

Stereoselective Synthesis of *Cis*- and *Trans*-Tetrasubstituted Vinyl Silanes Using a Silyl-Heck Strategy and Hiyama Conditions for Their Cross-Coupling

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Supporting Information Placeholder

ABSTRACT: We report a palladium-catalyzed, three-component carbosilylation reaction of internal symmetrical alkynes, silicon electrophiles, and primary alkyl zinc iodides. Depending on the choice of ligand, stereoselective synthesis of either *cis*- or *trans*-tetrasubstituted vinyl silanes is possible. We also demonstrate conditions for the Hiyama cross-coupling of these products to prepare geometrically defined tetrasubstituted alkenes.

Vinylsilanes have a wide variety of applications in organic synthesis, including Hiyama cross-coupling reactions, Tamao-Fleming oxidations, and desilylative halogenations.¹ Despite the development of numerous methods to prepare vinylsilanes,² the stereocontrolled synthesis of tetrasubstituted vinylsilanes remains challenging. Classically, these highly substituted vinylsilanes have been prepared by the carbometallation of silylacetylenes; however, these methods typically require multiple steps, and often produce products with low *E/Z* selectivity.³ Only three examples of stereoselective tetrasubstituted vinylsilane synthesis are known. Itami has reported a copper-catalyzed single-pot carbometallation of pyridyl-substituted silylacetylenes.⁴ This method addresses stereocontrol in the carbometallation; however, it requires several steps to implement and is limited to the production of pyridyl silanes (Scheme 1A). In 2016, Shintani and Nozaki reported an elegant palladium-catalyzed tandem alkyne silylboration/Suzuki reaction that allows for net *syn*-carbosilylation of alkynes; however, this method is only effective for diarylalkynes (Scheme 1B).⁵ Most recently, Nakamura described a related iron-catalyzed method that, while effective for aliphatic alkynes, is limited to benzylic electrophiles and provides only the *anti*-addition products (Scheme 1B).⁶ Moreover, both of these latter methods require the use of nucleophilic silyl reagents, which can be challenging to access due to silicon's low electronegativity.

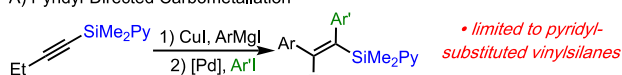
In the early 1990's, Murai reported the palladium-catalyzed carbosilylation of terminal alkynes using trimethylsilyl iodide and organometallic nucleophiles (Scheme 1C).⁷ This method is attractive because it takes advantage of silicon's natural electrophilicity. However, Murai reported that the method did not work with internal alkynes, and thus did not allow access to tetrasubstituted vinylsilanes.

Based upon the continued need for simple protocols that can assess highly substituted vinylsilanes, as well as our ongoing

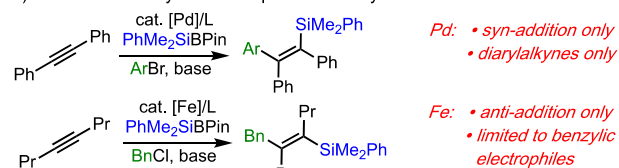
Scheme 1. Formation of Tetrasubstituted Vinylsilanes

PRIOR WORK:

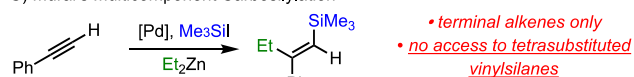
A) Pyridyl-Directed Carbometallation



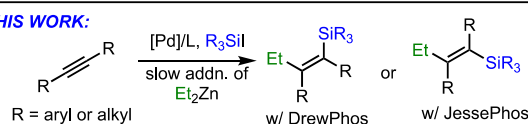
B) Pd- and Fe-Catalyzed Nucleophilic Carbosilylation



C) Murai's Multicomponent Carbosilylation

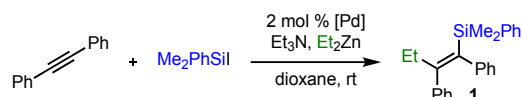


THIS WORK:



- Stereocontrolled access to *cis*- or *trans*- tetrasubstituted vinylsilanes
- Aromatic and aliphatic substitution tolerated

interest in developing silyl-Heck-type reactions,^{8,9} we have reinvestigated the use of electrophilic carbosilylation for the preparation of tetrasubstituted vinylsilanes. Through identification of both the proper order of addition of reagents and the correct ligands, the stereoselective synthesis of *syn*- and *anti*- tetrasubstituted vinylsilanes via carbosilylation of internal alkynes is now possible. This method is applicable to both diaryl- and dialkyl-alkynes, as well as a variety of silyl functionalities, allowing for highly general access to tetrasubstituted vinylsilanes. Finally, we also report general conditions that allow for the tetrasubstituted vinylsilanes to undergo Hiyama-coupling, which also allows for facile synthesis of stereodefined tetrasubstituted alkenes.

Table 1. Identification of Reaction Conditions for Diaryl Alkynes


| Entry | [Pd] | Me ₂ PhSiH ₃ (equiv) | Nucleophile (equiv) | Et ₃ N (equiv) | Conditions | Yield 1 (%) ^a |
|-------|--|--|--------------------------|---------------------------|---|---------------------------------|
| 1 | Pd(PPh ₃) ₄ | 1 | Et ₂ Zn (1) | 0 | Me ₂ PhSiH ₃ added last, over 0.5 min | <1 |
| 2 | Pd(PPh ₃) ₄ | 1 | Et ₂ Zn (1) | 0 | Et ₂ Zn added last, over 0.5 min | 6 |
| 3 | Pd(PPh ₃) ₄ | 1 | Et ₂ Zn (1) | 0 | Et ₂ Zn added last, over 1 h | 25 |
| 4 | (Ph ₃ P) ₂ PdCl ₂ | 1 | Et ₂ Zn (1) | 1 | Et ₂ Zn added last, over 1 h | 70 |
| 5 | (Ph ₃ P) ₂ PdCl ₂ | 1 | Et ₂ Zn (1) | 1 | Et ₂ Zn added last, over 4 h | 89 |
| 6 | (Ph ₃ P) ₂ PdCl ₂ | 3 | Et ₂ Zn (1.5) | 3 | Et ₂ Zn added last, over 4 h | 95 |
| 7 | (Ph ₃ P) ₂ PdCl ₂ | 3 | EtZnI (1.5) | 3 | EtZnI added last, over 4 h | 95 |

^aYield determined by GC.

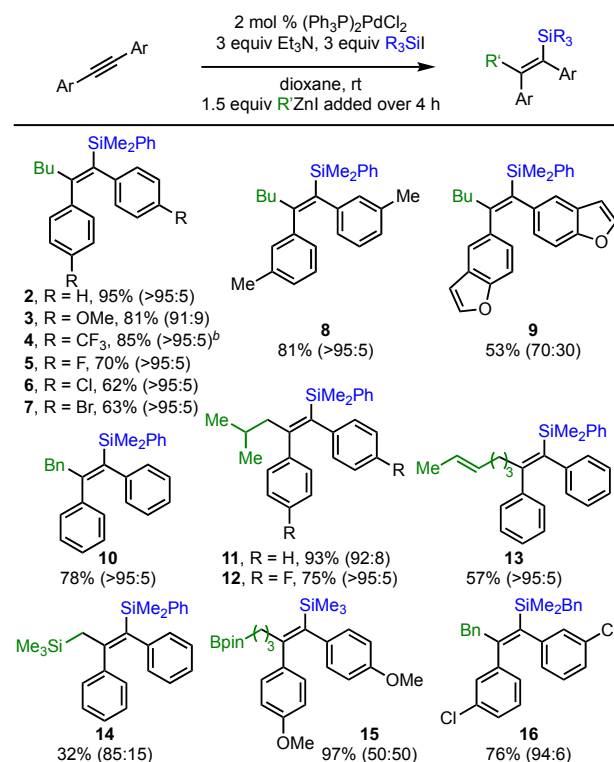
We began by reproducing the results reported by Murai, which involved the addition of the silyl iodide to a solution of Et₂Zn and diphenylacetylene. In our case, however, we replaced Me₃SiI with PhMe₂SiI with an eye towards downstream functionalization.¹⁰ Consistent with Murai's findings, only traces of the desired product were observed (Table 1, entry 1). Surprisingly, however, when the order of addition was switched and Et₂Zn was added to a solution of alkyne and silyliodide, noticeably more product was formed (entry 2). As described by Murai, the major byproduct was phenyldimethylethylsilane resulting from alkylation of the silylhalide by Et₂Zn. Murai suggested that this byproduct results from the direct reaction of the two reagents;^{7b} however, control experiments in our lab revealed that this side reaction is also palladium-catalyzed.¹¹ Combined, these results led us to investigate the slow addition of Et₂Zn, which further improved the yield (entry 3). Extending the time of slow addition, in combination with switching the precatalyst to (PPh₃)₂PdCl₂, the addition of Et₃N to the solution,¹² and adjustment of the stoichiometry resulted in nearly quantitative formation of the desired product (entries 4–6). Finally, to increase the utility of the method with more complex nucleophiles, we also investigated the use of alkylzinc halides as nucleophiles. This change resulted in an equally efficient reaction (entry 7). In all cases, only the product of *syn*-addition was observed.

The scope of the reaction, with respect to diaryl acetylene, alkylzinc iodide, and iodosilane is broad (Scheme 2). High yields and outstanding *syn*-selectivity were generally observed. Functional group compatibility is also high, and includes aryl ethers (**3**), trifluoromethyl groups (**4**), aryl halides (**5–7**), heterocycles (**9**), increased steric bulk (**8**, **11**, **12**), alkenes (**13**), and alkyl boronic esters and silanes (**14–15**). As a general trend, lower *syn*-selectivity was observed with increased electron-density on the alkene β to silicon.¹³

Our attention then turned to alkyl-substituted alkynes. We were initially disappointed to find that the conditions developed in Table 1 lead to poor *syn/anti* mixtures of products (Table 2, entry 1). To address this issue, we investigated the role of the ligand in stereoselection. Less electron-rich triarylphosphines gave poor reactivity (not shown). More electron-rich phosphines provided similar yield of product, but with low

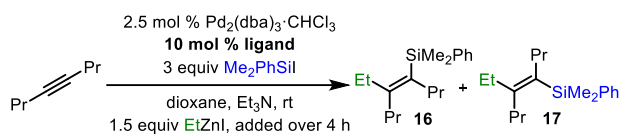
levels of selectivity (entry 2). Gratifyingly, however, we found that by using DrewPhos [(3,5-*i*-Bu₂C₆H₃)₃P],^{11a} which features *tert*-butylated phenyl groups, dramatically improved selectivity for *syn*-addition product **16** was achieved (entry 3). Equally surprising, with even larger ligands, a reversal in selectivity was observed and *anti*-addition product **17** was observed as the major product (entry 4). Ultimately, JessePhos [(3,5-*i*-Bu₂C₆H₃)₂P(*t*Bu)]^{8d} proved superior in this regard, providing both high yield and outstanding selectivity for **17** (entry 5). Thus, depending upon the choice of ligand, either the *syn*- or *anti*-addition product can be selectively prepared.

Scheme 2. Scope of Aryl-Substituted Vinylsilanes



^aIsolated yields, *syn/anti* ratios (reported in parentheses) were determined by GC analysis of the crude reaction mixture. ^b[(C₆F₅)₂P]PdCl₂.

Table 2. Effect of Ligand on Selectivity of Alkyl-Substituted Vinylsilanes

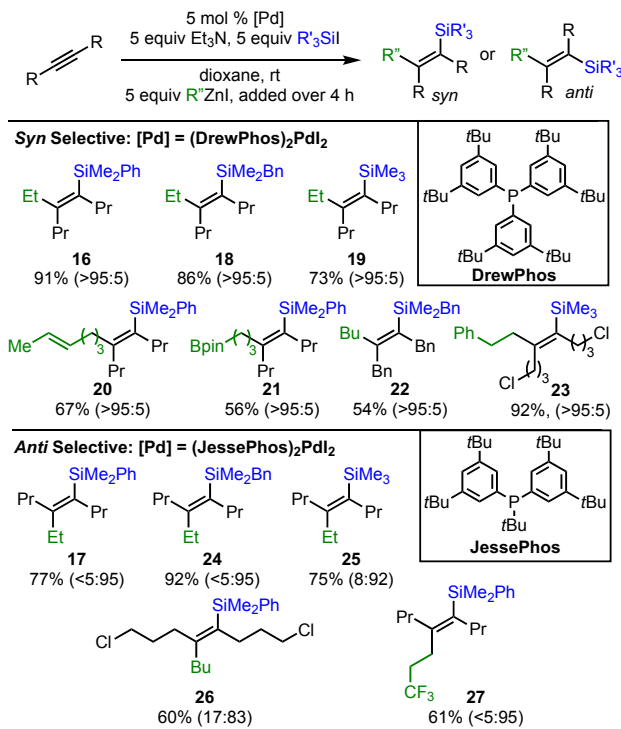


| Entry | Ligand | Combined Yield and Ratio 16/17 ^a |
|-------|---|---|
| 1 | Ph_3P | 88%, 65:35 |
| 2 | $(4\text{-OMeC}_6\text{H}_4)_3\text{P}$ | 66%, 60:40 |
| 3 | $(3,5\text{-}i\text{Bu}_2\text{C}_6\text{H}_3)_3\text{P}$ | 76%, 90:10 |
| 4 | $(o\text{-tol})_3\text{P}$ | 65%, 18:82 |
| 5 | $(3,5\text{-}i\text{Bu}_2\text{C}_6\text{H}_3)_2\text{P}(t\text{Bu})$ | 67%, <5:95 |

^aYields and *syn/anti* ratios determined by GC.

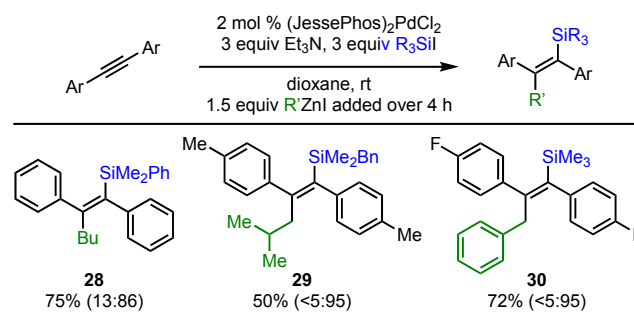
After additional optimization, which included use of preformed $\text{Pd}(\text{II})\text{I}_2$ precatalysts and adjustment of the stoichiometry,¹⁴ the scope of both the *syn*- and *anti*-selective conditions were explored (Scheme 3, top and bottom, respectively). Similar to the scope of the reaction with aryl-substituted alkynes, the reaction of alkyl-substituted alkynes was tolerant to a range of substitution on the silicon center (16–19, 24, 25). In addition, a range of functional groups were tolerated, including alkyl chlorides (23, 26), trifluoromethyl groups (27), boronic esters (21), alkenes (20), and aromatic groups (22, 23).

Scheme 3. Scope of Alkyl-Substituted Tetrasubstituted Vinylsilanes^a



^aIsolated yields, *syn/anti* ratios determined by GC analysis of the crude reaction mixture and reported in parentheses.

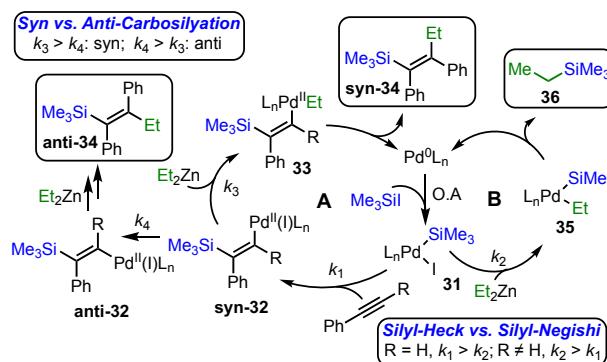
Scheme 4. Anti-Addition of Aryl Alkynes



^aIsolated yields, *syn/anti* ratios determined by GC analysis of the crude reaction mixture (reported in parenthesis).

With the discovery that JessePhos leads to *anti* products, we also investigated its use in the carbosilylation of diarylalkynes. We found that $(\text{JessePhos})_2\text{PdCl}_2$ is a suitable palladium precatalyst and leads to good yields of aryl-substituted tetrasubstituted vinylsilanes with excellent *anti*-selectivity (Scheme 4).

Figure 1. Mechanistic Discussion

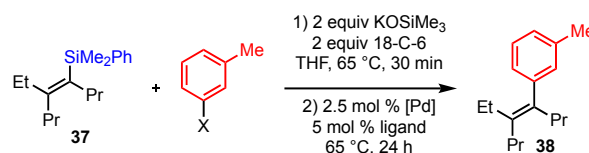


The newly discovered ability to prepare tetrasubstituted vinylsilanes using this method, particularly in the context of the earlier results reported by the Murai group, can be understood in the context of two competing silyl-Heck-like and silyl-Negishi reactions. Both proceed via oxidative addition of $\text{Pd}(0)$ to the silyl halide. As proposed by Murai,^{7b} the carbosilylation pathway (Figure 1, pathway A) proceeds via migratory insertion of the alkyne, transmetalation, and reductive elimination. With terminal alkynes, migratory insertion is evidently fast, and pathway A dominates. With internal alkynes, however, migratory insertion is slower, and direct transmetalation of the $\text{Pd}(\text{II})(\text{SiR}_3)\text{I}$ (31) can compete. With high concentration of organometallic nucleophile, this latter pathway dominates, resulting in silyl-Negishi alkylation.^{11a} However, by holding the concentration of the nucleophile low, the rate of transmetalation is suppressed and the carbosilylation pathway proceeds.

The ability to select *syn*- or *anti*-addition products based upon ligand appears to be predominately due to relative strength of the π -bond in intermediate 32. Electron-donors β to silicon are expected to weaken the bond. Simultaneously, larger ligands sterically destabilize this intermediate. When rupture of the π -bond (k_4) is faster than transmetalation (k_3), isomerization to the *anti*-product occurs.¹⁵

Lastly, we wished to demonstrate the utility of the tetrasubstituted vinylsilanes by converting them to stereodefined tetrasubstituted alkenes using a Hiyama reaction. Although Denmark's tetrasubstituted vinylsilanols can undergo cross-coupling,^{16,17} there is only a single example of a cross-coupling of a non-activated tetrasubstituted vinylsilane bearing all-carbon groups on silicon.^{18,19} Unfortunately, those conditions failed to result in cross-coupling of the tetrasubstituted vinylsilanes prepared in this study.¹⁴

Table 3. Hiyama Cross-Coupling Conditions



| Entry | X | [Pd] | Ligand | Yield (%) |
|-------|----|------------------------------------|--------|-----------------|
| 1 | I | Pd ₂ (dba) ₃ | none | 0 |
| 2 | I | [(allyl)PdCl ₂] | SPhos | 50 ^a |
| 3 | Br | [(allyl)PdCl ₂] | SPhos | 62 ^b |

^aYield determined by GC. ^bIsolated yield.

Anderson has demonstrated that all-carbon-bearing trisubstituted vinylsilanes can undergo Hiyama coupling with aryl iodides in the presence of 18-crown-6 and KOSiMe₃ using Pd₂(dba)₃ as the catalyst.²⁰ Unfortunately, those conditions also failed to cross-couple the more substituted tetrasubstituted vinylsilanes (Table 3, entry 1). However, by combining the use of 18-crown-6 and KOSiMe₃ with the use of SPhos as ligand (as identified in the Denmark studies),^{16,21} we were able to cross-couple both aryl iodides and aryl bromides in good yield (entries 2 and 3).¹⁴ As all-carbon-substituted vinylsilanes are easier to manipulate than the corresponding silanols, these conditions should prove to be a useful advance in Hiyama cross-coupling.

In conclusion, we have developed a three-component carbosilylation reaction for the synthesis of tetrasubstituted vinylsilanes directly from readily available or easily synthesized starting materials. This method allows for the formation of either the *syn*- or *anti*-addition vinylsilane products depending on the ligand choice. In addition, we have demonstrated the utility of the reaction through the development of a Hiyama cross-coupling reaction, which allows for the formation of stereodefined tetrasubstituted alkenes directly from these vinylsilane products. Current studies are focused on carbosilylation reactions on non-symmetric internal alkynes.

ASSOCIATED CONTENT

Supporting Information

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

Experimental details and data (PDF)

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Author Contributions

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Notes

The authors declare no competing financial interest.

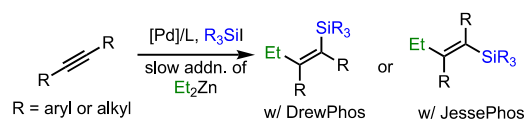
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REFERENCES

- Hiyama, T.; Oestreich, M., *Organosilicon Chemistry - Novel Approaches and Reactions*. Wiley-VCH: Weinheim, 2019.
- (a) Lim, D. S. W.; Anderson, E. A., *Synthesis of Vinylsilanes. Synthesis* **2012**, *44*, 983-1010, 10.1055/s-0031-1289729; (b) Anderson, E. A.; Lim, D. S. W., *Science of Synthesis*. Thieme Chemistry: Stuttgart, 2015; Vol. 1, p 59.
- (a) Negishi, E., Controlled carbometallation as a new tool for carbon-carbon bond formation and its application to cyclization. *Acc. Chem. Res.* **1987**, *20*, 65-72, 10.1021/ar00134a004; (b) Snider, B. B.; Karras, M.; Conn, R. S. E., Nickel-catalyzed addition of Grignard reagents to silylacetylenes. *Synthesis of tetrasubstituted alkenes. J. Am. Chem. Soc.* **1978**, *100*, 4624-4626, 10.1021/ja00482a066.
- Itami, K.; Kamei, T.; Yoshida, J.-i., Diversity-Oriented Synthesis of Tamoxifen-type Tetrasubstituted Olefins. *J. Am. Chem. Soc.* **2003**, *125*, 14670-14671, 10.1021/ja037566i.
- Shintani, R.; Kurata, H.; Nozaki, K., Intermolecular Three-Component Arylsilylation of Alkynes under Palladium/Copper Cooperative Catalysis. *J. Org. Chem.* **2016**, *81*, 3065-3069, 10.1021/acs.joc.6b00587.
- Iwamoto, T.; Nishikori, T.; Nakagawa, N.; Takaya, H.; Nakamura, M., Iron-Catalyzed anti-Selective Carbosilylation of Internal Alkynes. *Angew. Chem., Int. Ed.* **2017**, *56*, 13298-13301, 10.1002/anie.201706333.
- (a) Chatani, N.; Amishiro, N.; Murai, S., A new catalytic reaction involving oxidative addition of iodotrimethylsilane (Me₃SiI) to palladium(0). Synthesis of stereodefined enynes by the coupling of Me₃SiI, acetylenes, and acetylenic tin reagents. *J. Am. Chem. Soc.* **1991**, *113*, 7778-7780, 10.1021/ja00020a060; (b) Chatani, N.; Amishiro, N.; Morii, T.; Yamashita, T.; Murai, S., Pd-Catalyzed Coupling Reaction of Acetylenes, Iodotrimethylsilane, and Organozinc Reagents for the Stereoselective Synthesis of Vinylsilanes. *J. Org. Chem.* **1995**, *60*, 1834-1840, 10.1021/jo00111a048.
- (a) McAtee, J. R.; Martin, S. E. S.; Ahneman, D. T.; Johnson, K. A.; Watson, D. A., Preparation of Allyl and Vinyl Silanes by the Palladium-Catalyzed Silylation of Terminal Olefins: A Silyl-Heck Reaction. *Angew. Chem., Int. Ed.* **2012**, *51*, 3663-3667, 10.1002/anie.201200060; (b) Martin, S. E. S.; Watson, D. A., Preparation of Vinyl Silyl Ethers and Disiloxanes via the Silyl-Heck Reaction of Silyl Ditriflates. *J. Am. Chem. Soc.* **2013**, *135*, 13330-13333, 10.1021/ja407748z; (c) McAtee, J. R.; Martin, S. E. S.; Cinderella, A. P.; Reid, W. B.; Johnson, K. A.; Watson, D. A.,

- The first example of nickel-catalyzed silyl-Heck reactions: direct activation of silyl triflates without iodide additives. *Tetrahedron* **2014**, *70*, 4250-4256, 10.1016/j.tet.2014.03.021; (d) McAtee, J. R.; Yap, G. P. A.; Watson, D. A., Rational Design of a Second Generation Catalyst for Preparation of Allylsilanes Using the Silyl-Heck Reaction. *J. Am. Chem. Soc.* **2014**, *136*, 10166-10172, 10.1021/ja505446y; (e) McAtee, J. R.; Krause, S. B.; Watson, D. A., Simplified Preparation of Trialkylvinylsilanes via the Silyl-Heck Reaction Utilizing a Second Generation Catalyst. *Adv. Synth. Cat.* **2015**, *357*, 2317-2321, 10.1002/adsc.201500436; (f) Krause, S. B.; McAtee, J. R.; Yap, G. P. A.; Watson, D. A., A Bench-Stable, Single-Component Precatalyst for Silyl-Heck Reactions. *Org. Lett.* **2017**, *19*, 5641-5644, 10.1021/acs.orglett.7b02807; (g) Vulovic, B.; Watson, D. A., Heck-Like Reactions Involving Heteroatomic Electrophiles. *Eur. J. Org. Chem.* **2017**, *2017*, 4996-5009, 10.1002/ejoc.201700485.
9. (a) Also see: Hiroshi, Y.; Toshi-aki, K.; Teruyuki, H.; Masato, T., Heck-type Reaction of Iodotrimethylsilane with Olefins Affording Alkenyltrimethylsilanes. *Chem. Lett.* **1991**, *20*, 761-762, 10.1246/cl.1991.761; (b) Matsumoto, K.; Huang, J.; Naganawa, Y.; Guo, H.; Beppu, T.; Sato, K.; Shimada, S.; Nakajima, Y., Direct Silyl-Heck Reaction of Chlorosilanes. *Org. Lett.* **2018**, *20*, 2481-2484, 10.1021/acs.orglett.8b00847.
10. The results reported in Table 1 are qualitatively identical with use of Me₃SiI
11. (a) Cinderella, A. P.; Vulovic, B.; Watson, D. A., Palladium-Catalyzed Cross-Coupling of Silyl Electrophiles with Alkylzinc Halides: A Silyl-Negishi Reaction. *J. Am. Chem. Soc.* **2017**, *139*, 7741-7744, 10.1021/jacs.7b04364; (b) Vulovic, B.; Cinderella, A. P.; Watson, D. A., Palladium-Catalyzed Cross-Coupling of Monochlorosilanes and Grignard Reagents. *ACS Catal.* **2017**, *7*, 8113-8117, 10.1021/acscatal.7b03465.
12. We are unsure of the role of Et₃N in these reactions, but speculate that it might be involve in activating the silyliodide reagent towards oxidative addition by via formation of the silylammonium salt. See: Christenson, B.; Ullenius, C.; Hakansson, M.; Jagner, S., Addition of Me₂CuLi to enones and enoates effects of solvent and additives on the yield and stereoselectivity. *Tetrahedron* **1992**, *48*, 3623-3632, 10.1016/S0040-4020(01)88500-8.
13. In the case of **15**, both the electron-richness of the alkyne starting material and the specific alkyl zinc iodide contribute to the low E/Z ratio. See result for **2** and Supporting Information.
14. See Supporting Information.
15. For a related proposal, see: Amatore, C.; Bensalem, S.; Ghalem, S.; Jutand, A., Mechanism of the carbopalladation of alkynes by aryl-palladium complexes. *J. Organomet. Chem.* **2004**, *689*, 4642-4646, 10.1016/j.jorganchem.2004.05.032.
16. Denmark, S. E.; Kallemeyn, J. M., Stereospecific Palladium-Catalyzed Cross-Coupling of (E)- and (Z)-Alkenylsilanolates with Aryl Chlorides. *J. Am. Chem. Soc.* **2006**, *128*, 15958-15959, 10.1021/ja065988x.
17. Also see: Li, E.; Zhou, H.; Östlund, V.; Hertzberg, R.; Moberg, C., Regio- and stereoselective synthesis of conjugated trienes from silaborated 1,3-enynes. *New J. Chem.* **2016**, *40*, 6340-6346, 10.1039/C6NJ01019A.
18. Denmark, S. E.; Liu, J. H.-C., Sequential Silylcarbocyclization/Silicon-Based Cross-Coupling Reactions. *J. Am. Chem. Soc.* **2007**, *129*, 3737-3744, 10.1021/ja067854p.
19. For an example using internal carboxylate activation, see: Shindo, M.; Matsumoto, K.; Shishido, K., Intramolecularly Activated Vinylsilanes: Fluoride-Free Cross-Coupling of (Z)-β-(Trialkylsilyl)acrylic Acids. *Synlett* **2005**, *2005*, 176-178, 10.1055/s-2004-836033.
20. Anderson, J. C.; Munday, R. H., Vinyltrimethylphenylsilanes as Safety Catch Silanols in Fluoride-Free Palladium-Catalyzed Cross-Coupling Reactions. *J. Org. Chem.* **2004**, *69*, 8971-8974, 10.1021/jo048746t.
21. Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L., Catalysts for Suzuki-Miyaura Coupling Processes: Scope and Studies of the Effect of Ligand Structure. *J. Am. Chem. Soc.* **2005**, *127*, 4685-4696, 10.1021/ja042491j.



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