Alkyne Halosilylation

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Stereoselective Synthesis of Tetrasubstituted Olefins through a Halogen-Induced 1,2-Silyl Migration**

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All-carbon tetrasubstituted alkenes[1] have been demonstrated to have unique structural, physical, and electronic features.[2] Moreover, the geometry of these olefins often provides the foundation for establishing vicinal stereogenicity in sp^3-hybridized carbon centers through face-selective addition reactions (for example, hydrogenations, cycloadditions, dihydroxylations, among others).[3] The generation of stereodefined tetrasubstituted alkenes presents a particular challenge in synthetic chemistry. When endocyclic, alkene stereochemistry can be rather straightforward to control using several methods for geometrically defined olefin synthesis (for example, Wittig-type reactions, eliminations, metathesis).[4] In contrast, acyclic polysubstituted alkenes do not have that additional element of control, and these olefination methods are frequently problematic when extended to tetrasubstituted systems. Consequently, the syntheses of these alkenes with high geometrical control is a daunting challenge.

Nevertheless, there have been some remarkable achievements toward the syntheses of tetrasubstituted alkenes. Arguably, the most commonly employed method for accessing this structural motif is the carbometalation of alkynes.[5] Within these systems, there are still matters to address, such as addition regiocontrol, substrate tolerance, and metal selection. Given this frame of reference, new methods to access tetrasubstituted alkenes could prove highly useful. The activation of alkynes by non-Brønsted acid electrophiles toward functionalized alkenes, outlined by Koser, Gaunt, and others,[6] offers an alternative strategic approach. Herein, we report that halogen-based electrophiles can be used in conjunction with α-hydroxypropargylsilanes to generate tetrasubstituted vinylsilane products with excellent levels of stereoselectivity. We also demonstrate that elaboration of these vinylsilanes offers a general modular route to tetrasubstituted olefins.

We have recently described our efforts in stereoselective silicon-based additions to alkynes.[7] One such transformation is the platinum-catalyzed synthesis of (*Z*)-α-silylenones from α-hydroxypropargylsilanes (Figure 1).[7a] Mechanistically, we proposed that the Pt catalyst coordinates the alkyne, inducing

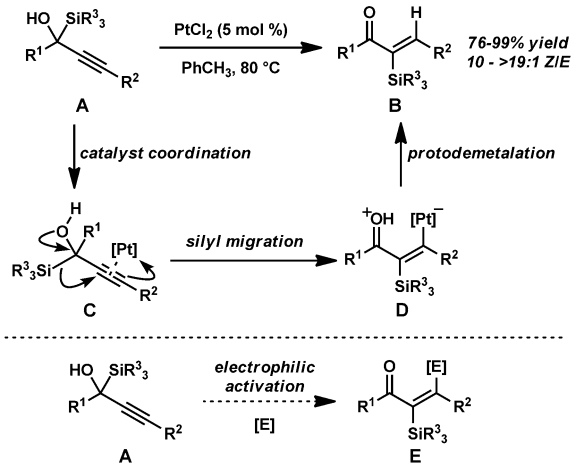

Figure 1. Pt-catalyzed *anti*-selective silicon migration to form (*Z*)-α-silylenones.

an *anti*-selective 1,2-silicon group migration to form intermediate **D**. Protodemetalation affords the stereodefined vinylsilane product.[8,9] We found this process attractive for the formation of stereodefined trisubstituted alkenes because the precursor α-hydroxypropargylsilanes were simple to access through acetylide addition to acylsilanes.[10] Furthermore, we were intrigued by the excellent *anti*-selectivity in this transformation, as the observation of related silicon migrations has been reported somewhat sporadically.[10c,11] From this fundamental migration process, we hypothesized that alternative electrophilic species may be used in alkyne activation to induce the 1,2-shift (**A**→**E**). Different electrophiles could offer the opportunity to provide β-substitution beyond hydrogen, incorporating an additional functional group for further elaboration.

To that end, we investigated the behavior of α-hydroxypropargylsilane **1** in the presence of a variety of electrophiles (Table 1). Using a standard set of conditions (CH_2Cl_2, 0 °C to 55 °C), several halogenating electrophiles were investigated. Chlorine- and fluorine-based species (*N*-chlorosuccinimide (NCS), trichloroisocyanuric acid (TCCA), Selectfluor) were generally unreactive. However, other *N*-halosuccinimides were remarkably effective at promoting the 1,2-silicon group shift. Both *N*-bromosuccinimide (NBS) and *N*-iodosuccinimide (NIS) accomplished the desired transformation, introducing a halogen atom at the β-position of the enone.[12,13] Importantly, the reaction proceeded with high stereoselectivity, forming the (*E*)-silylenone in greater than 19:1 geometrical purity. The transformation proceeded at room temperature with NBS, whereas the more reactive NIS

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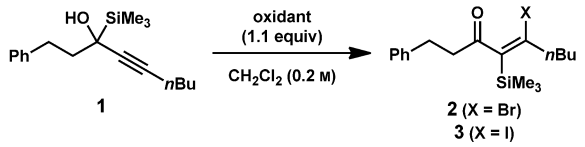
Table 1: Electron-withdrawing group analysis.



1

2 (X = Br)
3 (X = I)

Entry	Oxidant	*T* [°C]	Yield [%][a,b]	*E*:*Z*[c]
1	*m*CPBA[d]	50	NR	–
2	NCS	55	NR	–
3	TCCA[e]	50	NR	–
4	Selectfluor	23	NR	–
5	NBS	23	91	>19:1
6	NIS	23	90	15:1
7	NIS	0	90	>19:1

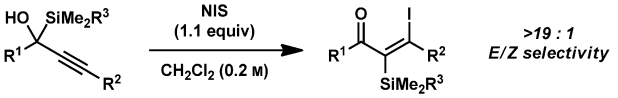
[a] Yield of the isolated product. [b] NR = no reaction. [c] Selectivity determined by ^{1}H NMR analysis of the crude reaction mixture. [d] *m*CPBA: *meta*-chloroperbenzoic acid. [e] TCCA: trichloroisocyanuric acid.

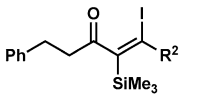
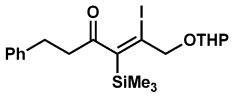
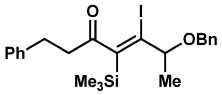
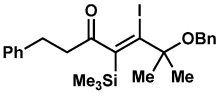
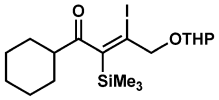
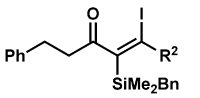
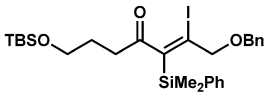
required lower temperatures to achieve a high degree of stereoselectivity.[14]

With a standard migration method in hand, we evaluated the scope of the iodination reaction (Table 2). Substrates with terminal, unbranched, or even branched propargylic substituents reacted smoothly, affording the (*E*)-silylenones with uniformly excellent geometrical selectivity (more than 19:1 in all cases).[15] The reaction was quite effective for several silicon species (Me_3Si-, $PhMe_2Si$-, and $BnMe_2Si$-). A particularly hindered alkyne substrate (entry 6) reacted to afford the desired enone, albeit requiring a longer reaction time and with diminished yield. Only in the case of the *tert*-butyl substituted alkyne did we not see the formation of the (*E*)-silylenone (entry 3).[16]

A similar evaluation of scope was conducted using NBS (Table 3). Without exception, the preparation of α-silyl-β-bromoenones occurred with high yields and excellent stereoselectivities. Even the notably hindered alkyne substrates were competent reactants (entries 3,6).[17] We consider this process a net *trans*-selective halosilylation, because the halogen atom and silicon group are added to the alkyne functional group in a *trans* fashion.

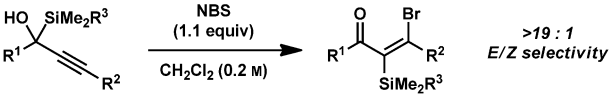
Table 2: NIS-induced 1,2-silicon migration.

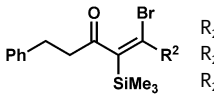
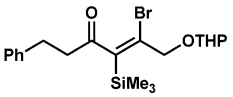
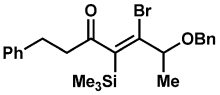
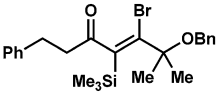
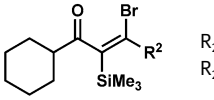
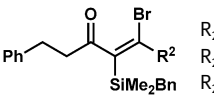


Entry	Product		*T* [°C]	*t*	Yield [%][a]
1		R_2 = H	−10	15 min	90
2		R_2 = *n*Bu	0	15 min	94
3		R_2 = *t*Bu	−10	3 h	0[b]
4			0	30 min	95
5			−15	30 min	93
6			−78→−10	6 h	63
7			0	20 min	92
8		R_2 = *n*Bu	0	15 min	94
9		R_2 = CH_2OTHP	0	15 min	92
10			−10	20 min	90

[a] Yield of the isolated product. [b] See Ref. [16].

Table 3: NBS-induced 1,2-silicon migration.

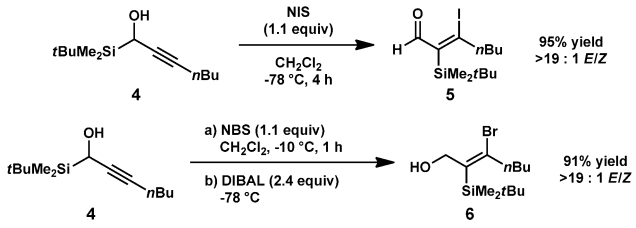


Entry	Product		*T* [°C]	*t*	Yield [%][a]
1		R_2 = H	−15	15 min	89[b]
2		R_2 = *n*Bu	0	15 min	91
3		R_2 = *t*Bu	−78→−10	2.5 h	75
4			0	15 min	92
5			−15	30 min	89
6			−78→−10	5 h	85
7		R_2 = CH_2OTHP	0	20 min	92
8		R_2 = Ph	−78→0	4 h	94
9		R_2 = *n*Bu	0	45 min	92
10		R_2 = CH_2OTHP	0	45 min	88
11		R_2 = Ph	−78→0	4 h	80

[a] Yield of the isolated product. [b] Yield of allylic alcohol after in situ reduction (DIBAL, −78 °C).

Not only were tertiary α-hydroxypropargylsilanes competent for the preparation of enones, but the corresponding secondary α-hydroxypropargylsilanes were also proficient reactants. Secondary α-hydroxypropargylsilane **4** was subjected to both NIS and NBS (Scheme 1). Each reaction proceeded effectively to afford only one isomer. Iodoenal **5** was isolated in excellent yield, whereas the related bromide was unstable and therefore subjected to in situ DIBAL reduction. The resulting allylic alcohol (**6**) was isolated in 91% yield with high *E*-selectivity.

With the *trans*-selective halosilylation of alkynes in hand, we hypothesized whether this transformation would provide



Scheme 1. Reactivity of secondary α-hydroxypropargylsilanes.

a method for the synthesis of all-carbon tetrasubstituted alkenes. We predicted that both the halogen atom and the silicon group would serve as convenient handles for cross couplings to form C–C bonds (Figure 2). Ultimately, this strategy would represent a straightforward and general

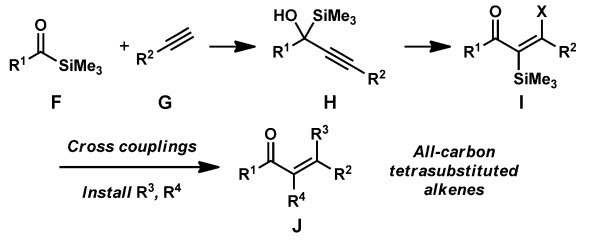
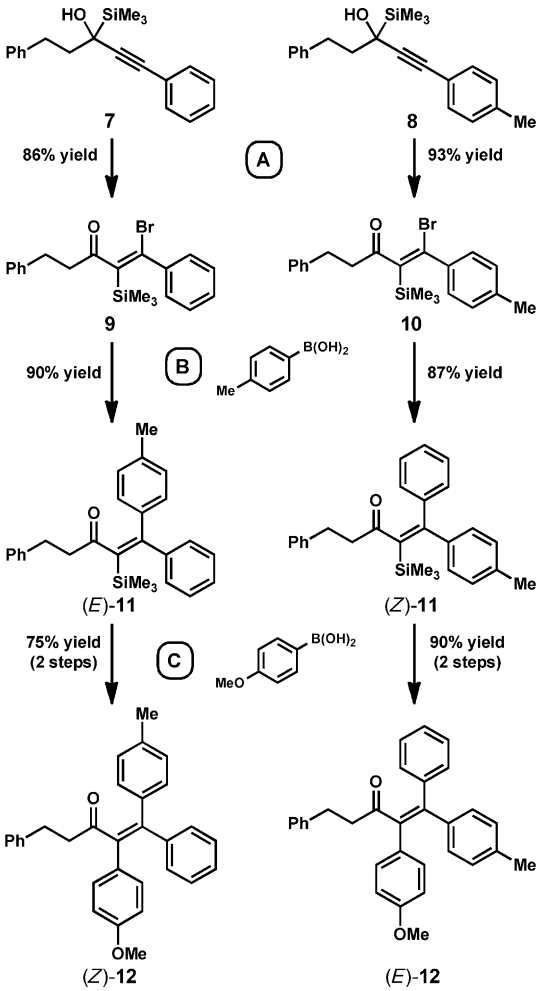


Figure 2. Modularity of the all-carbon tetrasubstituted alkene synthesis.

approach to synthesizing polysubstituted stereodefined olefins, wherein an acylsilane, terminal alkyne, and two coupling reagents can be introduced in a modular fashion. Furthermore, the stereochemistry generated in the silyl migration event should transfer directly to the final alkene products.

To demonstrate this approach, α-hydroxypropargylsilanes **7** and **8** were subjected to the reaction sequences shown in Scheme 2. For each silane, an NBS-mediated migration was followed by Suzuki–Miyaura cross coupling, stereoretentive iododesilylation,[18] and a second Suzuki–Miyaura cross coupling.[19,20] Using this migration as the key step for establishing geometrical control, complementary (*Z*)- and (*E*)-alkenes of **12** can be readily made in good yields and with very high maintenance of the stereochemistry throughout. Importantly, these types of complementary pairs of alkenes would otherwise be difficult to access selectively using standard olefination methods (Wittig-type reactions, among others).

In summary, we have described a *trans*-selective metal-free halosilylation of alkynes by way of a silicon group migration. A range of α-hydroxypropargylsilanes can be converted to the corresponding α-silyl-β-haloenones through treatment with an *N*-halosuccinimide under mild conditions. The transformations generally proceed in high yields and with remarkable *E*/*Z* selectivities. The enone products provide several functional groups for further synthetic manipulations, most aptly demonstrated by the direct conversion to geometrically defined all-carbon tetrasubstituted alkenes. This modular approach to tetrasubstituted olefins represents



Scheme 2. Selective formation of (*Z*)- and (*E*)-isomers of alkene **12.** Step A: NBS (1.1 equiv), CH_2Cl_2, −78→0 °C (for **7**) or 0 °C (for **8**). *E*/*Z* ratios: **9**: >19:1; **10**: >19:1. Step B: $ArB(OH)_2$ (2.0 equiv), $(Ph_3P)_2PdCl_2$ (0.05 equiv), Cs_2CO_3 (10 equiv), 1,4-dioxane/H_2O, 50 °C. Step C: 1) ICl (1.1 equiv), CH_2Cl_2, −78 °C; 2) $ArB(OH)_2$ (2.0 equiv), $(Ph_3P)_2PdCl_2$ (0.05 equiv), Cs_2CO_3 (10 equiv), 1,4-dioxane/H_2O, 50 °C. *E*/*Z* ratios: (*Z*)-**12**: 1:10.4; (*E*)-**12**: 11.3:1.

a notable departure from the carbometalation strategies that have been commonly employed toward these alkene products. Currently, efforts are directed toward further exploring the reactivity of these α-hydroxypropargylsilanes in other synthetically useful contexts.

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Keywords: alkene geometry · alkynes · stereoselectivity · halosilylation · migration

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[14] NCS did induce similar reactivity at more elevated temperatures in protic solvents (50 °C in EtOH), likely enabled through mild H-bond activation of the succinimide reagent.

[15] The stereochemistry of the migration was confirmed in several cases by NOE analysis. See the Supporting Information for details.

[16] The corresponding ynone was observed as the sole product from this attempted iodosilylation.

[17] Considering the impact of the halogen atom in entry 3 compared to the analogous iodination (Table 2, entry 3), the ynone compound seen in iodination likely arises through a rapid *trans* elimination of the silicon group and iodide species from the targeted enone product.

[18] a) A. Alimardanov, E.-i. Negishi, *Tetrahedron Lett.* **1999**, *40*, 3839 – 3842; b) Temperature control was crucial for the success of this transformation. When the reactions were performed at 0 °C, approximately 1:1 mixtures of alkene isomers were observed.

[19] For select examples of Suzuki–Miyaura cross couplings to synthesize stereodefined tetrasubstituted alkenes, see: a) A. N. Thadani, V. H. Rawal, *Org. Lett.* **2002**, *4*, 4317 – 4320; b) K. Itami, T. Kamei, J.-i. Yoshida, *J. Am. Chem. Soc.* **2003**, *125*, 14670 – 14671; c) M. Suginome, A. Yamamoto, M. Murakami, *Angew. Chem.* **2005**, *117*, 2432 – 2434; *Angew. Chem. Int. Ed.* **2005**, *44*, 2380 – 2382; d) C. Zhou, R. C. Larock, *J. Org. Chem.* **2005**, *70*, 3765 – 3777; e) M. Shimizu, C. Nakamaki, K. Shimono, M. Schelper, T. Kurahashi, T. Hiyama, *J. Am. Chem. Soc.* **2005**, *127*, 12506 – 12507; f) Y. Nishihara, M. Miyasaka, M. Okamoto, H. Takahashi, E. Inoue, K. Tanemura, K. Takagi, *J. Am. Chem. Soc.* **2007**, *129*, 12634 – 12635; g) W. You, Y. Li, M. K. Brown, *Org. Lett.* **2013**, *15*, 1610 – 1613.

[20] Although we predicted a direct Hiyama cross coupling with an α-silylenone or a variant would be possible, several conditions explored were unsuccessful, presumably owing to the instability of α-silylenones with the nucleophilic fluoride reagents that are generally required for transmetalation. For a discussion, see Ref. [7c].

