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Diversity-Oriented Synthesis of Multisubstituted Olefins through the Sequential Integration of Palladium-Catalyzed Cross-Coupling Reactions. 2-Pyridyldimethyl(vinyl)silane as a Versatile Platform for Olefin Synthesis

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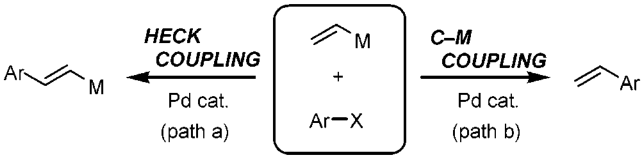
Abstract: A novel strategy for the diversity-oriented synthesis of multisubstituted olefins, where 2-pyridyldimethyl(vinyl)silane functions as a versatile platform for olefin synthesis, is described. The palladium-catalyzed Heck-type coupling of 2-pyridyldimethyl(vinyl)silanes with organic iodides took place in the presence of $Pd_2(dba)_3$/tri-2-furylphosphine catalyst to give β-substituted vinylsilanes in excellent yields. The Heck-type coupling occurred even with α- and β-substituted 2-pyridyldimethyl(vinyl)silanes. The one-pot double Heck coupling of 2-pyridyldimethyl(vinyl)silane took place with two different aryl iodides to afford β,β-diarylated vinylsilanes in good yields. The palladium-catalyzed Hiyama-type coupling of 2-pyridyldimethyl(vinyl)silane with organic halides took place in the presence of tetrabutylammonium fluoride to give di- and trisubstituted olefins in high yields. The sequential integration of Heck-type (or double Heck) coupling and Hiyama-type coupling produced the multisubstituted olefins in regioselective, stereoselective, and diversity-oriented fashions. Especially, the one-pot sequential Heck/Hiyama coupling reaction provides an extremely facile entry into a diverse range of stereodefined multisubstituted olefins. Mechanistic considerations of both Heck-type and Hiyama-type coupling reactions are also described.

Introduction

Carbon−carbon double bonds are ubiquitous and essential structural constituents in organic molecules and controlling the geometry of C═C bond has been one of the central issues in organic synthesis. Despite the impressive development in the stereoselective synthesis of disubstituted olefins, the stereoselective synthesis of tri- and tetrasubstituted olefins lags far behind.[1] In addition, certain multisubstituted olefins have emerged to possess interesting biological, chemical, and physical properties. Therefore, the strategic and diversity-oriented approach for such olefins is highly called for.

In pursuit of this objective, we had been attracted by the potentiality of the palladium-catalyzed Mizoroki−Heck-type coupling[2] and C−M cross-coupling (Kumada−Tamao−Corriu coupling, Negishi coupling, Migita−Kosugi−Stille coupling, Suzuki−Miyaura coupling, and Hiyama coupling)[3,4] reactions because those reactions are usually high-yielding and stereoselective. The alkenylmetals (C═C−M) are extremely appealing substrates for such reactions because both C═C and C−M functionalities can potentially be arylated under the palladium-catalyzed arylation conditions using aryl halides in two mechanistically different modes (Scheme 1). For example, Heck-type arylation at the C═C bond gives the substituted alkenylmetal (Scheme 1, path a). On the other hand, arylation at C−M functionality affords the metal-free alkene (Scheme 1, path b). If these two functionalities were rigorously discriminated toward the palladium-catalyzed arylation by the reaction conditions, sequential integration of these two reactions should pave the way for the stereoselective synthesis of multisubstituted olefins

Scheme 1



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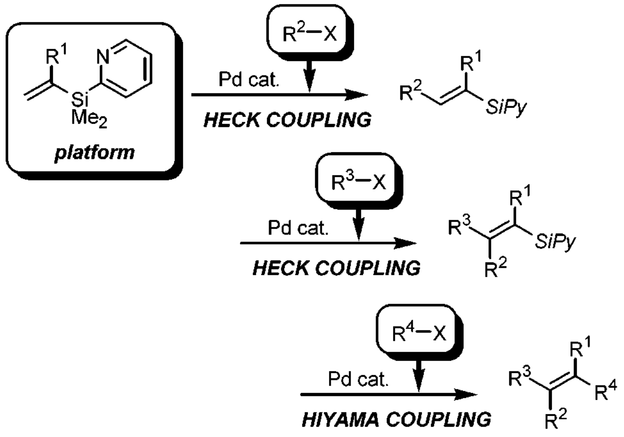
Scheme 2



where alkenylmetal acts as a platform for olefin synthesis (Scheme 2).

This strategy is an extremely flexible thus diversity-oriented approach for the synthesis of multisubstituted olefins. The installation of organic groups at the desired olefin carbon can be achieved by the appropriate order of added organic halides. Thus, the synthesis of regio- and stereoisomers of certain olefins can be achieved by simply changing the order of addition of organic halides. Moreover, the power of this strategy becomes apparent when considering the singularity with respect to the source of organic groups (i.e. organic halide). The commercial availability of such compounds makes this approach sufficiently diversity-oriented, thus fulfilling the recent demand for the generation of large combinatorial chemical libraries.[5] However, the development of such integrated cross-coupling reaction lags far behind though there are a number of catalysts and reagents reported to date for each of the reaction types.

On the basis of these backgrounds, we set out to establish the general protocol of the integrated cross-coupling reactions for the diversity-oriented synthesis of multisubstituted olefins. At the outset, there are two critical hurdles to be overcome for our strategy (Scheme 2) to be enlisted into service for multisubstituted olefin synthesis: (1) the two reaction pathways of alkenylmetal (Heck-type coupling and C−M cross-coupling) have to be perfectly controlled and be mutually switched, ideally with the slight changes of additive or reaction conditions (without any switching protocols, further integration should not be possible), and (2) a mild and efficient protocol for the double Heck-type coupling must be established although such a process has been known to be extremely sluggish with the typical Heck substrates (without such protocols, our strategy would end up in the production of disubstituted olefins).

Recently, we have been engaged in the development of removable directing groups,[6] which control the metal-mediated and -catalyzed processes by complex-induced proximity effect (CIPE).[7] We have established that a 2-pyridyldimethylsilyl (2-PyMe$_2$Si) group efficiently functions as such a removable directing group for various organometallic reactions.[8] Therefore, we began by addressing the above-mentioned issues by utilizing the 2-PyMe$_2$Si group for our strategy. During the course of this investigation, we have established that 2-pyridyldimethyl(vinyl)silane can be cross-coupled with various organic halides in the above-mentioned two mechanistically different modes (Heck-type coupling and Hiyama-type coupling) with the aid of palladium catalyst.[9,10] In this paper, we report on our strategy for the stereoselective synthesis of multisubstituted olefins by the sequential integration of palladium-catalyzed cross-coupling reactions of 2-pyridyldimethyl(vinyl)silane with organic halide (Scheme 2). The evolution of the efficient one-pot double Heck-type coupling, mechanistic studies for Heck-type and Hiyama-type cross-coupling reactions, and successful synthesis of multisubstituted olefins are also described.

Results and Discussion

1-1. Palladium-Catalyzed Heck-Type Coupling of 2-Pyridyldimethyl(vinyl)silane with Organic Iodide. It already is known that there are several difficulties with the Heck-type coupling of vinylsilane.[11] For example, the treatment of vinylsilane with aryl iodide under the typical Heck coupling conditions affords exclusively styrene derivative as a result of carbon−silicon bond cleavage.[12] Hallberg has discovered that the use of an equimolar amount of silver nitrate realizes the Heck-type coupling of vinylsilane.[13] Tanaka has reported the Heck-type coupling of chloro(vinyl)silanes.[14] Very recently, Jeffery has discovered that the addition of an equimolar amount of tetrabutylammonium acetate promotes the Heck-type coupling of vinyltrimethylsilane.[15]

We have already established that the Heck-type coupling of 2-pyridyldimethyl(vinyl)silane (**1**) with organic iodide took place with the aid of Pd$_2$(dba)$_3$/tri-2-furylphosphine (TFP)[16] catalyst

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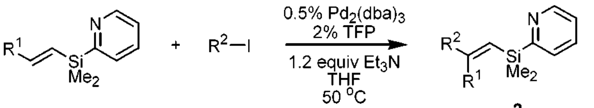
and triethylamine, giving the β-substituted vinylsilane **2** in extremely high yield (eq 1).[9] Noteworthy features of this process



(1)

2

1: R^1 = H
3: R^1 = Bu

R^2 = aryl, heteroaryl, alkenyl

90-95% yield
>99% stereoselectivity

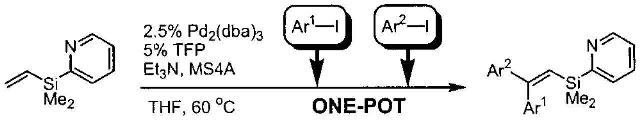
are that (1) the formation of styrene (C−Si bond cleavage) was completely suppressed, (2) the coupling occurred under mild conditions (50 °C) and at low catalyst loading (as low as 0.1 mol %), (3) virtually complete stereoselectivity (>99% *E*) was observed, (4) coupling occurred with a wide array of electronically and structurally diverse aryl, heteroaryl, and alkenyl iodides, and (5) the regio- and stereoselective coupling occurred even with the β-substituted vinylsilane **3**. Moreover, by taking advantage of the phase tag property of the 2-PyMe$_2$Si group,[8a,17,18] the coupling products **2** were isolated by simple acid−base extraction without using any chromatographic isolation technique. Recovery and reuse of the palladium catalyst were also possible.[9]

1-2. One-Pot Double Heck Coupling of 2-Pyridyldimethyl(vinyl)silane with Aryl Iodides. In our strategy, a mild and efficient protocol for the double Heck coupling must be developed (Scheme 2). However, such a process is known to be extremely sluggish and, therefore, such doubly arylated products were usually prepared by the stepwise reactions.[19−22]

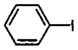
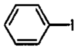
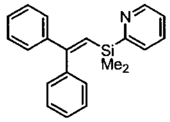
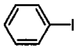
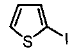
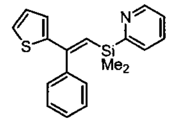
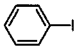
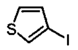
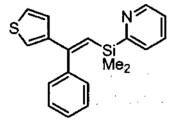
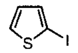
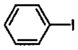
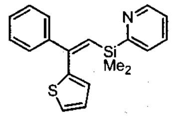
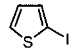
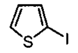
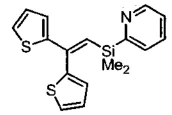
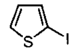
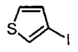
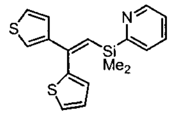
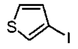
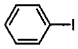
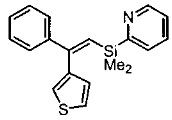
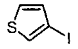
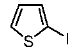
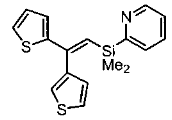
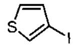
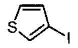
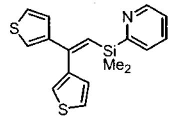
At the first outset, we began by establishing the conditions for the one-pot double Heck coupling of **1** with iodobenzene. After many experiments, the reaction with 2.4 equiv of iodobenzene, 3.0 equiv of Et$_3$N, and molecular sieve (MS4A) in THF at 60 °C afforded the doubly arylated product **4aa** in 74% yield (Table 1, entry 1). Without MS4A, we observed a small amount of silanol and siloxane, which were likely to be produced by the hydrolysis of **4aa**. The realization of previously difficult one-pot double Heck coupling is likely to be attributed to the strong directing effect of the pyridyl group on silicon.

With the feasibility of one-pot double Heck coupling established, we next examined the one-pot double Heck coupling with two different aryl iodides. To demonstrate the production of closely related library compounds, three aryl iodides (iodobenzene, 2-iodothiophene, and 3-iodothiophene) were subjected to the one-pot double Heck coupling of **1** (Table 1). Initially, Ar^1-I (1.0 equiv) was added to the reaction mixture to produce monoarylated product in situ. After completion of the first coupling, Ar^2-I (1.4 equiv) was added to the mixture and further heating of the reaction mixture afforded the doubly arylated product **4**. For all combinations examined, the reaction proved to be mild and high-yielding. Noteworthy features of this process are that (1) nine possible products (**4aa**−**4cc**) which arise from the three aryl iodides were stereoselectively prepared,[23] (2) stereoselective synthesis of β,β-diarylvinylsilane is accomplished in a one-pot process, and (3) both stereoisomers can be easily prepared by simply changing the order of addition.

Table 1. Palladium-Catalyzed One-Pot Double Heck Coupling of **1** with Aryl Iodides[a]



1 **4**

entry	Ar^1–I	Ar^2–I	product (yield, %)[b]	
1				**4aa** (74)
2				**4ab** (68)
3				**4ac** (67)
4				**4ba** (65)
5				**4bb** (74)
6				**4bc** (69)
7				**4ca** (72)
8				**4cb** (65)
9				**4cc** (72)

[a] All reactions were performed at 60 °C in THF (1.0 mL) with **1** (0.30 mmol), Ar^1−I (0.30 mmol), Ar^2−I (0.42 mmol), Pd$_2$(dba)$_3$·CHCl$_3$ (2.5 mol %), TFP (5 mol %), Et$_3$N (0.90 mmol), and MS4A (10 mg). [b] Isolated yields based on **1**.

We further extended this one-pot double Heck coupling to α-substituted vinylsilane **5**, with the hope for stereoselective preparation of tetrasubstituted olefins (Table 2). The mono-Heck coupling of **5** with iodobenzene proceeded well to give **6a** in good yield in the presence of Pd/TFP catalyst. However, in this case, we observed a small amount of 2-furyl group transferred product, which is likely derived from TFP via the well-known

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[17] For an excellent review on the strategic separations in organic synthesis, see: Curran, D. P. *Angew. Chem., Int. Ed.* **1998**, *37*, 1174.

[18] Borman, S. *Chem. Eng. News* **2001**, *79* (June 4), 49.

[19] Moreno-Mañas, M.; Pérez, M.; Pleixats, R. *Tetrahedron Lett.* **1996**, *37*, 7449.

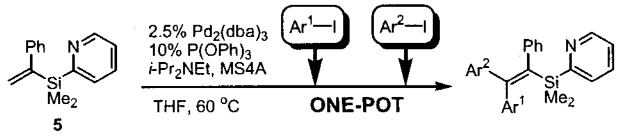
[20] For double Heck arylation of acrylates under high-pressure and high-temperature conditions, see: Sugihara, T.; Takebayashi, M.; Kaneko, C. *Tetrahedron Lett.* **1995**, *36*, 5547.

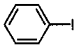
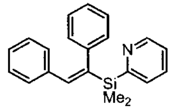
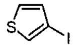
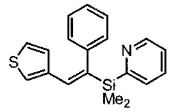
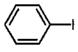
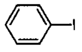
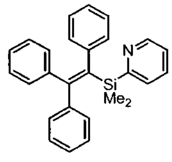
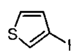
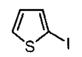
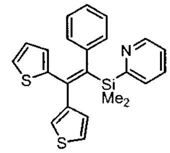
[21] Carretero has recently reported that one-pot double Heck arylation occurred with 1-sulfinylcyclopentanes. However, the second arylation does not occur at the same carbon where the first arylation takes place. de la Rosa, J. C.; Díaz, N.; Carretero, J. C. *Tetrahedron Lett.* **2000**, *41*, 4107.

[22] While preparing this manuscript, a sequential and multiple Heck arylation of vinyl ethers carrying a coordinating auxiliary has been reported: Nilsson, P.; Larhed, M.; Hallberg, A. *J. Am. Chem. Soc.* **2001**, *123*, 8217.

[23] The stereochemistry of **4** was determined by the NOE experiments. See Supporting Information for the details.

Table 2. Palladium-Catalyzed One-Pot Double Heck Coupling of **5** with Aryl Iodides



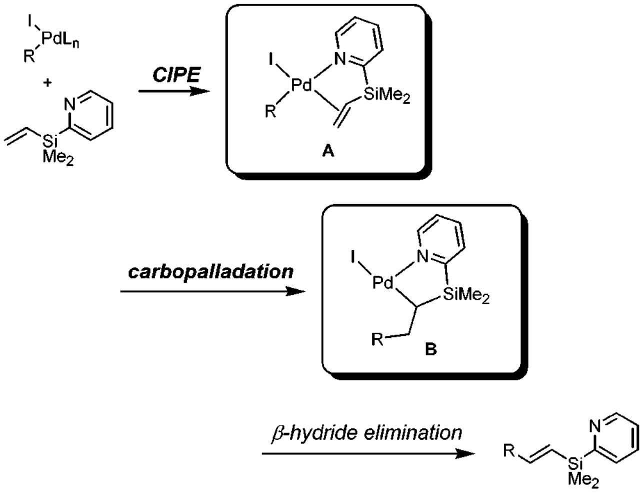
entry	Ar^1–I	Ar^2–I	product (yield, %)^c	
1^a		–	 **6a** (100)	
2^a		–	 **6c** (100)	
3^b			 **7aa** (48)	**6a** (6)
4^b			 **7cb** (28)	**6c** (7)

[a] The reactions were performed at 60 °C in THF (3.0 mL) with **5** (1.0 mmol), Ar^1-I (1.05 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (2.5 mol %), $P(OPh)_3$ (10 mol %), i-Pr_2NEt (1.1 mmol), and MS4A (10 mg). [b] The reactions were performed at 60 °C in THF (3.0 mL) with **5** (1.0 mmol), Ar^1-I (1.0 mmol), Ar^2-I (1.4 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (2.5 mol %), $P(OPh)_3$ (10 mol %), i-Pr_2NEt (3.0 mmol), and MS4A (10 mg). [c] Isolated yields based on **5**.

migration of aryl group on phosphorus to palladium.[24] Thus, we reexamined the reaction conditions for the Heck coupling of **5** and found that the ligand/base combination of $P(OPh)_3$ and diisopropylethylamine greatly improved the efficiency of the desired Heck coupling. The mono-Heck coupling of **5** with iodobenzene or 3-iodothiophene was completed within 1 h to give **6a** and **6c** in quantitative yields (entries 1 and 2). It should be noted that α,β-diarylvinylsilane with two different aryl groups such as **6c** cannot be prepared in a stereoselective fashion by the conventional alkyne hydrosilylation chemistry.[25] Subjection of **5** to the one-pot double Heck coupling with iodobenzene afforded the desired tetrasubstituted olefin **7aa** in 48% yield (entry 3). However, monoarylated compound **6a** (6%) was also found in the reaction mixture. Similarly, subjection of **5** to the one-pot double Heck coupling with 3-iodothiophene and 2-iodothiophene produced tetrasubstituted olefin **7cb** in 28% yield with virtually complete stereoselectivity (entry 4). Again, monoarylated compound **6c**, which failed to undergo a second Heck coupling, was produced in 7% yield. Nevertheless, the realization of a long-sought stereoselective synthesis of tetrasubstituted olefins attached with four different substituents is of great importance.

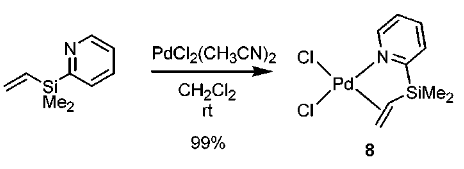
1-3. Relative Reactivity Evaluation of 2-Pyridyldimethyl(vinyl)silane. To evaluate the relative reactivity of 2-pyridyldimethyl(vinyl)silane, competitive reaction was carried out with methyl acrylate and styrene, the most commonly used reactive substrates in Heck chemistry.[2] The reaction was carried out with **1** (1.0 equiv), methyl acrylate (1.0 equiv), styrene (1.0 equiv), iodobenzene (1.0 equiv), and triethylamine (1.2 equiv) in the presence of $Pd_2(dba)_3$/TFP catalyst (5 mol % Pd). To our surprise, the only product detected in the reaction mixture was 2-pyridyldimethyl(styryl)silane (**2a**) (89% yield), which clearly signifies the high reactivity of **1** toward the Heck-type coupling.

Scheme 3



1-4. Mechanistic Considerations of Heck-Type Coupling of 2-Pyridyldimethyl(vinyl)silanes. It was quite interesting to observe that 2-pyridyldimethyl(vinyl)silanes possess unusually high reactivity toward the Heck-type coupling with organic iodides. This may be rationalized by assuming that the coordination of the pyridyl group to palladium might render the carbopalladation event kinetically and/or thermodynamically favorable (Scheme 3).[26]

To substantiate the governance of CIPE on the Heck-type coupling of **1**, we conducted the stoichiometric reaction of **1** with palladium(II) complex. First, **1** was treated with *trans*-$PhPdI(PPh_3)_2$ to see if the pyridyl group is coordinating to palladium during the carbopalladation process. However, because of the rapid β-hydride elimination from the intermediate **B**, we obtained the coupling product **2a** instead of the pyridyl-coordinated palladium(II) complex. Thus, we next examined the stoichiometric reaction of **1** with $PdCl_2(CH_3CN)_2$, and the palladium(II) complex **8** was isolated in 99% yield (eq 2).[27] In complex **8**, the coordination of the pyridyl group to palladium



(2)

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[24] Ortiz, J. V.; Havlas, Z.; Hoffmann, R. *Helv. Chim. Acta* **1984**, *67*, 1.

[25] Marciniec, B. *Comprehensive Handbook on Hydrosilylation*; Pergamon: Oxford, 1992.

[26] For chelation-controlled Heck arylation, see: (a) Andersson, C. M.; Larsson, J.; Hallberg, A. *J. Org. Chem.* **1990**, *55*, 5757. (b) Nilsson, K.; Hallberg, A. *J. Org. Chem.* **1992**, *57*, 4015. (c) Bernocchi, E.; Cacchi, S.; Ciattini, P. G.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1992**, *33*, 3073. (d) Badone, D.; Guzzi, U. *Tetrahedron Lett.* **1993**, *34*, 3603. (e) Larhed, M.; Andersson, C. M.; Hallberg, A. *Tetrahedron* **1994**, *50*, 285. (f) Buezo, N. D.; Alonso, I.; Carretero, J. C. *J. Am. Chem. Soc.* **1998**, *120*, 7129. (g) Alonso, I.; Carretero, J. C. *J. Org. Chem.* **2001**, *66*, 4453.

[27] Crystallographic data for **8**: $C_9H_{13}NSiCl_2Pd$, $M = 340.60$, orthorhombic, space group *Pbca* (No. 61), $a = 15.4551(7)$ Å, $b = 14.8687(5)$ Å, $c = 11.1172(4)$ Å, $V = 2554.7(1)$ Å^3, $Z = 12$, $D_c = 2.656$ g/cm^3, $\mu = 28.93$ cm^{-1}. Intensity data were measured on a Rigaku RAXIS imaging plate area detector with graphite-monochromated Mo Kα radiation ($\lambda = 0.71069$ Å). A total of 3313 reflections were collected. $R = 0.031$, $R_w = 0.021$.

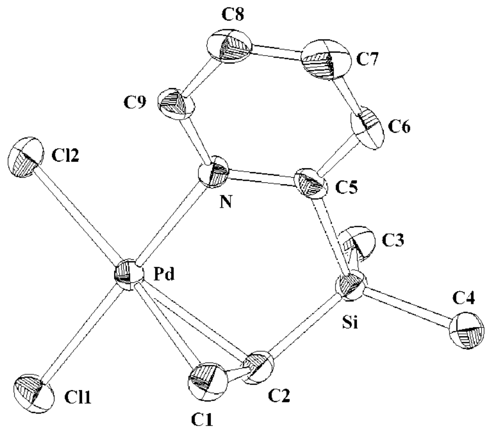
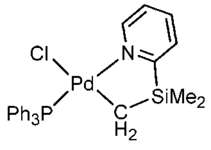


Figure 1. Molecular structure of **8**. Thermal ellipsoids are drawn at the 40% probability level. The hydrogen atoms are omitted for clarity.

was highly indicated by the noticeable changes of the pyridine ring chemical shift and nonequivalent two methyl groups on silicon in the ^{1}H NMR spectrum (see Supporting Information). The molecular structure of **8**, determined by X-ray crystallographic analysis, revealed the cis-coordination of pyridyl and vinyl groups to palladium (Figure 1). Although one of the two chlorine atoms of **8** should be an organic group in the real catalytic cycle, complex **8** can be regarded as a type **A** intermediate (Scheme 3). Thus, it might be reasonable to presume that the pyridyl-coordination is also taking place prior to the carbopalladation at intermediate **A** and the strong binding ability of **1** renders the carbopalladation event kinetically favorable.

In addition to this kinetic preference, stabilization of the palladium(II) intermediate (**B**) by complexation with the pyridyl group might also contribute to accelerate the carbopalladation process (Scheme 3). Although the isolation of such an intermediate by the carbopalladation across **1** met with no success because of the rapid β-hydride elimination, type **B** palladium(II) complex **9**, which lacks a β-hydrogen, can be prepared by using Hiraki's procedure[28] or the alternative procedure developed by ourselves.[8i] In complex **9**, the coordination of the pyridyl group to palladium was highly indicated by the noticeable changes of the pyridine ring chemical shift in the ^{1}H NMR spectrum. The molecular structure of **9**, determined by X-ray crystallographic analysis, revealed the coordination of the pyridyl group to palladium.[8i] Thus, it might be reasonable to presume that the pyridyl-coordination is also taking place after the carbopalladation at intermediate **B**, which may be the thermodynamical driving force of the carbopalladation process.



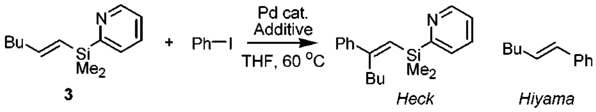
9

2. Palladium-Catalyzed Hiyama-Type Coupling of 2-Pyridyldimethyl(vinyl)silanes with Organic Halides.

Having established the Heck-type coupling reaction of 2-pyridyldimethyl(vinyl)silanes, we next turned our attention to the palladium-catalyzed Hiyama-type coupling reaction of 2-pyridyldimethyl(vinyl)silanes with organic halides.[4l−n]

2-1. Effect of Catalyst and Additive on the Palladium-Catalyzed Cross-Coupling Reaction of 3 with Iodobenzene.

As a model substrate, we selected 2-pyridyldimethyl(hexenyl)silane (**3**) because such β-substituted vinylsilanes are good substrates for addressing the regioselectivity issue.[29] As already stated, the $Pd_2(dba)_3$/TFP catalyst system promoted the Heck-type coupling of **3** with iodobenzene (eq 1). Although various palladium catalysts were examined, the only product detected was the Heck-type coupling product. This may be due to the strong directing effect of the pyridyl group and the poor transmetalation ability of silicon.[30] However, by adding tetrabutylammonium fluoride (TBAF) to the $Pd_2(dba)_3$/TFP catalyst system, the course of the reaction changed to the Hiyama-type coupling and the Heck-type coupling was completely suppressed (eq 3).[10] Moreover, we found that phosphine-free palladium complexes were more active catalysts, giving the Hiyama-type coupling product (1-phenylhexene) in extremely high yields. Among them, $PdCl_2(PhCN)_2$ was found to be the most active catalyst for the Hiyama-type coupling of **3** (eq 3).[31]



(3)

catalyst (5 mol%)	*additive (1.2 equiv)*	*ratio (Heck/Hiyama) (yield)*
$Pd_2(dba)_3$/TFP	*Et_3N*	*100/0 (94%)*
$Pd_2(dba)_3$/TFP	*TBAF*	*0/100 (59%)*
$PdCl_2(PhCN)_2$	*TBAF*	*0/100 (99%)*

2-2. Mechanistic Considerations of Hiyama-Type Coupling of 2-Pyridyldimethyl(vinyl)silanes.

These conspicuous and seminal results (eq 3) clearly brought to light several critical questions which have to be addressed: (1) why was the vinyl group instead of the pyridyl group transferred into the cross-coupling product (as well as the vinyl group, the pyridyl group is also known to transfer from silicon),[32] (2) what is the fate of pyridyl group, and (3) what is the mechanism?

Careful examination of the reaction mixture revealed that the pyridyl group was quantitatively converted into pyridine. This led us to investigate the reaction mechanism in more detail. First, 2-pyridyldimethyl(styryl)silane (**2a**) was allowed to react with 1.0 equiv of $PdCl_2(CH_3CN)_2$ in the presence of TBAF (1.2 equiv) and (*E*,*E*)-1,4-diphenyl-1,3-butadiene was isolated in 72% yield. This result unambiguously supports the occurrence of the transmetalation pathway.[33]

Next, we monitored the reaction of **2a** and TBAF in THF-d_8 by ^{1}H NMR and found that **2a** is converted into styryldimethylsilanol and pyridine within 30 min at 30 °C.[34] A small amount of water (ca. 5%) present in the commercially available THF solution of TBAF seemed to be the reactant in this case. Indeed,

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[28] Fuchita, Y.; Nakashima, M.; Hiraki, K.; Kawatani, M.; Ohnuma, K. *J. Chem. Soc., Dalton Trans.* **1988**, 785.

[29] Hatanaka, Y.; Goda, K.; Hiyama, T. *J. Organomet. Chem.* **1994**, *465*, 97.

[30] For the palladium-catalyzed cross-coupling reaction utilizing fluorosilicates, see: (a) Yoshida, J.; Tamao, K.; Takahashi, M.; Kumada, M. *Tetrahedron Lett.* **1978**, 2161. (b) Yoshida, J.; Tamao, K.; Yamamoto, H.; Kakui, T.; Uchida, T.; Kumada, M. *Organometallics* **1982**, *1*, 542.

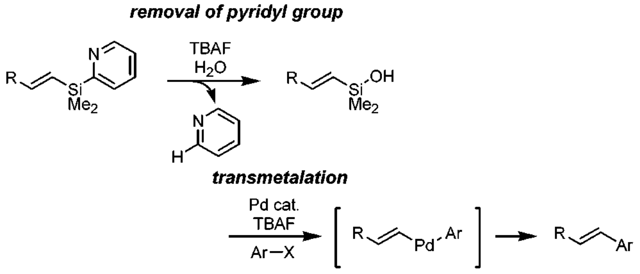
[31] The cine substitution product (2-phenylhexene) was formed in 1% yield.

[32] The transfer of substituted pyridyl group from Si to Pd in the presence of KF has been reported. Hagiwara, E.; Kusumoto, T.; Hiyama, T. 76th National Meeting of the Chemical Society of Japan, Yokohama, 1999.

[33] Weber, W. P.; Felix, R. A.; Willard, A. K.; Koenig, K. E. *Tetrahedron Lett.* **1971**, 4701.

[34] Protodesilylation of styryldimethylsilanol was found to take place upon letting the mixture stand for several hours to afford styrene quantitatively.

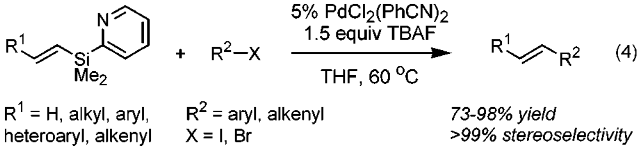
Scheme 4



silanol was not formed with anhydrous tris(diethylamino)sulfonium difluorotrimethylsilicate (TASF) instead. This 2-Py−Si bond cleavage is reminiscent of that attained by the KF-promoted methanolysis of 2-pyridylsilanes.[35]

Very recently, Mori[36] and Denmark[37] have reported that silanols can be cross-coupled with organic halides in the presence of palladium catalyst and we assume that our cross coupling using 2-pyridylsilanes is mechanistically similar to theirs (Scheme 4). Indeed, the cross-coupling reaction of styryldimethylsilanol with iodobenzene did occur under our reaction conditions giving *trans*-stilbene in 98% yield. After all, it seems plausible to deduce that the perfect switch of the reaction pathway (Heck-type coupling vs Hiyama-type coupling) stems from the selective removal of the Heck-coupling-directing pyridyl group and the introduction of an electronegative group that activates silicon as a leaving group (Scheme 4).

2-3. Sequential Heck/Hiyama Coupling Reactions. Under the standard set of reaction conditions (5 mol % of $PdCl_2(PhCN)_2$ and 1.5 equiv of TBAF in THF at 60 °C), various electronically and structurally diverse aryl and alkenyl halides were found to cross-couple with the pyridyl-substituted vinylsilanes in good to excellent yields (eq 4).[10] Not only aryl iodide but also aryl bromide was applicable.



We next examined the sequential Heck/Hiyama coupling reactions utilizing 2-pyridyldimethyl(vinyl)silanes (**1** and **5**) as a platform for multisubstituted olefin synthesis (Table 3). First, Heck-type coupling of 2-pyridyldimethyl(vinyl)silane was conducted with Ar^1-I under $Pd_2(dba)_3$/TFP catalyst. After the isolation of the initial coupling product, Hiyama-type coupling was conducted with Ar^2-I under the $PdCl_2(PhCN)_2$/TBAF system.

The present diversity-oriented synthesis of stilbene analogues may be exploited for the discovery of new lead compounds in this chemistry.[38] For example, compound **10b** is the key intermediate in the synthesis of oligophenylenevinylene-based photovoltaic devices.[39] The rapid synthesis of hydroxystilbenes such as **10c** is extremely intriguing since hydroxystilbenes are known to be good estrogen receptor ligands (both agonist and antagonist),[40] and are also found in natural products such as resveratrol, which recently have been shown to have cancer chemopreventive activity.[41] Moreover, recent screening of hydroxystilbene library revealed that such compounds selectively inhibit the B cell antigen receptor kinase cascade[42] or possess a novel antibacterial activity against MRSA bacterial strains.[43] Heteroaromatic compounds containing thiophene have attracted widespread interest because their linear and nonlinear optical properties are superior to those of the corresponding aryl analogues.[44] The rapid and diversity-oriented synthesis of such compounds (**10d**−**f**) is of great importance for understanding the structure−property relationships. Photochemically and biologically interesting styrylpyridines such as **10g** can also be prepared in a diversity-oriented manner.[45] This Heck/Hiyama coupling sequence is not limited to the synthesis of diarylethenes. By applying α-substituted vinylsilane **5** as a platform, triarylethenes (**11a** and **11b**) can also be prepared in a regio- and stereoselective fashion.

2-4. Sequential Double-Heck/Hiyama Coupling Reactions.

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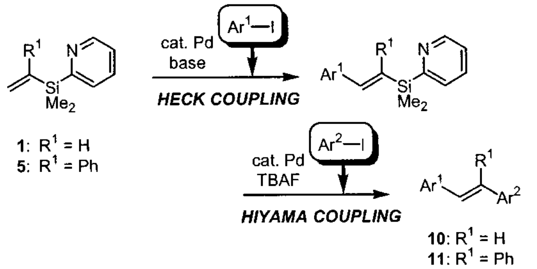
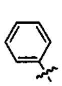
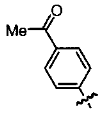
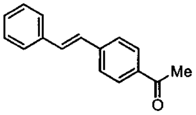
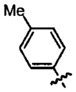
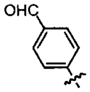
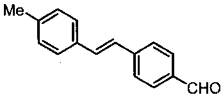
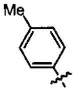
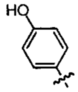
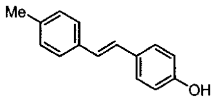
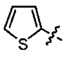
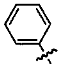
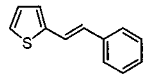
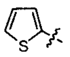
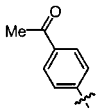
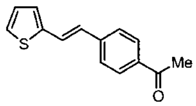
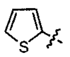
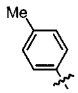
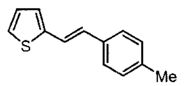
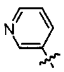
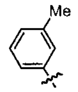
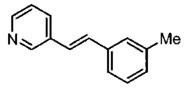
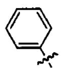
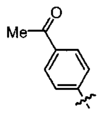
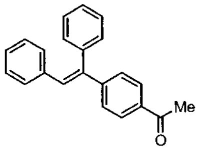
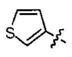
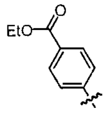
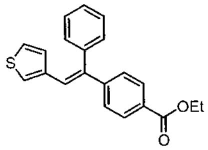
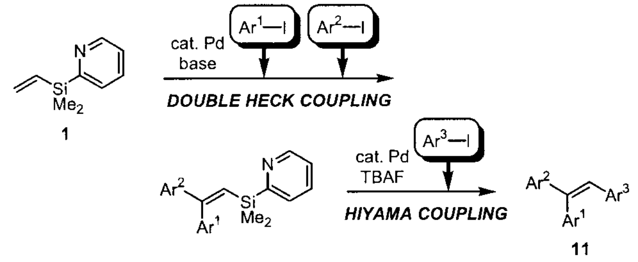
Table 3. Sequential Heck/Hiyama Coupling Reactions[a]

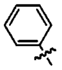
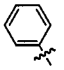
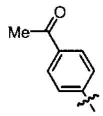
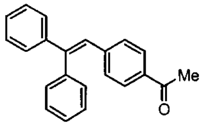
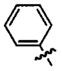
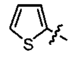
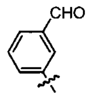
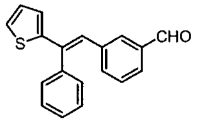
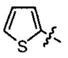
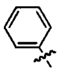
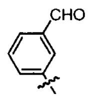
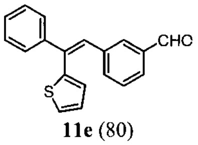
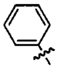
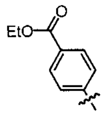
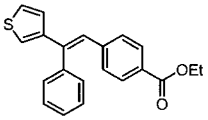
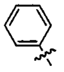
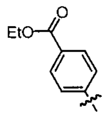
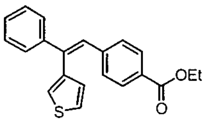


R^1	Ar^1	% yield of Heck coupling	Ar^2	product (% yield of Hiyama coupling)
H		93[b]		 **10a** (84)
H		95[b]		 **10b** (91)
H		95[b]		 **10c** (85)
H		92[b]		 **10d** (90)
H		92[b]		 **10e** (100)
H		92[b]		 **10f** (93)
H		95[b]		 **10g** (97)
Ph		100[c]		 **11a** (57)
Ph		100[c]		 **11b** (71)

[a] The Heck-type coupling reactions were performed with vinylsilane (1.0 equiv), Ar^1-I (1.1 equiv), Et_3N (1.2 equiv), $Pd_2(dba)_3$·$CHCl_3$ (0.5 mol %), and TFP (2 mol %) in THF at 50 °C. The Hiyama-type coupling reactions were performed with vinylsilane (1.5 equiv), Ar^2-I (1.0 equiv), TBAF (1.5 equiv), and $PdCl_2(PhCN)_2$ (5 mol %) in THF at 60 °C. [b] Reference 9. [c] See Table 2 for the conditions of Heck-type coupling of **5**.

Table 4. Sequential Double-Heck/Hiyama-Type Coupling Reactions[a]



Ar^1	Ar^2	Ar^3	product (% yield of Hiyama
			 **11c** (75)
			 **11d** (84)
			 **11e** (80)
			 **11f** (100)
			 **11g** (100)

[a] See Table 1 for the conditions of double Heck coupling. The Hiyama-type coupling reactions were performed with vinylsilane (1.5 equiv), Ar^2-I (1.0 equiv), TBAF (1.5 equiv), and $PdCl_2(PhCN)_2$ (5 mol %) in THF at 60 °C. [b] See Table 1 for the yield of double Heck coupling.

The sequential double-Heck/Hiyama coupling reactions were also examined (Table 4). As in Table 1, two aryl iodides (Ar^1-I and Ar^2-I) were cross-coupled with **1** in a one-pot process to give *β*,*β*-diarylvinylsilane **4**. The Hiyama-type coupling of **4** was conducted with Ar^3-I under the $PdCl_2(PhCN)_2$/TBAF system to produce triarylethenes **11** in high yields. For example, treatment of **4aa** with 4-iodoacetophenone in the presence of Pd/TBAF catalyst afforded the triarylethene **11c** in 75% yield. Stereoisomeric **4ab** and **4ba** were cross-coupled with 3-iodobenzaldehyde to give the stereoisomeric triarylethenes **11d** and **11e** in high yields. Similarly, stereoisomeric **4ac** and **4ca** were cross-coupled with 4-iodobenzoic acid ethyl ester to give the stereoisomeric triarylethenes **11f** and **11g** in quantitative yields. To the best of our knowledge, this is the first general procedure for the stereoselective production of triarylethenes bearing three different aryl groups.[46,47] Strategic synthesis of regio- and stereoisomers (**11a**/**11c**, **11d**/**11e**, and **11b**/**11f**/**11g**) is of great importance since triarylethenes, as exemplified by the breast cancer drug tamoxifen, are known to be ligands for the estrogen

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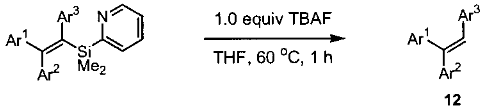
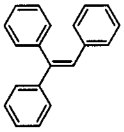
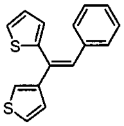
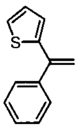
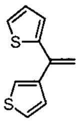
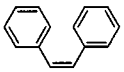
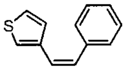
(46) For the synthesis of triarylethenes through the palladium-catalyzed sequential Stille-type arylation of *β*,*β*-dibromostyrenes, see: Shen, W.; Wang, L. *J. Org. Chem.* **1999**, *64*, 8873.

Table 5. Synthesis of Di- and Triarylethenes by Protodesilylation[a]

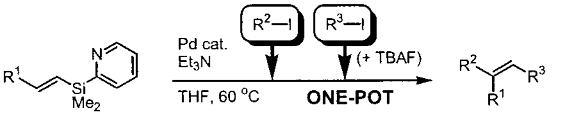


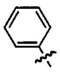
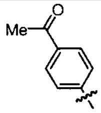
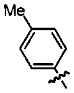
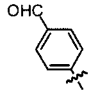
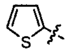
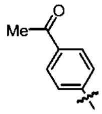
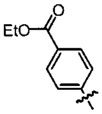
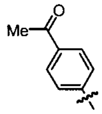
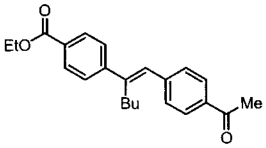
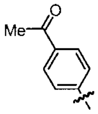
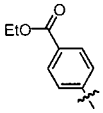
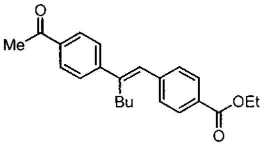
12

entry	silane	product (yield, %)[b]	
1	**7aa**		**12a** (99)
2	**7cb**		**12b** (100)
3	**4ab**		**12c** (98)
4	**4cb**		**12d** (91)
5	**6a**		**12e** (100)
6	**6c**		**12f** (92)

[a] All reactions were performed at 60 °C for 1 h with vinylsilane (0.30 mmol) and TBAF (0.30 mmol) in THF.

Table 6. One-Pot Sequential Heck/Hiyama Coupling Reactions[a]



R^1	R^2	R^3	product (yield, %)[b]
H			**10a** (69)
H			**10b** (92)
H			**10e** (93)
Bu			 **13** (71)
Bu			 **14** (79)

[a] All reactions were performed with the vinylsilane (0.30 mmol), R^2—I (0.27 mmol), R^3—I (0.20 mmol), Et_3N (0.32 mmol), TBAF (0.46 mmol), $Pd(OAc)_2$ (10 mol %), and TFP (10 mol %) in THF (0.9 mL) at 60 °C. [b] Yields based on R^3—I.

receptors, which play an important regulatory role in the reproductive, skeletal, and cardiovascular systems and are validated therapeutic targets for diseases such as breast cancer and osteoporosis.[48] The diversity-oriented synthesis of such triarylethenes is particularly interesting for new drug discovery. Moreover, it should also be mentioned that thiophene-containing triarylethenes demonstrated herein have recently emerged as a promising structural motif in organic electroluminescence materials.[49]

3. Protodesilylation of 2-Pyridyldimethyl(vinyl)silanes with TBAF. We also examined the synthesis of tetraarylethenes through the Hiyama-type cross-coupling reaction of triaryl-substituted vinylsilanes **7** with aryl iodides. However, all attempts to transfer these sterically condensed alkenyl groups met with no success. Since the stereoselective synthesis of tetraarylethene, bearing four different aryl groups, is one of the hardest synthetic challenges in current organic synthesis, the development of more active catalyst and/or active alkenylmetal species must be needed in this approach. Instead, we obtained the protodesilylation products. This TBAF-mediated protodesilylation does not require the palladium catalyst. In light that this protodesilylation may be a useful alternative for the stereoselective synthesis of di- and trisubstituted olefins, we conducted several protodesilylations of 2-pyridyldimethyl(vinyl)silanes (Table 5).

The protodesilylation of **7aa** and **7cb** afforded triarylethenes **12a** and **12b** in quantitative yields (entries 1 and 2). This double-Heck-coupling/protodesilylation sequence from **5** is a useful alternative to the Heck-coupling/Hiyama-coupling sequence from **5** for the stereoselective synthesis of triarylethenes. The protodesilylation of **4ab** and **4cb** gave 1,1-diarylethenes **12c** and **12d** in 98% and 91% yield, respectively (entries 3 and 4). By using the conventional Heck arylation of styrene derivatives, such 1,1-diarylethenes are only produced as minor products. The protodesilylation of **6a** and **6c** gave 1,2-*cis*-diarylethenes **12e** and **12f** in 100% and 92% yield, respectively (entries 5 and 6). This Heck-coupling/protodesilylation sequence from **5** is a good complement to the Heck/Hiyama coupling sequence from **1** with regard to the stereochemistry of 1,2-diarylethenes.

4. One-Pot Sequential Heck/Hiyama Coupling Reactions. In light of the ability of 2-pyridyldimethyl(vinyl)silane to cross-couple with organic halide in two mechanistically different modes (Heck-type coupling and Hiyama-type coupling), we next embarked on the one-pot sequential cross-coupling reaction, in

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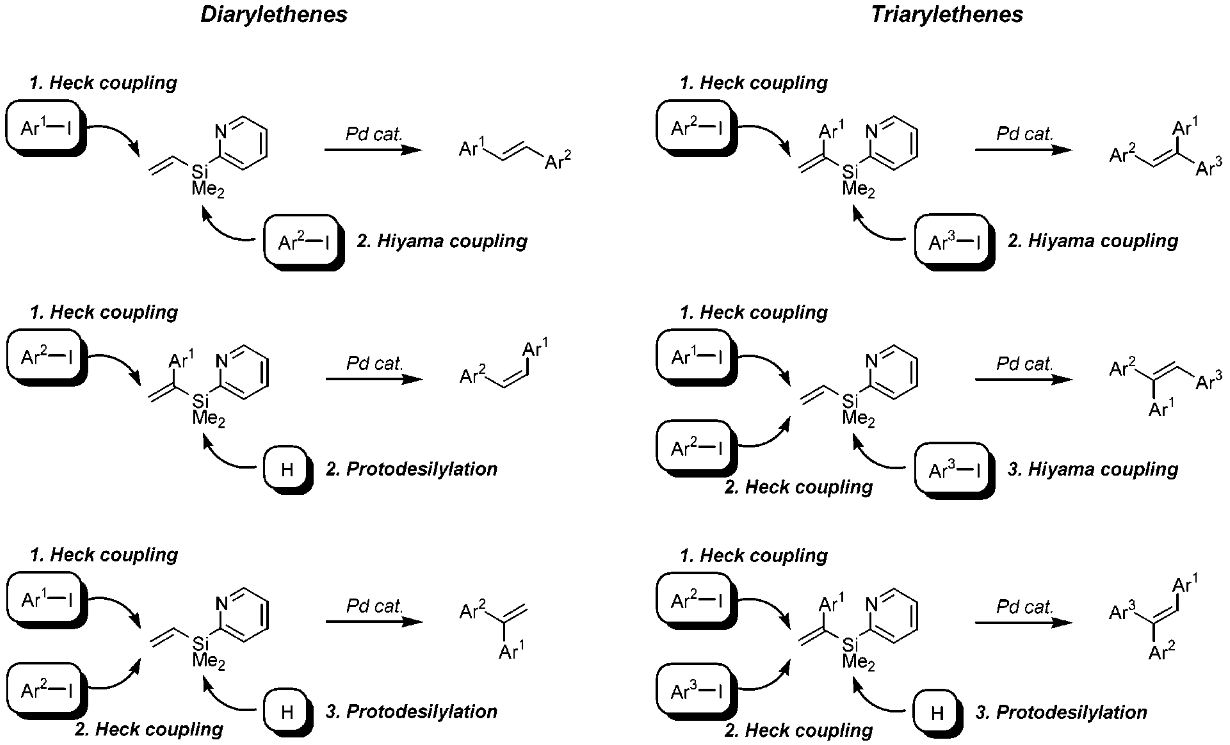
(47) The palladium-catalyzed reaction of aryl iodides with diarylacetylenes in the presence of formic acid and triethylamine produces triarylethenes. However, when an unsymmetrical diarylacetylene was used as a substrate, the mixtures of regioisomers were obtained. Cacchi, S.; Felici, M.; Pietroni, B. *Tetrahedron Lett.* **1984**, *25*, 3137.

(48) (a) Gao, H.; Katzenellenbogen, J. A.; Garg, R.; Hansch, C. *Chem. Rev.* **1999**, *99*, 723. (b) Simoni, D.; Roberti, M.; Invidiata, F. P.; Rondanin, R.; Baruchello, R.; Malagutti, C.; Mazzali, A.; Rossi, M.; Grimaudo, S.; Dusonchet, L.; Meli, M.; Raimondi, M. V.; D'Alessandro, N.; Tolomeo, M. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2669. (c) Meegan, M. J.; Hudhes, R. B.; Lloyd, D. G.; Williams, D. C.; Zisterer, D. M. *J. Med. Chem.* **2001**, *44*, 1072. (d) Rubin, V. N.; Ruenitz, P. C.; Boudinot, F. D.; Boyd, J. L. *Bioorg. Med. Chem.* **2001**, *9*, 1579. (e) Weatherman, R. V.; Clegg, N. J.; Scanlan, T. S. *Chem. Biol.* **2001**, *8*, 417 and references therein.

(49) (a) Azuma, H.; Hosokawa, C.; Kusumoto, T. Japanese Kokai Tokkyo Koho JP2000053677, 2000; *Chem. Abstr.* **2000**, *132*, 173451. (b) Okutsu, A.; Onikubo, S.; Tamano, M.; Enokida, T. Japanese Kokai Tokkyo Koho JP10152677, 1998; *Chem. Abstr.* **1998**, *129*, 47262. (c) Kreuder, W.; Lupo, D.; Salbeck, J.; Schenk, H.; Stehlin, T.; Hoerhold, H. H.; Lux, A.; Teuschel, A.; Wieduwilt, M. PCT International Application WO9610617, 1996; *Chem. Abstr.* **1996**, *125*, 99554.

Scheme 5



which the Heck-type cross-coupling occurs first and the Hiyama-type cross-coupling takes place thereafter (Table 6). In our preliminary screening of the reaction conditions, we established that $Pd(OAc)_2$, instead of $Pd_2(dba)_3{\cdot}CHCl_3$ or $PdCl_2(PhCN)_2$, is a superior palladium source for this one-pot process.[10] The vinylsilane **1** was initially cross-coupled with iodobenzene (R^2-I) in the presence of $Pd(OAc)_2$/TFP catalyst. After the initial reaction was completed, 4-iodoacetophenone (R^3-I) and TBAF were added to the mixture. The sequential cross-coupling product **10a** was obtained in 69% yield. Similarly, **1** underwent one-pot sequential Heck/Hiyama coupling with other different aryl iodides giving 1,2-*trans*-diarylethenes **10b** and **10e** in excellent yields. The β-substituted vinylsilane **3** was also found to undergo one-pot sequential Heck/Hiyama coupling to afford trisubstituted olefin. The advantage of this strategy is apparent as both regioisomers (**13** and **14**) were prepared in regio- and stereoselective fashion by simply changing the order of addition.

Conclusion

In conclusion, we have established that the 2-pyridyldimethyl(vinyl)silane serves as an extremely versatile platform for the stereoselective synthesis of multisubstituted olefins (Scheme 5). The Heck-type coupling, the one-pot double Heck coupling, the Hiyama-type coupling, and the one-pot sequential Heck/Hiyama coupling are now viable in this strategy. Especially, the integrated cross-coupling reaction described herein provides an extremely facile entry into a diverse range of stereo-well-defined multisubstituted olefins. A noteworthy feature of these processes is that any stereo- and regioisomers can, in principle, be prepared by simply changing the order of Ar-X addition. The strategy described herein is sufficiently diversity-oriented and would enable the production and screening of a large number of molecules (multisubstituted olefins) against the targets of interest.

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Supporting Information Available: Experimental procedures, characterization of all new compounds, NOE data for **4**, **6c**, **13**, and **14**, and crystallographic data for **8** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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