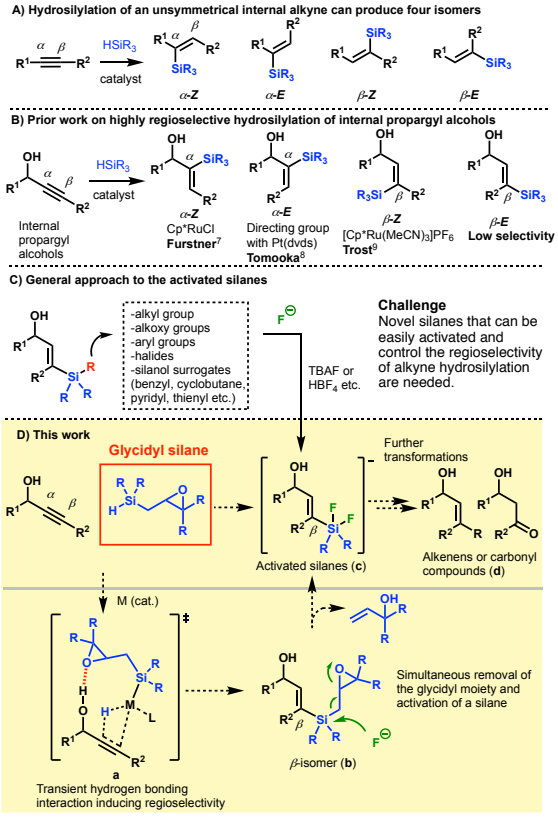

Figure 1. Hydrosilylation of unsymmetrical internal alkynes.

In addition, we sought to expediently convert vinylsilane products to pentacoordinate fluorosilicate intermediates for further chemical derivatization. Expedient vinylsilane conversion depends on the identity of functional groups bound to a silane (Figure 1C).[11] Although a variety of silane-bound functional groups such as alkyl, alkoxy, aryl groups, and silanol surrogates etc., have been reported,[12] none can enable conversion to an activated silane as well as regioselective alkyne hydrosilylation.

To address both of these problems (regiocontrol and efficient activation of vinylsilane intermediates), we envisioned a strategy based on the use of a novel silane with a removable alcohol recognition motif (Figure 1D) whereby an intermolecular hydrogen bond organizes substrate, catalyst, and silane (**a**) orientation.[13] The choice of a glycidyl group as an alcohol recognition motif facilitates its simultaneous removal from silane (**b**) and activation of the silane (**c**) for subsequent transformations (**d**) because the Si–C bond cleavage is facilitated by formation of an allyl alcohol leaving group.[14] Fluoride ions are appropriate for unmasking since they can activate a silane for subsequent chemical transformations and induce the Si–C bond cleavage by a formation of a thermodynamically more stable Si–F bond.

We herein report this novel tactic for chemical transformation of internal propargylic alcohols to synthetically useful building blocks using unprecedented glycidyl silanes. The highly regioselective hydrosilylation of internal propargyl alcohols using glycidyldiphenyl silanes was achieved in the presence of a Pt(0) catalyst. Moreover, the resulting *β-E* silylalkenes were then subjected to simultaneous removal of the glycidyl group and the activation of the silanes as pentacoordinate fluorosilicate intermediates for further transformation under mild conditions. We also elucidate the necessary structural requirements for the silane substrate to ensure the high regioselectivity, broad substrate scope, and synthetic value of the resulting *β-E* silylalkenes and demonstrate application of this method to the total synthesis of nigerapyrone C.

After multiple attempts at the hydrosilylation reaction (Figure 2 and Table S1), we found that the combination of ((3,3-dimethyloxiran-2-yl)methyl)diphenylsilane (**1a**), which was easily prepared via a 2-step synthesis from commercially available materials, i.e. chlorodiphenylsilane and prenylmagnesium bromide[15], and internal propargylic alcohol **2** in the presence of Pt(dvds)[16] (aka Karstedt's catalyst) significantly enhanced the reaction regioselectivity (β/α > 20:1).[17,18] In sharp contrast to the reaction of **1a**, silanes **1c** and **1d**, which bear linkers of different lengths, gave diminished or no regiocontrol. Additionally, derivatives **1f**, **1g**, and **1h**, which lack the epoxide moiety, also afforded *E*-silylalkenes as a mixture of regioisomers. These results clearly indicate that epoxide-bearing silanes with appropriate carbon chains are necessary to control the regioselectivity in the hydrosilylation of internal propargyl alcohols, but that the size of the silyl group does not significantly affect the regioselectivity. The use of a diisopropyl-substituted silane **1e** (i.e. Ph replaced with *i*Pr) provided no desired product. In contrast, derivative **1b** lacking the *gem*-dimethyl group adjacent to the epoxide moiety of **1a** afforded a better yield with a high regioselectivity, indicating that the *gem*-dimethyl group is not required. Reducing the temperature from room temperature to 0 °C increased the yield (77%) while maintaining high regioselectivity. However, decreasing the temperature to −10 °C did not result in a further increase in yield.

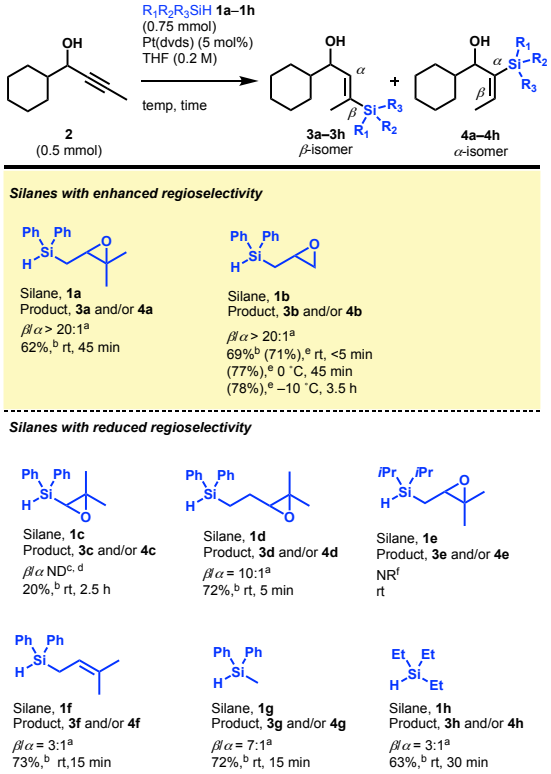

Figure 2. Screening for silanes. [a]Determined by ^{1}H NMR spectroscopy of the crude products. [b]Isolated yield. [c]Not determined. [d]Starting material remained. [e]Determined by ^{1}H NMR spectroscopy using dimethyl terephthalate as an internal standard. [f]No reaction.

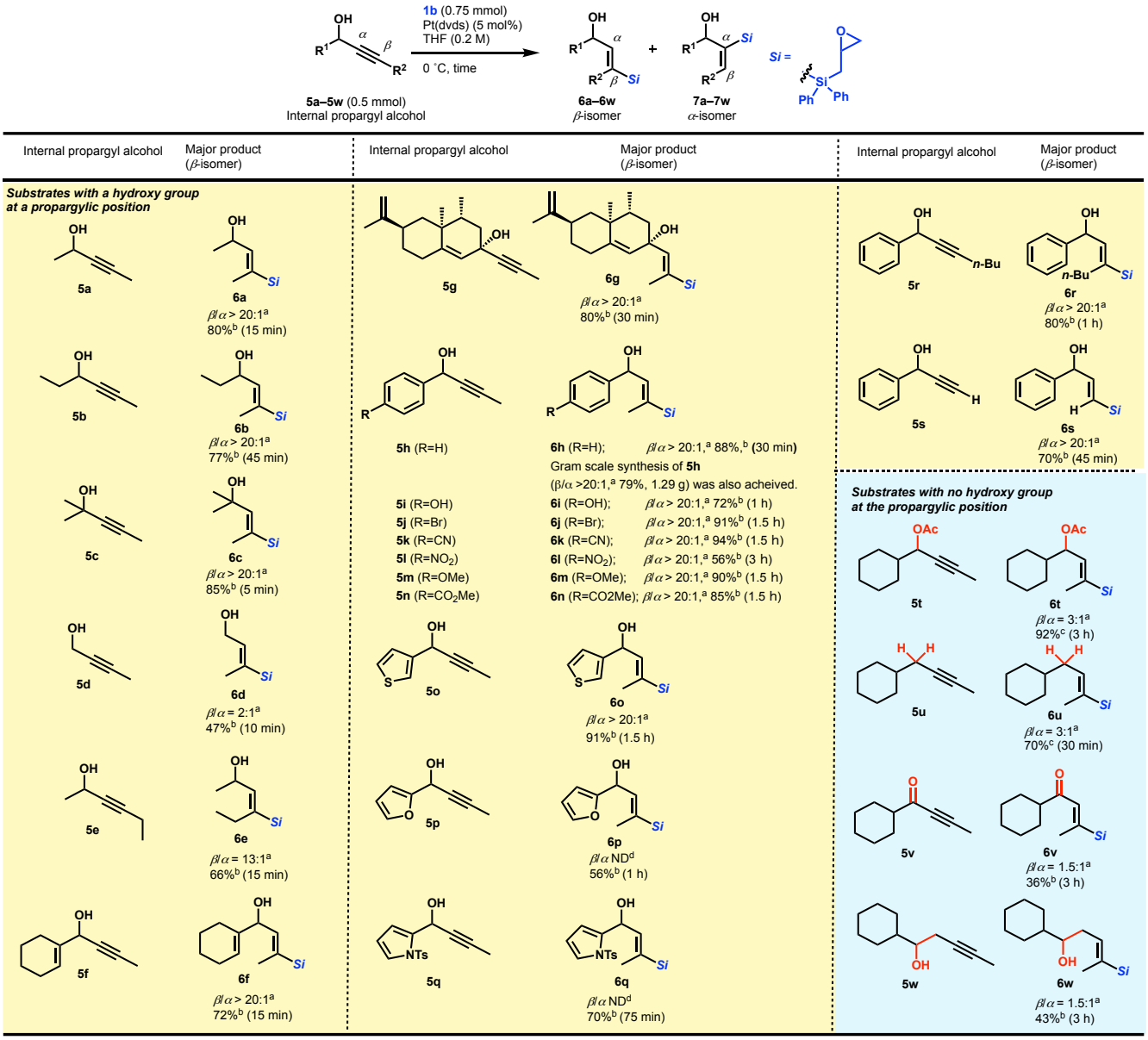

Figure 3. Substrate scope of the alkynes. [a]Determined by ^{1}H NMR spectroscopy of the crude products. [b]Isolated yield of the β-isomer. [c]Isolated yield of a mixture of the α- and β-isomers. [d]The ratio was not determined by ^{1}H NMR spectroscopy of the crude products. However, the corresponding α-isomer was not isolated in this case.

With the optimized reaction conditions in hand, a variety of unsymmetrical internal alkynes were established as effective substates (Figure 3). Pent-3-yn-2-ol **5a**, which lacks the cyclohexyl moiety of **2**, exhibited high β-selectivity (β/α > 20:1) and a high yield (**6a**, 80%), suggesting that steric hindrance around the alkyne is not crucial to achieve high regioselectivity. Noteworthy, **5a** is a challenging substrate with small differences between the electronic and/or steric properties about the two alkyne carbon atoms. There are no examples of β-selective hydrosilylation of **5a** in the literature, which highlights the value of the present method.[19] Similarly, hex-4-yn-3-ol (**5b**) and 2-methylpent-3-yn-2-ol (**5c**) also afforded high regioselectivities (β/α > 20:1).[20] Decreased selectivity (β/α = 2:1, **6d**) was observed for 2-butyn-1-ol (**5d**), but alkyne **5e**, which was homologated at each of the propargylic positions of **5d**, exhibited high regioselectivity (β/α = 13:1, **6e**). Substrate **5f**, which possesses an olefin at the β-position of the hydroxy group – a potentially reactive site – did not afford the alkene hydrosilylation product but rather the alkyne hydrosilylation product with high regioselectivity (β/α > 20:1, **6f**). Moreover, high regioselectivity was observed for **5g**, obtained by derivatization of the natural product nootkatone. To our delight, various aromatic substrates containing hydrogen (**5h**), hydroxy (**5i**), bromo (**5j**), cyano (**5k**), nitro (**5l**), methoxy (**5m**), and methoxycarbonyl (**5n**) groups were converted to the corresponding β-silylalkenes (**6h**–**6n**) in high yields with excellent regiocontrol, thereby suggesting that this system tolerates a wide range of functional groups without loss of regioselectivity. Substrates containing heteroaromatic rings, such as thiophene (**5o**), furan (**5p**), and pyrrole (**5q**), were also converted to the corresponding β-silylalkenes (**6o**–**6q**).

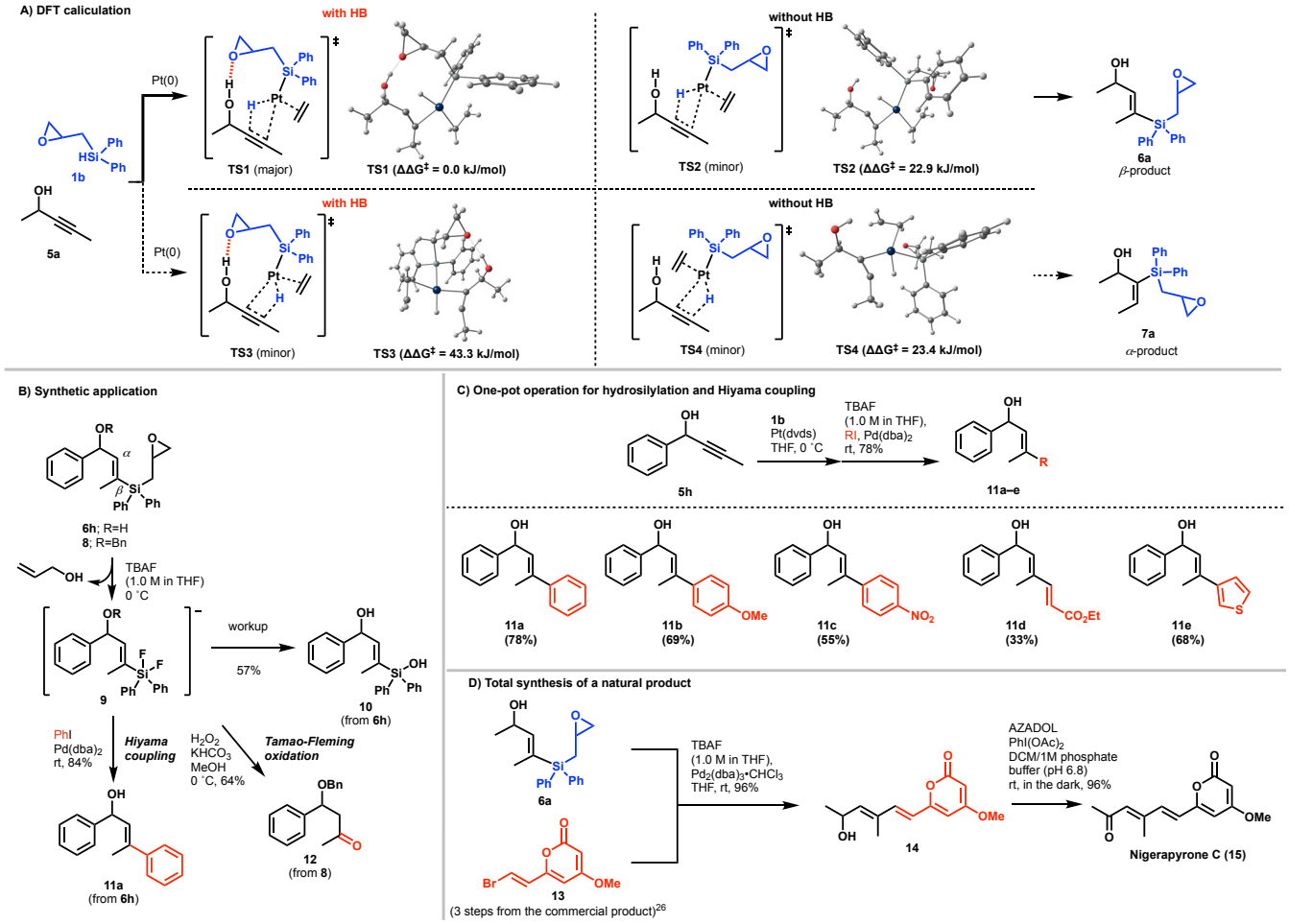

Figure 4. Mechanistic study and synthetic applications of our protocol: A) DFT calculation. B) Hiyama coupling and Tamao–Fleming oxidation of *β*-silylalkenes. C) The one-pot operation. D) Total synthesis of a natural product, nigerapyrone C.

Notably, even the reaction of **5r**, which possesses a bulkier alkyl chain on the alkyne β-position, proceeded with excellent *β-E* selectivity. The terminal alkyne **5s** afforded the corresponding *β*-silylalkene **6s** with high regiocontrol. A gram-scale synthesis of **6h** was achieved without any loss in regioselectivity or yield (1.29 g of **6h** was obtained). The effect of the propargylic hydroxy group on the regioselectivity of the hydrosilylation was then investigated. Thus, the hydrosilylation of acetylated derivative **5t**, derivative **5u** lacking the hydroxy group, oxidized derivative **5v**, and derivative **5w** possessing a hydroxy group at the homopropargylic position, showed significantly reduced regiocontrol (*β*/*α* = 1.5:1 to 3:1, **6t**–**6w**), indicating that the propargylic hydroxy group strongly contributes to the observed *β*-selectivity.

To gain insight into the high regioselectivity of this hydrosilylation process, density functional theory (DFT) calculations were conducted (Figure 4A). Generally, Pt(0)-catalyzed hydrosilylation reactions proceed via the Chalk–Harrod mechanism, in which hydroplatination of the alkyne determines regioselectivity.[8,21,22] To clarify the effect of an intermolecular hydrogen bond (HB) between the epoxy group and the hydroxy group, the transition states of the hydroplatination step were calculated for a β-product with an HB (**TS1**), a β-product without an HB (**TS2**), an α-product with an HB (**TS3**), and an *α*-product without an HB (**TS4**) using silane **1b** and propargylic alcohol **5a** as model substrates.[23] An ethylene ligand was used instead of the dvds ligand for simplification. Consistent with the observed results, the free energy of **TS1** producing a *β*-silylalkene with an HB between the epoxy group and the hydroxy group was much lower than those of the other transition states, indicating that the HB between the epoxy group and the hydroxy group is crucial for determining the regioselectivity. Interestingly, **TS2**, which produced a *β*-silylalkene without an HB, gave almost the same free energy value as **TS4**, which produced an α-silylalkene without an HB, which validates the important of the hydrogen bond in determining regioselectivity.

We then moved on to investigate the synthetic application of the resulting *β-E* silylalkenes (Figure 4B). Treatment of **6h** with TBAF afforded silanol **10** in 59% yield, which indicates that the oxiran-2-ylmethyl group was rapidly removed as an allyl alcohol to generate pentacoordinate fluorosiliconate **9** *in situ*, as expected. In addition, **6h** and **8** were successfully subjected to the Hiyama coupling (PhI, $Pd(dba)_2$) and Tamao–Fleming oxidation (H_2O_2, $KHCO_3$, MeOH) reactions to afford styrene derivative **11** and ketone **12** in 89 and 67% yields, respectively, after treatment with TBAF. These results demonstrate that the

epoxy moiety on the silane not only controls the high β-regioselectivity of the hydrosilylation reaction but also plays a pivotal role as a convenient leaving group removed by a fluoride ion to afford an activated silane for the Hiyama coupling and Tamao–Fleming oxidation reactions. Subsequently, we performed a one-pot transformation involving hydrosilylation, removal of the glycidyl moiety, and a Hiyama coupling reaction, which achieved the formal hydrocarbation[24] of an alkyne in a regioselective manner (Figure 4C). This one-pot reaction smoothly proceeded to afford **11a–e** from **5h** in moderate to excellent yields without the production of the α-isomer, which demonstrates the great potential of this sequence in the efficient transformation of alkynes to yield a range of functionalities. The applicability of this method was further demonstrated through the first total synthesis of a natural product, nigerapyrone C (Figure 4D).[25] Pleasingly, vinylsilane **6a** underwent cross-coupling with bromoalkene **13**[26] with retention of the alkene stereochemistry in excellent yield (**14**; 96%). Finally, oxidation of the allylic alcohol **14** with AZADOL led to nigerapyrone C in 96% yield. This convergent synthetic route linking the aliphatic chain to the aromatic ring will provide rapid access to various natural product analogs.

In summary, we have achieved the regioselective hydrosilylation of internal propargyl alcohols and direct transformation of the resulting vinylsilanes to the activated silanes using an unprecedented silane. The glycidyl group of the silane induced a high regioselectivity in the hydrosilylation of internal propargyl alcohols via hydrogen bonding with the hydroxy group at the propargylic position. The resulting β-*E* silylalkenes were then subjected to simultaneous removal of the glycidyl group and the activation of the silanes as a pentacoordinate fluorosiliconate intermediate for further transformation under mild conditions (i.e., TBAF at 0 °C). These simultaneous reactions significantly increase the overall synthetic efficiency of our process compared to the previously reported method based on directing groups that are covalently introduced into alkyne substrates.[8] DFT calculations support a unique transition state with an intermolecular hydrogen bond between the epoxide group and the hydroxy group, which allows us to understand the regioselectivity of the process. The new concepts disclosed herein provide innovative insight in the context of molecular design not only for hydrosilylation processes, but also for other transition metal-catalyzed transformations. Currently, other applications besides hydrosilylation reactions of this methodology are under investigation in our laboratory, and the results will be presented in due course.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures, characterization data, and calculated data (PDF)

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The manuscript was written through contributions of all authors. / All authors have given approval to the final version of the manuscript. /

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Notes

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Table of Contents