Development of a General Method for the Hiyama-Denmark Cross-Coupling of Tetrasubstituted Vinyl Silanes

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Hiyama-Denmark, tetrasubstituted-alkenes, vinyl silanes, palladium, cross-coupling

ABSTRACT: General conditions for the Hiyama-Denmark cross-coupling of tetrasubstituted vinyl silanes and aryl halides are reported. Prior reports of Hiyama-Denmark reactions of tetrasubstituted vinyl silanes have required the use of vinyl silanols or silanolates, which are challenging to handle, or internally activated vinyl silanes, which lack structural generality. Now, unactivated tetrasubstituted vinyl silanes, bearing bench-stable tetraorganosilicon centers, and aryl halides can be coupled. The key to this discovery is the identification of dimethyl(5-methylfuryl)vinylsilanes as bench stable and easily prepared cross-coupling partners that are readily activated under mild conditions in Hiyama-Denmark couplings. These palladium-catalyzed cross-couplings proceed well with aryl chlorides, though aryl bromides and iodides are also tolerated, and the reactions display high stereospecificity in the formation of tetrasubstituted alkenes. In addition, only a mild base ($KOSiMe_3$) and common solvents (THF/DMA) are required, and importantly toxic additives (such as 18-crown-6) are not needed. We also show that these conditions are equally applicable to Hiyama-Denamrk coupling of trisubstituted vinyl silanes.

Tetrasubstituted alkenes are important scaffolds with wide utility in a variety of applications, including in commercial drugs, bioactive molecules, natural products, and materials chemistry, and they have widespread utility as synthetic intermediates.[1] Although traditional approaches to alkene synthesis (Wittig reactions, alkene metathesis, etc.) struggle with stereochemical control in these highly substituted systems, a variety of cross-coupling methods have been reported for their stereoselective synthesis.[1] The most widely developed of these is Suzuki-Miyaura cross-coupling,[2] however there are still limited methods to synthesize the required highly substituted vinyl boronic acids and esters,[3,4] and in general, vinyl boronic acids and esters pose challenges with respect to isolation and handling.[5] Thus, the development of new routes for the stereocontrolled synthesis of tetrasubstituted alkenes continues to be in high demand.[1]

Hiyama-Denmark cross-coupling represents an attractive alternative to Suzuki-Miyaura reactions, as silicon is earth abundant and non-toxic, and vinyl silanes (particularly those with four organic substituents on the silicon center) are generally highly stable, easily isolable, and tolerate many types of reaction conditions.[6] These characteristics make Hiyama-Denmark cross-coupling attractive as a method for late-stage functionalization and complex molecule synthesis.[6c] However, while we and others have recently described stereocontrolled routes to prepare tetrasubstituted vinyl silanes,[7] Hiyama-Denmark couplings of tetrasubstituted vinyl silanes are exceptionally rare.[6a-c, 6e-h] In fact, only two methods for Hiyama-Denmark coupling of tetrasubstituted vinyl silanes have been previously described, and both require activated organosilanes. The first method, pioneered by Denmark, involves the use of silanolates (or silanols, Figure 1A, top).[8] Although the development of this class of reagents as effective cross-coupling partners represented a major advance in Hiyama-Denmark-type reactions, the oxygenated silanes themselves can be challenging to prepare and handle as they readily form disiloxanes, particularly if exposed to air or water.[9] The second method (reported by Shindo, Figure 1A bottom) requires a free carboxylic acid *cis* to the silane.[10,11] This functionality presumably activates the silicon center via the formation of a cyclic silicate, and thus is not general to other classes of vinyl silanes.[12,13] Neither of these published conditions allows for the cross-coupling of unactivated tetrasubstituted vinyl silanes. The greater stability of these unactivated reagents, compared to silanolates or internally activated vinyl silanes, has no doubt been responsible for the lack of reactivity in this general class of vinyl silanes.

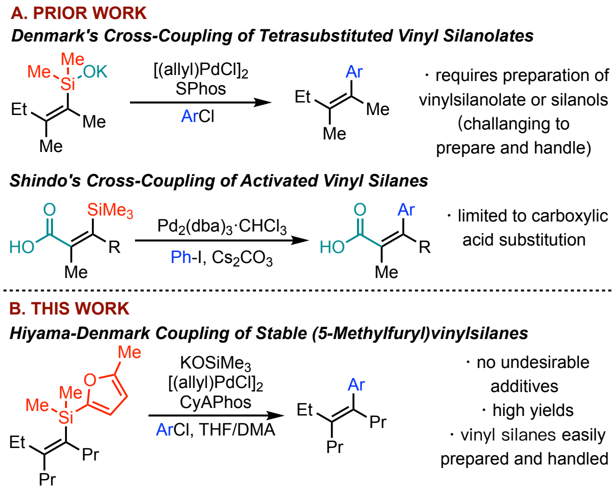
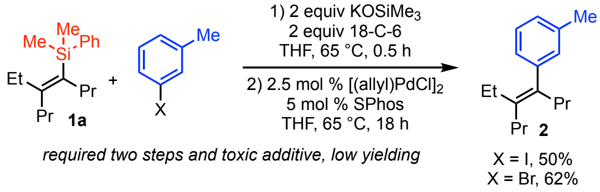


Figure 1. Hiyama-Denmark Cross-Coupling of Tetrasubstituted Vinyl Silicon Species

Development of general conditions for the cross-coupling of highly substituted, unactivated vinyl silanes would greatly expand the utility of the Hiyama-Denmark reaction. In turn, this would also increase access to highly substituted, stereo-defined alkenes. Herein we report such conditions. Specifically, we have identified dimethyl(5-methylfuryl)vinyl silanes to be uniquely reactive in Hiyama-Denmark cross-coupling reactions. We report conditions that allow tetrasubstituted vinyl silanes of this type to undergo facile coupling with a range of aryl halides to give tetrasubstituted alkenes with excellent functional group tolerance and high levels of stereochemical control (Figure 1B). The reaction proceeds in high yield and in a single operation under mild conditions. Importantly, it does not require the use of exogenous additives beyond the catalyst, common solvents, and a mild base. These conditions can also be applied to the cross-coupling of trisubstituted vinyl silanes with equal effectiveness. Finally, using modifications of previously reported methods, the required 5-methylfurylsilanes are easily prepared from 2-methylfuran (a biomass-derived feedstock).[14]

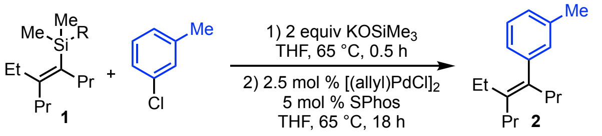
Scheme 1. Single Example of a Cross-Coupling of an Unactivated Vinyl Silane Using Two-Step Procedure and 18-C-6 Additive

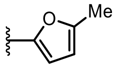


In our previous report describing the synthesis of tetrasubstituted vinyl silanes,[7d] we confronted the lack of Hiyama-Denmark technology for cross-coupling such highly substituted vinyl silanes. No previously reported conditions were able to cross-couple such silanes to aryl halides. At the time, with dimethylphenylsilane **1a** as a model substrate, we found that the use of 18-crown-6 (18-C-6, an additive for the Hiyama-Denmark coupling of trisubstituted vinyl silanes reported by Anderson)[15] and Buchwald's SPhos ligand[16] (previously used by Denmark in Hiyama-Denmark reactions of silanolates)[8a] with $KOSiMe_3$ as the base[17] delivered the desired cross-coupling product **2**, albeit in only modest yields (Scheme 1). Although this was an advance in the field, these conditions required super-stochiometric amounts of 18-C-6 (which has a high molecular weight, is expensive and toxic,[18] and can be challenging to separate from the desired products). In addition, the method was tedious as it required two separate operations (a pre-stir step to activate the vinyl silane, followed by a separate addition of the palladium catalyst and aryl halide). As such, we chose not to develop those conditions beyond the initial demonstration reaction. Instead, we focused on the development of more practical conditions for a Hiyama-Denmark coupling of highly substituted vinyl silanes, with the goal of developing single operation conditions that did not require the use of expensive or highly toxic additives.

Preliminary mechanistic analysis of the 18-C-6 conditions suggested that the reaction proceeded via a vinylsilanolate intermediate resulting from the protodearylation of the Ph-Si bond of **1a**.[19] We postulated that this was likely the most challenging step in the overall process, and that identification of suitable substituents that more readily underwent protodesilylation would result in improved cross-coupling conditions. As such, we investigated the Hiyama-Denmark coupling of a series of vinyl silanes bearing different substituents on silicon (Table 1). We continued to employ the two-step procedure but omitted the 18-C-6 additive. We also chose to focus initially on the use of aryl chloride coupling partners due to their wide commercial availability. Under these conditions, even with the use of electron-donating alkyl substitution on the aromatic ring, none of the desired product was observed (entry 2). Alkyl substituents, including benzyl, which had previously been shown to be effective in protodesilyation reactions and Hiyama-Denmark couplings of less substituted vinyl silanes,[20] also lead to minimal product (entries 3-4). We also studied the reaction of 1-napthyl substituted vinyl silane (entry 5), as protonation would likely be easier as a result of weakened aromaticity. However, as in the other cases, no desired product was observed.

Table 1. Effect of Silicon Substitution



Entry	Substrate	R	Yield of 2 (%)[a]
1	**1a**	Ph	0
2	**1b**	4-Me-C_6H_4	0
3	**1c**	Me	0
4	**1d**	Bn	4
5	**1e**	1-naphthyl	0
6	**1f**		32[b]

[a] Yield determined by GC using nonane as an internal standard. [b] Isolated yield.

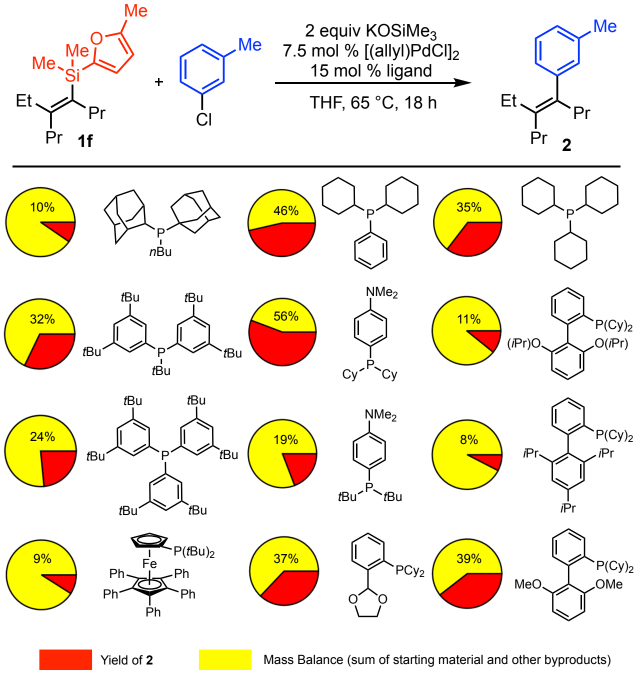
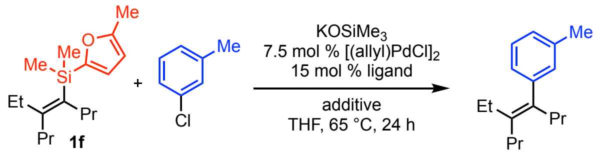


Figure 2. High Throughput Ligand Screen

In an effort to further promote protodesilylation, we turned to heteroaromatic substituents. This area has seen prior development. For example, Hiyama, Denmark, and others have reported the coupling of di- and tri-substituted thienyl vinyl silanes,[20b, 21] however, our attempts to prepare tetrasubstituted thienyl vinyl silanes were not successful. Likewise, Hiyama-Denmark reactions of pyridyl silanes have also been reported,[22,] however, Itamo and Yoshida have previously shown that tetrasubstituted systems do not undergo cross-coupling.[7a] We were thus drawn to furyl groups, as they are more electronic rich than pyridyl groups. Furyl- or 5-methylfuryl-substituted silanes have been previously used in photochemical or oxidation reactions; [23] however, they have not been explored in cross-coupling.[24,25, 26] Gratifyingly, 5-methylfuryl substituted vinyl silane **1f** resulted in product **2** in 32 % yield (entry 6), marking the first successful Hiyama-Denmark reaction of this type without need for added 18-C-6. Importantly, vinyl silane **1f** can be easily synthesized from 2-methylfuran using a slight modification of our previously reported carbosilylation reaction.[7d,19]

With a promising substrate class in hand, we turned to High-Throughput Experimentation (HTE) to identify better catalytic conditions (Figure 2). For simplicity of the method, we also decided to pursue reaction conditions wherein vinyl silane activation and cross-coupling could be achieved in a single operation and without need for a pre-activation step. In these experiments, we examined a variety of ligands noted for promoting difficult cross-coupling reactions, as well as several palladium sources.[19] The most efficient catalysts derived from $[(allyl)PdCl]_2$ and several dicyclohexyl-substituted phosphine ligands provided significant amounts of the desired product **2**. Among these, CyAPhos[27] provided the best results and was selected for further study.

Table 2. Additional Reaction Optimization of Single-Operation Procedure.

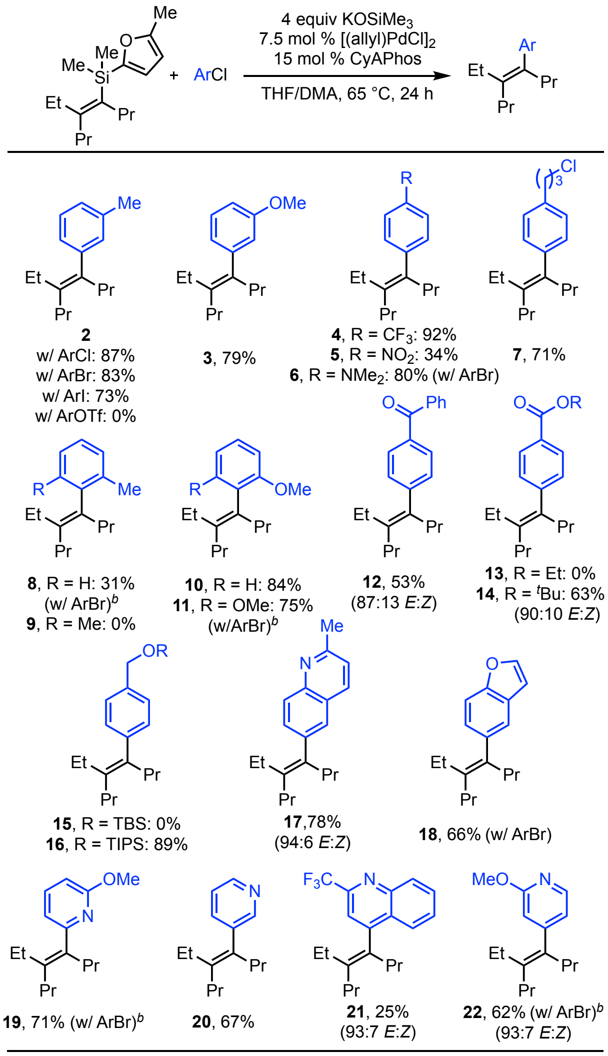


Entry	$KOSiMe_3$ (equiv)	Additive (equiv)	Yield of 2 (%)[a]
1	2	none	62
2	4	none	80
3	4	DMPU (2)	99
4	4	DMPU (1)	93
5	4	DMA (2)	90
6	4	DMA (1)	98
7	4	DMF (1)	74

[a]Yield determined by GC using nonane as an internal standard.

On larger (1 mmol) scale, these initial conditions provided product **2** in 62 % yield using a single-operation reaction setup (Table 2, entry 1). We also found that increasing the amount of $KOSiMe_3$ led to an increased yield (entry 2). (We note that the source of $KOSiMe_3$ was extremely important for the success of this reaction. These observations correlate directly with the purity of the commercial reagent.)[28] We next sought to investigate the role of the potassium cation in the reaction. Our suspicion was that the role of 18-C-6 in Anderson's conditions was to sequester the cation and render the trimethylsilanolate more nucleophilic. This line of thinking lead us to investigate the use of added *N,N'*-dimethylpropyleneurea (DMPU) as a more easily removed (and possibly less toxic) additive compared to 18-C-6.[29] We were pleased to see that addition of 2 equivalents of DMPU to the reaction conditions resulted in a quantitative yield of the model compound (entry 3). However, less DMPU resulted in lower yields (entry 4). More excitingly, however, we found that use of the simple amide solvent dimethylacetamide (DMA) as an additive (in place of DMPU) also provided a significant increased yield of product **2** (entry 5). We were particularly drawn to the use of DMA in the reaction because it is cheap, widely available, less toxic, and easy to remove during the purification of products. Further investigation revealed that, unlike DMPU, the use of a single equivalent of DMA was optimal, resulting in a nearly quantitative yield of tetrasubstituted alkene product and greater than 95:5 E/Z selectivity (entry 6).[30] Interestingly, when DMF was used in place of DMA, lower yield was observed as compared to without the additive (entry 7 vs. entry 2). This indicates a more complex role for DMA in the reaction, see below.

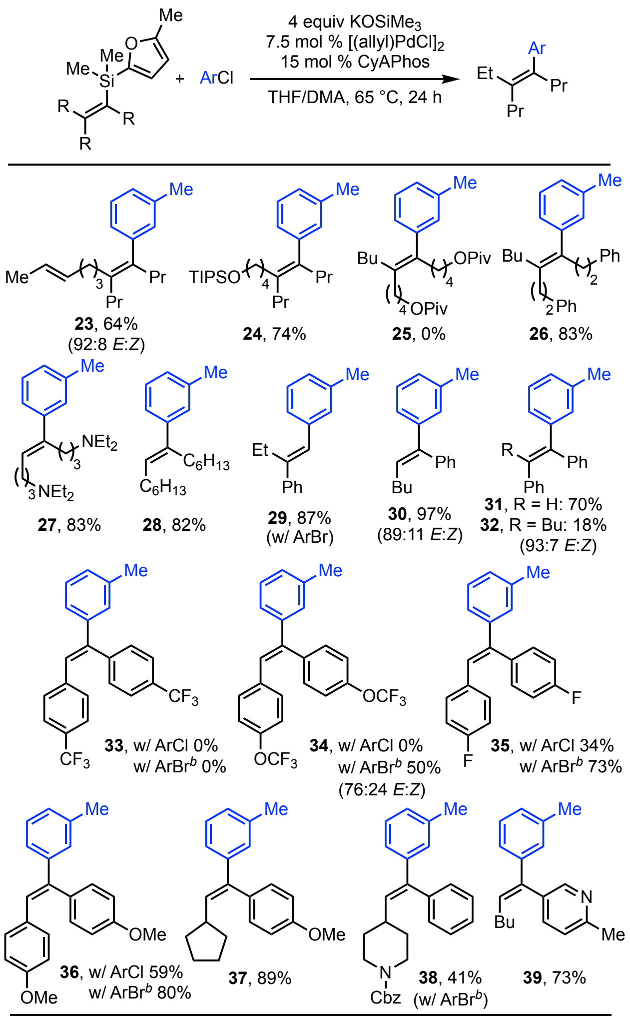
Scheme 2. Scope of Aryl Halides[a]



[a]Isolated yields, 1 mmol scale. Reactions were run with 0.2 M THF, 1.5 equiv ArCl, and 1 equiv DMA relative to the vinyl silane. Unless noted, *E/Z* ratios were >95:5. Ratios were determined by NMR or GC analysis of the crude material. [b]Without DMA additive.

With this optimized, mixed-solvent system in hand, the scope of the reaction was explored. We began by investigating the aryl halide cross-coupling partner (Scheme 2). We were pleased to find that in addition to aryl chlorides, aryl bromides and iodides were also highly competent in the reaction and resulted in **2** in similar yields. Aryl triflates, however, did not couple, most likely due to unproductive cleavage of the S–O bond.[31] The scope, with respect to aryl chlorides, is broad, and in general very high levels of stereochemical retention with respect to the alkene geometry is observed. Electron-withdrawing substitution (**3-5**) and electron-donating substitution (**6, 10-11**) on the aryl chlorides also led to product formation with good to excellent yields. The reaction was tolerant of a variety of functional groups, such as ethers (**3**), trifluoromethyl groups (**4**), nitroarenes (**5**), amines (**6**), alkyl chlorides (**7**), and ketones (**12**). Although *ortho*-methyl substitution was only tolerated to a limited extent (**8-9**), aryl halides with smaller *ortho* substituents were excellent substrates (**10-11**). Ethyl esters were not tolerated (**13**, due to a background reaction with $KOSiMe_3$), but *tert*-butyl esters (**14**) were compatible. Similarly, TBS-protected alcohols were incompatible (**15**), but larger TIPS ethers were tolerated (**16**). Finally, both oxygen and nitrogen containing heterocycles could be incorporated into tetrasubstituted alkene products using this method (**17-22**).

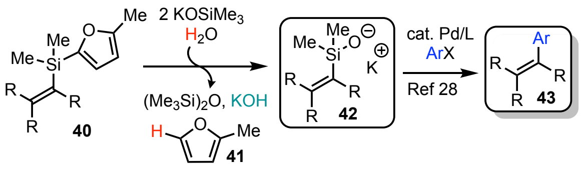
Scheme 3. Scope of Vinyl Silanes[a]



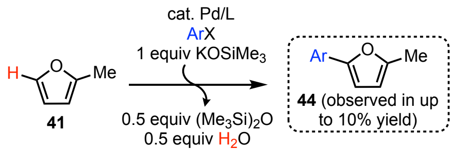
[a] Isolated yields, 1 mmol scale. Reactions were run with 0.2 M THF, 1.5 equiv ArCl, and 1 equiv DMA relative to the vinyl silane. Unless noted, *E/Z* ratios were >95:5. Ratios were determined by NMR or GC analysis of the crude material [b] Without DMA additive.

The scope of the alkene substitution on the vinyl silane was next explored (Scheme 3). We found that in addition to tetrasubstituted vinyl silanes, trisubstituted vinyl silanes (prepared using modifications of known procedures)[32] could participate in the reaction, allowing for the formation of both tri- and tetrasubstituted alkenes in good yields. Similar to the scope of aryl chlorides, high alkene stereospecificity was generally observed. As with the prior examples, good functional group tolerance was observed, and included alkenes (**23**), aromatic groups (**26**, **33-37**), amines (**27**), fluorinated compounds (**34-35**), silylethers (**24**), ethers (**36**, **37**), carbamates (**38**)**,** saturated heterocycles (**38**), and heteroaromatics (**39**). A few limitations were noted. First, alkyl pivalates were not compatible (**25**). In addition, tetrasubstituted vinyl silanes bearing aromatic groups beta to the silicon center proceeded with limited yield (**32**). However, the related trisubstituted substrates reacted well (**31**). In addition, the electronic property of the vinyl silane can affect the outcome of the reaction, with strongly electron-deficient vinyl silanes being poor substates. This effect is highlighted by the series of fluorinated products **33-35**, where the yield is strongly correlated to the electron density of the aromatic substituents. In a few cases (noted in the scheme), reactions proceeded better without addition of DMA. Most often, this occurred with aryl bromides (Scheme 2), or with vinyl silanes bearing aromatic substitution (Scheme 3). As Hiyama-Denmark coupling of di- and mono-substituted vinyl silanes have already been previously reported,[6] we did not study those substrates in this study.

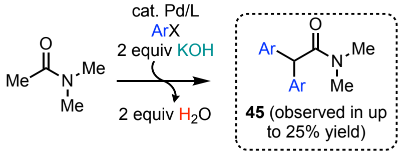
With regard to mechanism, initial studies indicate that the dimethyl(5-methylfuryl)vinyl silanes **40** are converted to the corresponding dimethylsilolate **42** by action of $KOSiMe_3$ (Eq 1).[19] This is no doubt due to the electron-richness of the methylfuryl group, which allows it to protodesilylate faster than the vinyl group. We then propose that the mechanism proceeds to alkene **43**, as has been rigorously established by Denmark's elegant studies.[33] A quizzical feature of this proposed pathway, however, is the source of the proton required for initial protodesilyation. Labeling studies with added D_2O demonstrated that water could be a viable source of proton in the reaction.[19] However, after careful titration of the reagents and solvents used in this study, we were unable to account for sufficient adventitious water to satisfy the stoichiometry required for it to be the sole proton source. Moreover, when we investigate water as an additive to the reaction, severely diminished yields were observed when more than 0.5 equiv of water were added to the reaction.[19] Combined, these results indicate that adventitious water is not the primary source of protons in the reaction.



Eq. 1



Eq. 2



Eq. 3

Perplexed by these observations, we then carefully analyzed the reaction for minor byproducts that might account for the protons needed in the reaction; two such byproducts were observed. First, small amounts of aryl furan **44** (Eq 2) were observed in many of the reactions. Control reactions with added ethyl furan indicate that this product arises from a palladium-catalyzed Heck-type mechanism of the liberated 2-methylfuran **41** with excess aryl halide in the reaction.[19,34] This off-cycle pathway liberates water as a byproduct, and accounts for up to 5-10% of the required proton (Eq 2). In addition, we observed the double arylation of DMA (**45**) as a byproduct in up to 25% yield, which no doubt arises via a palladium-catalyzed α-arylation mechanism.[35] The formation of this byproduct releases two equiv of water, and accounts for an additional 50% of the required proton (Eq 3). When combined with traces of water found in the $KOSiMe_3$ and other reagents, these side products fully account for the protons needed in the proposed pathway. Notably, this pathway indicated also that there are possibly two roles for DMA in the reaction – both as a potential mild activating agent for $KOSiMe_3$ *and* as a source for the slow release of proton during the course of the reaction. As α-arylation is not possible with DMF, this pathway also helps to explain why DMF was not a successful additive in the reaction.

In conclusion, we have developed a method for the cross-coupling of highly substituted vinyl silanes with aryl halides to form valuable tetrasubstituted alkene compounds. The conditions for the reaction are general, mild, and tolerate a wide range of functional groups. In addition, this method utilizes easily prepared and bench-stable 2-methylfuryl-substituted vinyl silanes and does not require toxic or expensive stoichiometric additives for the activation of the silane.

ASSOCIATED CONTENT

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Notes

The authors declare no competing financial interest.

Supporting Information

Experimental details and spectral data (PDF and NMR FIDs).
The Supporting Information is available free of charge on the ACS Publications website.

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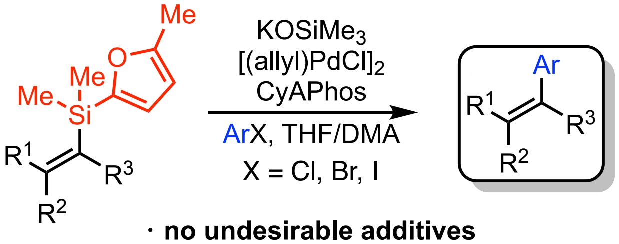

- **no undesirable additives**
- **aromatic and heteroaromatic halides**
- **vinyl silanes easily prepared and handled**